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Adrenal Surgery

A Clinical Study on Incidentalomas, Aldosteronomas and Laparoscopic Adrenalectomy

by

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Academic Dissertation

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To my family
and friends

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Abbreviations

ACTH	**Adrenocorticotropic hormone**
AIDS	**Acquired immunodeficiency syndrome**
APA	**Aldosterone-producing adenoma**
BMI	**Body mass index**
CNS	**Central nervous system**
CRH	**Corticotropin-releasing hormone**
CT	**Computed tomography**
DHEA	**Dehydroepiandrosterone**
DNA	**Deoxyribonucleic acid**
DOPA	**3,4-dihydroxyphenylalanine**
DTPA	**Diethyltriaminepentaacetic acid**
FNA	**Fine needle aspiration**
IHA	**Idiopathic hyperaldosteronism**
MEN	**Multiple endocrine neoplasia**
MIBG	**^{131}I-meta-iodobenzylguanidine**
MRI	**Magnetic resonance imaging**
MSH	**Melanocyte-stimulating hormone**
MTC	**Medullary thyroid carcinoma**
PA	**Primary aldosteronism**
PRA	**Plasma renin activity**
US	**Ultrasound**
VHL	**von Hippel-Lindau disease**
VMA	**Vanillylmandelic acid**

List of Original Publications

This thesis is based on the following original publications, which will be referred to by their Roman numerals.

I Sirén J., Haapiainen R., Huikuri K., Sivula A.

Incidentalomas of the Adrenal Gland:
36 Operated Patients and Review of Literature.
World Journal of Surgery 17, 634-639, 1993

II Sirén J., Tervahartiala P., Sivula A., Haapiainen R.

The Natural Course of Adrenal Incidentalomas:
A 7-Year Follow-up Study.
World Journal of Surgery, 2000, in press

III Sirén J., Välimäki M., Huikuri K., Sivula A., Voutilainen P., Haapiainen R.

Adrenalectomy for Primary Aldosteronism:
A Long-Term Follow-Up Study in 29 Patients.
World Journal of Surgery 22, 418-421, 1998

IV Sirén J., Haglund C., Huikuri K., Sivula A., Haapiainen R.

Laparoscopic Adrenalectomy for Primary Aldosteronism:
Clinical Experience in 12 Patients
Surgical Laparoscopy & Endoscopy 9, 9-13, 1999

V Sirén J., Haglund C., Haapiainen R.

An Institutional Experience with 40 First Lateral
Transperitoneal Laparoscopic Adrenalectomies
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Introduction

In Helsinki University Central Hospital approximately 15 adrenal operations are performed annually. This clinical study concentrates on the indications of operative treatment of incidentally discovered adrenal masses, the results of adrenalectomy for primary aldosteronism, and on the results of the novel method laparoscopic adrenalectomy.

Incidental discovery of an adrenal mass during radiologic examinations is common. Clearly, not all incidentalomas should be operated on, but the criteria and safety for nonoperative treatment have been under continuous debate. In studies I and II we review incidentalomas operated on at our institution, and report the natural course of incidentalomas left to watchful management during the 7-year follow-up.

Primary aldosteronism is a rare syndrome characterized by hypertension, hypokalemia, suppressed plasma renin activity, and elevated serum aldosterone levels. The operative treatment is successful only in cases of aldosterone-producing neoplasia; all other cases should be treated medically. In study III, we present the results of operative therapy for primary aldosteronism at our institution.

The introduction of laparoscopic cholecystectomy in the late 1980s ushered in a new surgical era. The benefits of minimally invasive surgery allowed laparoscopic methods to rapidly replace open operations in many indications. When starting with this novel method in adrenalectomy, we decided to prospectively collect data of these operations to find out the results and safety of this method. The results of 40 first laparoscopic operations are presented in studies IV and V.

Review of the Literature

Historical Background of Adrenal Surgery

The adrenal glands were first described as "glandulae quae renibus incumbent" (glands lying on the kidney) by Bartholomaeus Eustachius in 1564.[1] During the 17th - 19th centuries the glands were called "capsulae suprarenales", because the adrenal medulla rapidly autolyses after death and the finding in an autopsy reminds a capsule.[2] The present names "suprarenal gland" or "adrenal gland" both describe the anatomic location of these glands. The anatomic division into a cortex and a medulla was defined by Cuvier in 1805.[3]

The function was unknown and controversial until 1855, when Thomas Addison of Guy's Hospital, London, published his observations in patients with destruction of both adrenal glands, and found out that the adrenal glands were essential to life.[4] After this finding the importance of these organs was realised, and scientists all over the world were attracted to research their function.

In 1895 two English physiologists, George Oliver and Edward Sharpey-Schafer showed that adrenal medulla contained a substance that elevated the blood pressure in dogs, and named this extract "adrenaline". Two years later John Abel, professor of pharmacology at Johns Hopkins University School of Medicine, U.S.A., purified the extract and named the active compound "epinephrine".[5]

The biochemical studies of the structure and synthesis of adrenocortical steroids in the 1930s by Reichtenstein in Switzerland and Kendall and Hench in the U.S.A. resulted in the award of the Nobel Prize in physiology and medicine in 1950.[5] Pheochromocytoma (from the Greek *phaios*, dark, and *chroma*, color) was first described in 1886 by Frankel.[5] Harvey Cushing described the clinical features of hypercortisolism in 1912[6] and JW Conn described primary aldosteronism in 1955.[7]

The first successful adrenalectomy was carried out by Knowsley-Thornton who removed a large adrenal tumor in 1889,[2] and the first adrenalectomies for pheochromocytoma were performed in 1926 by Charles Mayo, in the United States and Roux in Switzerland.[8]

Embryology of the Adrenal Gland

The adrenal cortex is of mesodermal origin. It arises during the fifth gestation week from mesenchymal cells between the root of the mesentery and the urogenital ridge. The cortex is formed of two parts: a thick fetal cortex surrounded by a second thin layer of cells that will later form the adult cortex. After birth, the fetal cortex undergoes rapid degeneration and the adult cortex starts to proliferate. The fetal cortex vanishes totally during the first year of life, and the adult cortex becomes fully differentiated by the 12th year. Ectopic adrenocortical tissue is common in newborn infants, and is situated near the adrenal glands or in relation to the structures formed from the urogenital ridge. This tissue usually atrophies and disappears after a few weeks of life, but in adrenogenital syndrome or any form of adrenocorticotropic hormone (ACTH) stimulation it persists.[5] The chromaffin cells of adrenal medulla originate from the neuroectoderm. Cells from the neural crest migrate and invade the fetal cortex during the second month of gestation. Sympathetic neurons are formed from the same precursors, which migrate to their destinations adjacent to the arterial vessels and cranial nerves of the head and neck, and sympathetic plexus and chains in the neck, thorax, abdomen and pelvis.[9] In fact, some cells in the abdominal preaortic sympathetic plexus and paravertebral sympathetic chain differentiate to primitive adrenal medullary cells. Most of them degenerate after birth, but ectopic medullary tissue, so-called cromaffin bodies or paraganglia, is not uncommon.[10] The organs of Zuckerkandl[11] are small collections of medullary tissue between the root of the inferior mesenteric artery and the aortic bifurcation. This collection is prominent at birth, and enlarges up to the third year after birth before it starts to degenerate. Ten to twenty per cent of pheochromocytomas develop in these

ectopic sites,[12] the organs of Zuckerkandl being one of the most frequent sites. These cells of neural crest origin can also develop into malignant neuroblastomas or ganglioneuroblastomas (partly differentiated neuroblastomas) and benign ganglioneurinomas. The incidence of all these tumors of neural crest origin is higher in children than adults.

Anatomy of the Adrenal Glands

The adrenal glands lie retroperitoneally on each side of the vertebral column at the level of 11th - 12th thoracal vertebrae. They are in close contact with the superior poles of the kidneys and surrounded by perirenal fat and Gerota's fascia. The normal adrenal gland weighs about 6 g and is 5 cm long, 2.5 cm wide and 1 cm thick.

The right adrenal is pyramidal in shape with the base embracing the right kidney. It is situated anterior to the diapraghm and the right kidney and posterior to the vena cava and liver. The medial border lies towards the right celiac ganglion and the right inferior phrenic artery. The anterior surface is medially posterior to the inferior vena cava and laterally in contact with the right lobe of the liver. Sometimes the lateral part of the anterior surface is covered by peritoneum, but usually it is situated behind the liver. The posterior surface is in contact with the diaphragm and superior pole of the right kidney.[13,14]

The left adrenal is semilunar in shape. The medial border lies towards the left celiac ganglion, left inferior phrenic artery and left gastric artery. The anterior surface is covered with the peritoneum of the omental bursa and is superomedially near the spleen, the splenic artery, and the tail of the pancreas. The posterior surface is medially in contact with the left crus of the diaphragm and laterally with the medial aspect of the superior pole of the kidney.[13,14]

The rich arterial supply comes from small branches from three main sources: superior suprarenal arteries from the inferior phrenic artery, middle suprarenal arteries from the aorta and inferior suprarenal arteries from the renal artery. Additional small branches

may come from intercostal arteries, the left ovarian or left internal spermatic arteries. Some small branches supply the medulla directly, but most of them form a network of sinusoidal capillaries at the cortex and pass as small venules through the medulla to the medullary veins.[13,14]

The venous drainage mainly takes place into a single suprarenal vein leaving the gland through the hilum. On the left side, the hilum is situated at the inferior medial corner of the gland and on the right side at the medial border of the gland. The right adrenal vein is only 5 mm long and drains directly to the vena cava, whereas on the left side the vein is longer, usually joins the inferior phrenic vein near the gland and drains to the left renal vein. Small accessory veins are not uncommon, and may drain into the inferior phrenic, renal, and portal veins.[15]

The lymphatic drainage is mainly through the para-aortic and paracaval lymph nodes to the lumbar trunks and thoracic duct. The sympathetic nerve supply is rich. It originates at the spinal medulla between T-3 and L-3 and passes through the hilus to the adrenal medulla. These preganglionic sympatethic fibres terminate in synapses to the pheochromocytes and regulate the secretion of epinephrine. Parasympathetic nerves from vagal nerve through the celiac ganglion also enter the medulla. The adrenal cortex has only a vasomotor nerve supply.

On section, the gland consists of a golden yellow thicker cortical layer, constituting about 85% of the gland, and a thinner reddish-brown medulla. The microscopic examination shows a thin capsule, a cortex comprising three concentric layers: zona glomerulosa, zona fasciculata and zona reticularis, and a well-vascularized medulla.[16]

Adrenal Physiology

Adrenal Cortex

The adrenal cortex synthesizes three types of steroid hormones from plasma cholesterol: glucocorticoids, mineralocorticoids, and sex steroids. Glucocorticoids have widespread

effects on the metabolism of carbohydrate, protein, and fat. Mineralocorticoids are essential to the maintenance of sodium balance and extracellular fluid volume. Sex steroids have only minor effects on normal subjects, and can be considered as side products in steroidogenesis.

There are two structural types of adrenocortical steroids: C 21 steroids, which have a 2-carbon side chain attached at position 17 of the 19 carbon cyclopentanoperhydrophenanthrene nucleus, and C 19 steroids that have a keto or hydroxyl group at position 17. C 19 steroids have androgenic activity and C 21 steroids have both glucocorticoid and mineralocorticoid activity. The C 21 steroids are classified as glucocorticoids or mineralocorticoids, depending on which effect predominates.

The hormones secreted in physiologically significant amounts are the glucocorticoids cortisol and corticosterone, the mineralocorticoid aldosterone and the androgen dehydroepiandrosterone (DHEA). Aldosterone is synthesized in the zona glomerulosa, cortisol in zona fasciculata, and sex steroids in zona fasciculata and zona reticularis. The steroid synthesis takes place in mitochondrios and endoplasmic reticulum.[17]

The first step in steroid synthesis is the conversion of cholesterol into pregnenolone. Pregnenolone is further converted in three main pathways into aldosterone, cortisone and DHEA. Cortisone is secreted, and bound with high affinity to corticosteroid-binding globulin. Aldosterone is mostly secreted in its free form. The weak androgen DHEA is secreted mainly as DHEA-sulphate, and is converted in peripheral tissues into testosterone and estrogens.[18]

The glucocorticoid secretion is principally regulated by hormonal interactions among the hypothalamus, pituitary, and adrenal glands. Neural stimuli, as in the response to stress, cause the release of corticotropin-releasing hormone (CRH), and other agents from hypothalamic neurons. This stimulates ACTH secretion from the pituitary gland. ACTH acts on the adrenal cortex and increases the secretion of corticosteroids. Glucocorticoids have a negative feed-back effect on synthesis and secretion of CRH and ACTH. ACTH is secreted in brief episodic bursts of varying amplitude at different times of the day. The timing of this circadian rhythm is synchronized with the solar day by dark-light shifts. Plasma ACTH and cortisol levels are highest at the time of waking in the morning, low

in the evening, and almost undetectable a few hours after the beginning of sleep.[19]

The physiological effects of cortisol are mediated by its binding to a glucocorticoid receptor. This complex principally inducts or inhibits the transcription of many different genes. Glucocorticoids have various effects on: 1) the metabolism (glycogen metabolism, gluconeogenesis, peripheral glucose utilization, and lipid metabolism), 2) immunologic function and inflammatory process (lymphocyte apoptosis, T- and B-cell function, monocyte and macrophage function, and mediators of inflammation), 3) musculoskeletal and connective tissue metabolism, 4) fluid and electrolyte homeostasis, 5) the central nervous system and behavior, and 6) the gastrointestinal system.[19]

The renin-angiotensin system and serum potassium concentration directly are the major regulators of aldosterone secretion, although various other minor modulators, including ACTH, exist. Changes in the circulating blood volume and sodium and potassium concentrations regulate the renin synthesis and release by the juxtaglomerular cells in the renal cortex. Renin levels increase when renal blood flow decreases, or in hypernatremia or hypokalemia. Renin cleaves angiotensin I from angiotensinogen in the liver. Angiotensin-converting enzyme, mainly in the lung, converts angiotensin I into biologically active angiotensin II, which in turn increases both peripheric vascular resistance by vasoconstricion and aldosterone production. Aldosterone mediates its physiological effects by binding in mineralocorticoid receptors in tubules of the kidney, which increases the number of open sodium and potassium channels. This leads to increased potassium excretion to and increased sodium and water resorption from the urine. The renin secretion is suppressed by the result of increased intravascular volume and decreased serum potassium concentration.[18,19]

Adrenal Medulla

Adrenal medulla functions under direct control of the central nervous system (CNS) and synthesizes catecholamines along the sympathetic nervous system. In this sympathoadrenal system the catecholamines are synthesized from tyrosine. The limiting

step of the synthesis is hydroxylation of tyrosine to 3,4-dihydroxyphenylalanine (DOPA) by tyrosine hydroxylase. DOPA is further converted into dopamine, and dopamine into norepinephrine. This synthesis takes place throughout the sympathoadrenal system. In the adrenal medulla norepinephrine may further be converted into epinephrine by the action of phenylethanolamine n-methyltransferase. This enzyme is induced by glucocorticoids, and the major source of epinephrine are chromaffin cells next to the adrenal cortex where high concentrations of glucocorticoids are present.[18,20]

The function of the sympathoadrenal system is regulated by CNS, and different components of the system are affected differently by physiological stimuli. The adrenal medulla and sympathetic nervous system usually function in tandem, but sometimes the sympathetic nervous system is suppressed while the adrenal medulla is stimulated. This suggests that circulating and locally-released cathecolamines serve different functions. The physiological effects of catecholamines are mediated through different types of α- and β-adrenergic, and dopaminergic receptors. The principal effects are: 1) cardiovascular (effects on cardiac output and vascular resistance), 2) visceral (vegetative functions), and 3) metabolic effects (mobilization of energy reserves from storage depots, regulation of oxygen uptake, and maintenance of the constancy of extracellular fluid).[20]

Surgical Aspects of Adrenal Gland Disorders

Adrenal Hypofunction

The proper function of the adrenal gland is important to the body's ability to cope with stresses such as infections, hypotension, and surgery.

Primary adrenal insufficiency follows the destruction of the adrenal cortex itself. The adrenal medulla may be spared or destroyed, but the symptoms are primarily caused by the missing cortical function. The chronic form of primary adrenal insufficiency is called

Addison's disease. The most common cause (70 to 90%) of Addison's disease is autoimmune adrenalitis, alone or in combination with hypofunction of other endocrine glands (autoimmune polyendocrine syndromes), most often autoimmune thyroiditis. Other causes are tuberculosis, adrenoleucodystrophy, systemic fungal infections, acquired immunodeficiency syndrome (AIDS), metastatic carcinoma or lymphoma, and familial glucocorticoid deficiency.[21] The acute form of primary adrenal insufficiency is usually encountered in critically ill patients and is caused by adrenal haemorrhage, necrosis, or thrombosis. The underlying cause can be meningococcal or other kinds of sepsis, coagulation disorder, or anticoagulation treatment. It is also associated with traumatic shock, severe burn, or major surgery.[22] Surgical removal of both adrenal glands was followed by death to acute primary adrenal insufficiency before the corticosteroid replacement therapy was available.

Secondary adrenal insufficiency is the result of a pituitary disease and insufficient ACTH production. Tertiary adrenal insufficiency is due to hypothalamic disease and insufficient CRH production.[19] It is also possible after discontinuation of corticosteroid treatment, or cessation of corticosteroid overproduction followed by surgical treatment of Cushing's syndrome.[21]

The clinical manifestations of adrenal insufficiency usually include fatigue, weakness, mental depression, dizziness, orthostatic hypotension, anorexia and weight loss, gastrointestinal symptoms such as nausea, vomiting and diarrhea, and hyponatremia, hypoglycemia and anemia.[23] In primary adrenal insufficiency, hyperpigmentation due to the excess of ACTH and melanocyte-stimulating hormone (MSH) is a classic symptom. Aldosterone deficiency leads to increased excretion of sodium and decreased excretion of potassium. Hyponatremia and hyperkalemia result. Water is excreted in excess with sodium, and severe dehydration with decreased circulatory volume, hypotension and circulatory collapse will follow. Cortisol deficiency contributes to the hypotension and produced disturbances in carbohydrate, fat and protein metabolism, and severe insulin sensitivity. Insufficient amounts of carbohydrate are formed from protein, too little fat is broken down; hypoglycemia and diminished liver glycogen result. Weakness due to the deficient neuromuscular function follows. Cardiac output is reduced and circulatory

failure can occur even if blood volume is maintained. In Addison's disease these symptoms usually develop slowly, but can lead to acute adrenal crisis precipitated by acute infection, trauma, surgery, and salt loss.

It is of critical importance to every surgeon operating on adrenal glands to be able to recognize the symptoms of adrenal insufficience in acute adrenal insufficiency or addisonian crisis. If untreated, the patient dies in a course of a few hours. Treatment of acute adrenal insufficiency should be instituted immediately once the condition is suspected. The therapy consists of high-dose intravenous hydrocortisone starting with a bolus of 100mg followed by an infusion of 200 mg during the next 24 hours, volume and sodium correction with isotonic saline solution, and glucose to control the hypoglycemia.[21] Mineralocorticoids are not required in acute insufficiency.

To prevent acute adrenal insufficiency after bilateral or unilateral adrenalectomy for Cushing's syndrome, replacement therapy must be started at operation with the dose described above. The dosage is gradually reduced to a maintenance level, described below, during one week. In case of unilateral adrenalectomy the dosage is further reduced enabling the function of the remaining adrenal gland and the pituitary to normalize. This can usually be accomplished by 6 months[24] but may take as long as 24 months, and about 25% of patients will never taper off exogenous steroids.[25,26]

Chronic adrenal insufficiency is treated with oral hydrocortisone administered in the morning and afternoon. Night doses are avoided, because they can cause insomnia or psychic disturbances. The daily dose is 15 to 30 mg, two thirds given in the morning. The dose should be the smallest dose that relieves symptoms, to prevent the side-effects of glucocorticoid treatment. Instead of hydrocortisone synthetic glucocorticoids may be used. In primary adrenal insufficiency mineralocorticoid replacement with fludrocortisone is also indicated with a single daily dose of 50 to 200 microg. The fludrocortisone dose is monitored by measuring blood pressure, serum potassium and plasma renin activity, which is kept at the upper-normal range. The patient must increase the dose of hydrocortisone whenever under physical stress, such as infection or injury.[21]

Adrenal Cortical Hyperfunction

Hypersecretion of adrenocortical hormones produces distinct clinical syndromes. Excessive production of glucocorticoids produces Cushing's syndrome, hypersecretion of aldosterone results in hyperaldosteronism, and excess androgen output produces adrenal virilism. These syndromes frequently have overlapping features. Feminization caused by adrenal overproduction of estrogen is extremely rare.

Hypercortisolism

Hypercortisolism, or Cushing's syndrome, may be ACTH-dependent (80%) or it may be independent of ACTH regulation. The causes of ACTH-dependent hypercortisolism are hypersecretion of ACTH by the pituitary (70%), and secretion of ACTH (or rarely CRH) by a nonpituitary tumor (ectopic ACTH syndrome, 10%), e.g. an oat cell carcinoma of the lung, malignant tumors of the thymus or the pancreas, and carcinoid tumors. The pituitary form was described by Harvey Cushing, and it is therefore called Cushing's disease. The causes for ACTH-independent Cushing's syndrome are cortisol-producing adrenocortical adenoma (10%) or carcinoma (10%), or rarely a primary adrenocortical nodular hyperplasia.[27] The proportion of adenomas and primary hyperplasias is considerably greater than that of carcinomas in a recent surgical series (72%, 20%, and 8% respectively).[28]

The clinical features develop gradually and include centripetal obesity, moon facies, buffalo hump, thin limbs with muscular hypotrophy and weakness, hypertension, hirsutism and menstrual disorders, thin atrophic skin with striae and easy bruising, and psychiatric disturbances.

If clinical suspicion of Cushing's syndrome arises, screening tests with high sensitivity should be done. The cardinal biochemical features of Cushing's syndrome are excess secretion of cortisol, loss of the normal feedback system, and disturbance of the normal circadian rhythm of cortisol secretion, and the tests rely upon these parameters. The

diagnosis can be excluded with normal 1 mg overnight dexamethasone suppression test or 24h urinary free cortisol collection with normal cortisol level.[29] Midnight plasma cortisol measurement has also shown to be sensitive, but cannot be done on outpatient basis.[30] However, the diagnosis is not always easy, and borderline cases exist. Furthermore, the test results may be abnormal for a variety of reasons other than Cushing's syndrome, for example obesity, and further testing is frequently needed. If the screening tests show borderline abnormal results, the workout should be continued with more specific tests, such as the 2-day low-dose dexamethasone test (2 mg x 2 days). This will lower the plasma cortisol level in patients without Cushing's syndrome.[31] The distinction between ACTH-dependent and -independent cases is made by measuring the plasma ACTH level. The differential diagnosis of ACTH-dependent Cushing's syndrome can further be carried out by measuring plasma corticotropin before and after a high dose dexamethasone (8 mg) suppression. In Cushing's disease, the plasma levels of ACTH are normal or slightly elevated and are suppressed by dexamethasone. In ectopic ACTH syndrome, the basal level is usually markedly elevated and cortisol production is not suppressed by dexamethasone. In ACTH-independent Cushing's syndrome, the plasma ACTH levels are low and no suppression for dexamethasone is noticed. CRH-stimulation test with or without selective catheterization of petrosal veins shows an increase in ACTH levels in pituitary Cushing's syndrome.[27,30] Along with the development of diagnostic methods it has become apparent that some adrenal adenomas and hyperplasias in fact do produce subclinical quantities of glucocorticoids, without clinical Cushing's syndrome. Baseline values of serum cortisol or urinary 17-hydroxysteroids and 17-ketosteroids are normal or at the upper limit. The diurnal rhythm of cortisol production is lost, and so is pituitary control with suppression of ACTH production and function of the contralateral gland. The significance of this so-called pre-Cushing's syndrome has not yet been determined, and the subject is under debate.[32,33]

Indications for adrenal surgery depend on the underlying abnormality. In ACTH-dependent Cushing's syndrome, the treatment is directed to the pituitary gland or extra-pituitary ACTH source. In Cushing's disease, the pituitary adenoma may be removed

surgically or treated with irradiation. If this is not possible or successful, bilateral adrenalectomy is usually indicated. If the patient does not tolerate surgery, corticosterone production may be blocked by adrenal enzyme inhibitors aminoglutethimide, ketokonazole or metyrapone.[19,34] In most cases of ectopic ACTH syndrome, the source of ACTH production is nonresectable, or cannot be found, and hypercortisolism should be controlled by enzyme inhibitors. In patients with an indolent tumor and a long life expectancy, medical adrenalectomy with mitotane, or bilateral adrenalectomy, is indicated.[19] The treatment in ACTH-independent Cushing's syndrome is unilateral adrenalectomy in adenoma and carcinoma patients and bilateral adrenalectomy in primary hyperplasia patients.

Before adrenal surgery in Cushing's syndrome the metabolic disturbances should be corrected. Glucocorticoid production may be blocked with enzyme inhibitors (or mitotane), and possible hypertension, diabetes and psychiatric disorders are treated.[27] Anticoagulation with low-molecular-weight heparin to prevent thromboembolic complications and prophylactic antibiotics are usually recommended, although the benefits of these treatments have not been proved.[35]

The surgical risks in Cushing's syndrome are related to many unfavourable effects of glucocorticoids: wound healing is delayed, resistance to infections is impaired, patients are obese, and tissues fragile and bleed easily. Hypercoagulable state due to increased factor VIII activity is usual. Diseases further impairing recovery, such as diabetes, hypertension, and arteriosclerosis, are often present. The recent mortality and morbidity rates for bilateral adrenalectomy range from 0% to 4%, and 4% to 10%, respectively, and are higher than for unilateral adrenalectomy for Cushing's syndrome, or for adrenalectomy in general.[35,36]

Untreated Cushing's syndrome is associated with a 5-year mortality of 50%.[37] The long-term outcome after adrenalectomy in Cushing's syndrome is different among the subgroups. Five-year survivals for primary hyperplasia, adenoma, and Cushing's disease patients are favourable, 100%, 93% and 86% respectively. However, the majority (70%) of operated patients have symptoms, chronic fatigue being the most common complaint. Nelson's syndrome develops in 15% to 25% of patients with Cushing's disease after

bilateral adrenalectomy. This syndrome is characterized by progressive expansion of the pituitary gland and hyperpigmentation due to excess ACTH secretion. Five-year survival for ectopic ACTH syndrome, and carcinoma patients is poor, 39% and 9%, respectively.[19,36,38]

Hyperaldosteronism

Primary aldosteronism (PA), Conn's syndrome, is caused by excessive production of aldosterone in adrenal glands. This leads to hypertension, hypokalemia and suppressed plasma renin activity (PRA). Secondary hyperaldosteronism is merely a compensatory reaction of renin-angiotensin-aldosterone system to external stimuli. It is often related to hypertension and edematous disorders (e.g. cardiac failure, the nephrotic syndrome, hepatic cirrhosis with ascites).

PA accounts for around 1% of all hypertensive patients.[39,40] It may be caused by a variety of disorders: aldosterone-producing adenoma (APA)(60-80%), bilateral adrenocortical hyperplasia (idiopathic hyperaldosteronism, IHA)(20%), aldosterone-producing adrenocortical carcinoma (1%), glucocorticoid-remediable hyperaldosteronism (<1%), renin-responsive adrenocortical adenoma (<<1%), and primary adrenocortical hyperplasia (<<1%).[41] Extra-adrenal production of aldosterone from tumors of ectopic adrenocortical tissue is extremely rare.[42] APA, also called aldosteronoma, is usually a solitary tumor in only one adrenal gland. IHA affects both adrenal glands and consists of micro- or macronodular hyperplasia. However, APA is frequently associated with micro- (43%) or macronodules (19%)[43] and, furthermore, rare cases of solitary bilateral adenomas[44] and unilateral hyperplasia (primary adrenal hyperplasia)[41] have been described. The rare glucocorticoid-remediable hyperaldosteronism is typically diagnosed in young adults with a family history of hypokalemia-associated hypertension. It can be identified with the dexamethasone suppression test, and treated by glucocorticoids.[45] Renin-responsive adrenocortical adenoma has been considered a rare disease, but recent observations in Australia suggest

it to be a common finding (incidence up to 10%) among the hypertensive normokalemic population.[46,47]

PA is usually diagnosed in middle-aged patients with a female to male ratio of 2:1. The symptoms of PA are mostly due to hypertension and hypokalemia and include headache, weakness, fatigue, nocturia, polydipsia, chest pain, numbness, and muscle cramps. The diagnosis is usually suspected in patients with hypokalemia and hypertension refractory to treatment. The diagnostic workout consists of 1) screening tests 2) confirmation of the diagnosis, and 3) differentiation between APA and IHA, in connection with the localization of APA. The diagnosis is suggested if hypokalemia, inappropriately high urinary excretion of potassium, and suppressed plasma renin activity together with a normal or high serum aldosterone level are shown. Computed tomography (CT) is usually done at this stage and, if the finding is suggestive of APA, no further confirmation is needed.[48] When necessary, the diagnosis can be confirmed by showing high urinary excretion of aldosterone during a volume load.[49] Various methods can be used to differentiate between APA and IHA. The most reliable is adrenal venous sampling for aldosterone measurement,[50] but because it is an invasive method with a complication rate of 5%, and the technique is difficult, and is reserved to problematic cases; adrenal venous sampling is not used at our institution. CT (or magnetic resonance imaging [MRI], which has not been shown to be better than CT) is an accurate method to show APA, and when it shows unilateral and solitary nodule larger than 1 cm, there is no need for further investigations.[51] However, if it shows a small solitary nodule, or multiple unilateral or bilateral nodules, it is unreliable in differentiating APA from IHA, because adenomas are often associated with non-aldosterone-secreting nodules.[52] In these cases the diagnosis should be confirmed with adrenal venous sampling, ^{131}I-6-β-iodomethyl norcholesterol scan with dexamethasone suppression, or a postural test during a volume load.[49]

Operative treatment is the treatment of choice for PA caused by an aldosterone-producing neoplasia (APA or carcinoma), but medical treatment with aldosterone antagonists (spironolactone) is better in most cases of hyperplasia.[53] Before surgery the hypokalemia must be corrected with spironolactone or oral potassium substitution, or

both.

Adrenalectomy for APA corrects the hypokalemia and almost always normalizes the renin-angiotensin-aldosterone system. Hypertension is not always cured. In the collected literature, calculated from 694 cases, the long-term cure rate of operatively treated APA patients was 69%.[53] Postoperatively, however, the hypertension is better controlled in most patients. The long duration of the hypertension preoperatively is believed to cause adaptive and irreversible vascular changes that maintain hypertension.[54]

Virilizing and Feminizing Syndromes

The effects of adrenal virilizing and feminizing syndromes depend on the sex and age of the patient. Virilizing features are also often associated with Cushing's syndrome, as described above.

Congenital adrenal hyperplasia refers to a group of disorders due to congenital defects in hydroxylation of cortisol precursors and low cortisol levels. This leads to increased secretion of ACTH, resulting in adrenal hyperplasia. The production of adrenal androgens and precursors of corticosteroids is thus increased. The clinical picture depends on the specific enzyme defect, and can include pseudohermaphroditism, macrogenitosomia and growth disturbances. Excess aldosterone production can cause hypertension. Severe defects can cause adrenocortical insufficiency and even death of acute adrenocortical failure.[55] The congenital adrenal hyperplasia is treated with hydrocortisone, which arrests the ACTH secretion.[56]

Androgen-producing tumors, adenomas or carcinomas, cause virilization with hirsutism, baldness, acne, deepening of voice, amenorrhea, atrophy of the uterus, clitoral hypertrophy, decreased breast size, and increased muscularity.[57] Feminizing adrenal tumors are rare and usually malignant.[58] The treatment of virilizing and feminizing tumors is adrenalectomy. The possibility of concomitant cortisol production with suppression of ACTH secretion and suppression of the contralateral gland must not be anticipated, and hydrocortisone replacement therapy may be indicated.

Pheochromocytoma

The reported annual incidence of pheochromocytoma in Sweden is 3/1 000 000,[12] and in the United States it is 8/1 000 000.[59] Pheochromocytoma is sometimes discovered only at autopsy: in a 50-year autopsy study of 40 078 autopsies, 54 pheochromocytomas were found, 41 of them without prior clinical suspicion. Pheochromocytoma was the probable cause of death in 75% of the clinically unsuspected cases, and many of these deaths were related to minor surgical procedures.[60]

The presenting symptoms are manifestations of catecholamine excess, and include hypertension (56 to 90%), headache (49 to 56%), sweating (44 to 47%), palpitations (34 to 37%), dizziness (15%), anxiety (15%), congestive heart failure (12%), hypertension during anesthesia (7%), and impaired glucose tolerance (7%).[61,62] Today, a considerable proportion (22%) of pheochromocytomas are found on screening for inherited syndromes or as incidentalomas.[62] Usually the symptoms occur paroxysmally, but approximately 50% of the patients have sustained hypertension.[61] However, symptoms may be atypical, and clinical suspicion remains the most important factor in the identification of pheochromocytoma. It should be suspected in patients with unusually labile or intermittent hypertension, pregnant women with new hypertension, and children with hypertension. Pheochromocytoma is called a "10% tumor", because about 10% of these tumors are malignant, bilateral, multifocal, extra-adrenal, hereditary, and occur in children.

The clinical behavior of pheochromocytomas does not correlate with the histopathologic features; the only reliable signs of malignancy are the presence of local invasion into surrounding tissues and the presence of a metastatic tumor in sites other than along the sympathetic chain. Even tumors with invasion to capsule and vascular invasion often have benign behavior. Diploid nuclear deoxyribonucleic acid (DNA) pattern in flow cytometry has been suggested to be a reliable sign of benign behavior,[63] but this finding has been questioned.[64] Extra-adrenal pheochromocytomas are often multicentric and they are commonly believed to be more frequently malignant (40%),[9] but the data is

somewhat conflicting.[65]

Pheochromocytomas are associated with many unusual syndromes, most of them familial: multiple endocrine neoplasia (MEN) 2A and 2B, von Hippel-Lindau disease (VHL), von Recklinghausen's disease, tuberous sclerosis, Sturge-Weber disease, and Carney's syndrome. In MEN 2 syndromes with pheochromocytoma, the medulla of the contralateral gland is always hyperplastic, although true tumors are not always present, and over 50% of the patients will develop a pheochromocytoma to the contralateral gland.[66] Prophylactic contralateral adrenalectomy is therefore advocated by some surgeons,[67] but others resect only macroscopic pheochromocytomas because of the substantial morbidity and mortality with the Addisonian state after bilateral adrenalectomy.[66] Recently, the association of pheochromocytoma to carrier status of VHL disease is suggested to be present in 20% of all pheochromocytoma patients, and screening for this disease is suggested. The conventional screening procedure includes CT or MRI of the brain, CT of the abdomen, ultrasonography (US) of the testes, and ophthalmoscopy. Despite the extensive and costly screening program needed, it is considered warranted, because of the risk of hemangioblastoma of the central nervous system has an excellent prognosis if recognized and removed promptly.[68] The gene responsible for VHL has been identified,[69] and can be used for screening for VHL.[70]

Biochemical testing for possible pheochromocytoma is usually done with 24-hour urine collection for metanephrines and vanillylmandelic acid (VMA), with a false negative rate of only 2%.[8,71] However, metanephrines are not specific, as 10 to 20% of patients may have mildly elevated values without pheochromocytoma. Elevated urinary fractionated catecholamines may be used to confirm the diagnosis.[71] CT has shown to be an excellent localization technique for adrenal pheochromocytomas.[8,62] MRI is equally good, and T2-weighted images show a characteristic high-intensity signal.[72] However, CT is less useful than MRI in extra-adrenal pheochromocytomas, metastatic or recurrent disease, and pheochtomocytomas associated with MEN 2. ^{131}I-meta-iodobenzylguanidine (MIBG) scintigraphy in combination with CT localize most of these tumors.[73,74]

Patients must be prepared for surgery by preoperative α-adrenergic blockade, usually

with phenoxybenzamine. α-blocker is started at least one week before surgery, and β-blocker is usually added a few days before surgery to control tachycardia and arrhythmias. Labetalol, which is a combined α- and β-blocker, has also shown to be effective. The initial experience of combination therapy with α-adrenergic blockade and α-methylthyrosine, a catecholamine-synthesis blocker, has been encouraging.[75] Calcium channel blockers in combination with α-adrenergic blockade may also be used.[62] To compensate for the previously contracted intravascular volume, preoperative liberal oral fluid and salt intake or intravenous fluids given a few days before surgery are also beneficial. Anesthesiologists must be prepared to treat both hypertension and hypotension during and after anesthesia. Adequate monitoring with invasive blood pressure measurement and Swan-Gantz catheter, when appropriate, is essential. Hypertension is usually controlled with sodium nitroprusside infusion, and hypotension, commonly present after tumor excision, can be controlled with volume correction and dopamine.[61,63] Patients also need postoperative monitoring for 24 hours to ensure stabilization of blood pressure.

Operative approach is selected according to the location, size, and type of the tumor. Preoperative localizing studies are today considered to be sufficiently accurate to allow excision of the tumor without exploration of contralateral gland and retroperitoneal space in whole.[61-63] Single small adrenal pheochromosytomas can be removed laparoscopically.[8,76] Alternatively, the posterior approach may be used. The anterior approach is necessary when localization studies show multicentric or extra-adrenal pheochromocytoma, or when malignancy is suspected by local invasion, and in cases of metastatic disease. The strategy is to remove the tumor intact with minimal manipulation, and to achieve control of the adrenal vein as soon as possible.

Postoperatively, 24-hour urine collection for metanephrines and VMA is indicated to ensure that all gross tumor has been removed. Annual screening for at least 5 years has been recommended, because metastatic disease may appear years after surgery.[77] Perioperative mortality has been less than 1%, and morbidity 16%.[8] Long-term outlook is very good.[62]

Surgery is the best treatment for malignant pheochromocytomas. Metastases should be

excised and if complete resection is not possible, the size of the tumor should be reduced to better control the catecholamine levels.[77] In a series of 20 malignant pheochromocytomas, metastases occurred at presentation in 11, 10-30 months postoperatively in 7, and 9 and 28 years later in two cases.[78] Median survival has been 16 months (range 3 to 60 months) from the diagnosis of metastases.[78] Combination chemotherapy and MIBG therapy can give palliation if complete surgical resection is not possible.[63]

Adrenocortical Carcinoma

Adrenocortical carcinoma is a rare disease. The annual incidence of adrenocortical carcinoma in Finland from 1970 to 1994 has varied between 2.1 and 3.7/1 000 000, with a female-male ratio of 1:1.5.[79]

The typical clinical features of adrenocortical carcinoma include large tumor size, an abrupt onset of disease, abdominal pain, pyrexia, and symptoms of hormonal syndromes described earlier. Symptoms related to hormonal overproduction can be found in 50% of the patients, and 60% show activity in hormonal studies. Hypersecretion of more than one adrenocortical hormone is found in 35%, pure hypercortisolism in 30%, virilization in 22%, feminization in 10%, and hyperaldosteronism in 2.5% of functioning carcinomas.[80] Adrenocortical carcinoma metastasize often to the lung (72%), the liver (55%), and sometimes to the peritoneum (33%), the bone (24%), the contralateral adrenal gland (15%), and the brain (10%).[81]

The size of the tumor is of importance: adrenal masses 5 cm or more in diameter are frequently but not invariably malignant, and the larger the mass, the more likely it is to be malignant.[82] Imaging studies cannot reliably differentiate between benign and malignant tumors, although the findings may be suggestive.[82] Features suggesting malignancy in CT include: irregular shape and border of the tumor, central necrosis, calcifications, inhomogeneous enhancement pattern, and evidence of local invasion or metastases.[83] MRI has not proven to be better than CT, and the appearances of carcinoma are non-specific. MRI is useful in demonstrating the invasion of adjacent

structures and venous invasion to inferior vena cava or renal vein.[72] In scintigraphy, the uptake is usually very weak or lacking, although cases of hyperfunctioning, well-differentiated carcinomas with clear uptake are found.[82]

The criteria of malignancy in adrenocortical tumors are not precise. The only definitive criteria are metastasis, and local invasion to adjacent structures. Histologic features suggesting malignancy are: diffuse architectural pattern with broad fibrous and trabecular bands, foci of confluent necrosis, hemorrhagic areas, fibrosis and calcifications, capsular invasion, venous and sinusoidal invasion, nuclear pleomorphism, high mitotic rate, low contents of clear cells in the tumor, and negative immunohistochemical staining for vimentin.[81] Cytologic features suggesting malignancy are: extreme cellularity, loss of cohesion of the cells, cellular and nuclear pleomorphism, abundance of mitosis, atypical mitosis, and aneuploidy by flow cytometry.[84,85] None of the histologic or cytologic features are pathognomonic, only suggestive, but the probability of malignancy grows along with the number of these features present in the tumor. Genetic studies are also only suggestive: smaller adenomas are usually polyclonal, whereas larger adenomas with a higher prevalence of nuclear polymorphism and carcinomas are monoclonal.[86] Insulin-like growth factor II gene overexpression and abnormalities at the 11p15 locus are found in 93% of malignant, but only in 9% of benign adrenocortical tumors.[87]

Adrenocortical carcinomas are classified in stages I to IV.[88] In Stage I, the tumor is no more than 5 cm in diameter and weighs 50 g or less, and in Stage II larger than 5 cm or weighs more than 50 g; both without local invasion, and local lymph node or distant metastasis. In Stage III, there is either local invasion or local lymph node metastasis, but no distant metastasis. Tumors with local invasion and lymph node metastasis, or distant metastasis belong to Stage IV.

Surgery is indicated in Stages I, II and III. The average postoperative survival in Stage IV is only 3 months, and surgery is indicated only in young patients with solitary metastasis. Mitotane treatment is started 1 month preoperatively in hypercortisolism and when operating on patients with distant metastasis. Concomitant cortisol replacement therapy is indicated to avoid addisonian crisis. Ketokonazole can be used if the patient

does not tolerate mitotane. The function of the contralateral kidney must be ensured preoperatively if the imaging studies suggest local extension to the kidney. On the right side, surgeons should be prepared to liver resection and tumor invasion to vena cava. A wide exposure is essential for vascular control, lymphnode dissection and possible tumor extension to adjacent organs. Usually wide subcostal laparotomy is appropriate, but thoracoabdominal approach may be necessary with large right-sided tumors, or if the vena cava is involved with a tumor thrombus. The strategy is to resect the tumor en bloc with all invaded adjacent organs and regional lymph nodes. The tumor must be dissected free cautiously to avoid rupturing the capsule. A cleavage plane between the tumor and liver can often be found, and a formal liver resection is rarely necessary. The tumor and the kidney may also be separated if a cleavage plane is found, associated nephrectomy does not seem to have an effect on survival. However, nephrectomy is often necessary to obtain proper clearance of local lymph nodes.[81]

Mitotane has been used as adjuvant therapy after surgery, but it has been proven effective only in patients with inoperable, recurrent and metastatic tumors.[89] Only 60 to 70% of patients can tolerate the high dosage needed, because of associated neurotoxicity, nausea, and diarrhea.[90] Radiation therapy is usually ineffective, but clinical trials of polychemotherapy,[91] and trials with new drugs like paclitaxel may provide new therapeutic alternatives in the future.[92]

The intraoperative and 30-day postoperative mortality is about 10%, most of it due to the extensive operations needed.[80] The overall 5-year survival ranges from 16 to 34% and for curatively operated patients from 32 to 62%.The tumor stage is the most important factor predicting prognosis, the 5-year survival in Stage I and II is 53%, in Stage III 24%, and in Stage IV 0%.The prognosis is better with patients younger than 45 years of age, and in patients with androgen- or precursor-secreting, and nonsecreting tumors.[80]

Incidentaloma

Incidentalomas are unexpectedly discovered adrenal tumors found in CT, MRI, US, or

other radiologic examination carried out for symptoms not related to adrenal patophysiology. The incidence of incidentalomas in CT examinations has varied from 0.35 to 1.30%,[93-96] and in autopsy series adrenal adenomas are found in 1.4 to 8.7%, but these series include also small adenomas that cannot be found in radiologic examinations.[97,98]

Most of the incidentalomas (70 to 94%) are nonfunctioning small cortical adenomas, and other nonfunctioning benign tumors, like hyperplasia, myelolipoma, cysts, lipomas, and calcifications after haemorrhage.[99] So, in most cases, the incidentalomas are clinically insignificant, and do not necessitate any therapy. However, asymptomatic, but hormonally active, or malignant tumors must be identified and removed. Therefore all incidentalomas have to be carefully evaluated. History is important, possible paroxysmal symptoms related to pheochromocytoma must be asked. Physical findings of hypercortisolism and virilizing or feminizing symptoms must be sought. If the history and physical status are normal, and imaging studies do not propose a malignant tumor, further examination is needed.

Pheochromocytoma is the most frequently (up to 10% of incidentalomas) found hormone-producing incidentaloma,[100,101] cortisol producing adenomas[95,102] and aldosteronomas[102,103] are also occasionally identified. Subclinical cortisol production, pre-Cushing's syndrome, can be found in 10% of incidentalomas,[104] but the clinical significance of this condition is not clear.

The recommendations for hormonal screening vary, but basic hormonal testing for pheochromocytoma is always considered necessary.[105] Screening for hypercortisolism is usually recommended,[106,107] but might lead to a high number of false positive results and unnecessary diagnostic workout or operations.[105] Serum potassium measurement is usually considered to be necessary only in patients with hypertonia,[105] but others suggest urinary aldosterone measurements for all patients.[108] Due to the rarity of virilizing or feminizing syndromes and lack of specific tests, screening for them is seldom advocated.[105]

Adrenocortical carcinomas are usually large at detection, and therefore the size of the incidentaloma is most commonly used as a criterion for suspicion of malignancy. No

carcinomas <2.5 cm in diameter have been reported,[108] and most of them are larger than 6 cm in diameter at detection.[106,109] When the diameter of the tumor grows, also the possibility of adrenocortical carcinoma grows. Various cut-off sizes for surgery are therefore proposed, from 2.5 cm to 6 cm, 4cm being perhaps the most used value.[110]

Metastases in adrenal glands are common in lung cancer, breast cancer, and melanoma. However, over 25% of adrenal masses in these patients are not metastases, and the distinction can be done by using fine needle aspiration (FNA).[96]

The majority of incidentalomas are not operated on, because hormone overproduction or signs of malignancy are not present. The natural course of incidentalomas is not known, and therefore various recommendations for follow-up of these patients exist.[108,110] The possible benefit of follow-up has not been shown. Follow-up with CT or some other imaging method is usually recommended, but repeated hormonal testing is seldom advocated.[110]

Rare Tumors of the Adrenal Gland

Malignant neuroblastomas and ganglioneuroblastomas (partly differentiated neuroblastomas) are embryological tumors derived from the neural crest, and they comprise the most common malignancy in infants. They can arise anywhere along the sympathetic chain, most common primary site being within the abdomen, specifically in the adrenal medulla (40%) or the paraspinal ganglia (25%). It is proposed that half of them mature to benign ganglioneurinomas, sometimes found incidentally or at autopsy.[111,112]

Myelolipomas are rare benign neoplasms composed of mature adipose and hematopoietic tissues. They are hormonally inactive, most of them are asymptomatic, and usually found incidentally or at autopsy. Sometimes they grow large and cause abdominal or flank discomfort, or pain related to necrosis or haemorrhage. The clinical diagnosis relies on radiologic evaluation, with a typical finding of well circumscribed tumor with various amounts of fat, calcification, and soft tissue. FNA with

hematopoietic tissue confirms the diagnosis, if diagnosis in CT is equivocal. Surgery is not indicated for asymptomatic myelolipomas.[113] Adrenal lipomas are rare asymptomatic incidental findings, and surgery is not indicated if the diagnosis can be confirmed.[114]

Adrenal cysts can be histopathologically classified as endothelial cysts (45%), pseudocystic lesions (39%), epithelial cysts (9%), and parasitic cysts (7%). Symptomatic cysts should be surgically removed.[115]

Primary adrenal lymphoma is rare, and the finding is bilateral in most cases. Prognosis seems to be poor. Adrenal lymphomas have usually a B-cell phenotype, and association with Epsteinn-Barr virus has been suggested.[116]

Occasionally sarcomas and other neoplasms (e.g. tumors of vascular origin) derived from various types of tissues in the adrenal gland are encountered.

Multiple Endocrine Neoplasia Syndromes

Pheochromocytoma constitutes one component of MEN 2A and 2B syndromes. MEN 2 syndomes are disorders with an autosomal dominant pattern of inheritance, and approximately 40% of carriers develop pheochromocytomas.[117] MEN 2 has two variants, MEN 2A (Sipple's syndrome), and MEN 2B. MEN 2A is the more common variant, and is a combination of medullary thyroid carcinoma (MTC), pheochromocytoma (in 50%) and hyperplasia of the parathyroid glands (in 10 to 35%).[118] It also comprises 3 subtypes: MTC-only, MEN 2A/cutaneous lichen amyloidosis,[119] and MEN 2A/Hirschprung's disease.[120] MEN 2B is characterized by a marfanoid habitus and mucosal neurinomas in combination with MTC and pheochromocytoma - without parathyroid hyperplasia. The presence of MEN 2 can now be verified by genetic screening.[121] The susceptibility gene for MTC is situated on chromosome 10q involving the RET proto-oncogene.[122] There is no association for pheochromocytoma and MEN 1 (Wermer's syndrome), a combination of parathyroid, pancreatic islet cell, pituitary, and occasionally carcinoid tumors. It is, however, a rare cause of Cushing's syndrome (pituitary tumor producing ACTH or ectopic production of

ACTH or CRH from carcinoid tumors), and is sometimes associated for cortical adenomas and hyperplasia, especially when the patient has a gastro-entero-pancreatic endocrine tumor.

Operative Approaches to the Adrenal Gland

Open Approaches

There are four principal open approaches to the adrenal gland: anterior transperitoneal (laparotomy), lateral flank (lumbotomy), posterior, and thoracoabdominal approach. The first adrenalectomy in 1889 by Knowsley-Thornton was performed through a T-shaped transperitoneal incision. On the first adrenalectomy for pheochromocytoma in 1926 Mayo used a flank incision. The posterior approach was first described by Young in 1936.[123]

Anterior transperitoneal adrenalectomy can be performed through a midline or transverse subcostal incision. This approach allows the exploration of the entire peritoneal cavity and gives access to both adrenal glands. On the right side, the dissection starts with the mobilizaton of the hepatic flexure of the colon, and Kochers maneuver. The liver is retracted upward to expose the adrenal gland. When this does not give adequate exposure, the right lobe can be mobilized and pulled over to the midline.[124] The adrenal gland is then identified, the adrenal vein ligated and the attachments containing the small arteries are dissected and ligated, and the gland is removed. On the left side, the exposure is achieved by dividing the gastrocolic ligament and entering the lesser sack. The splenic flexure is mobilised down if necessary, and the adrenal gland is exposed by opening the retroperitoneum below the inferior border of the pancreas and the spleen. When necessary, the spleen and the tail of the pancreas are mobilized and pulled over to the midline. The adrenal vein can then be ligated and the gland dissected free. Occasionally the kidney and the adrenal gland are situated caudally, and the gland can be reached through the mesentery of colon. Sometimes the gland is positioned so high that

it can be reached above the pancreas by dividing the gastrohepatic omentum and retracting the stomach inferiorly.

Lateral adrenalectomy can be performed through an intercostal, transcostal, or subcostal incision. The retroperitoneal space is entered and on the right side the colon and duodenum are reflected medially, and the liver is reflected upward. On the left side the colon is reflected medially and the pancreas upward. The adrenal gland is then identified, when necessary, by dissecting the perinephric fat and exposing the upper pole of the kidney first.[125]

The posterior approach is the most direct route to the adrenal gland, but the exposure is limited and it is best suited for benign tumors smaller than 5cm in size.[123,126] A hockey-stick incision, starting 5 to 6 cm from the midline at the 10th rib downwards and turning sharply over the 12th rib and following its course laterally, is usually used. The 12th rib, and 11th rib when necessary, are resected, and the retroperitoneal space is entered. The pleura is freed and reflected upward, and dissection in the perinephric fat exposes the upper pole of the kidney and above it the adrenal gland. The upper margin is first dissected to allow the gland to come down. The vein is ligated and the gland is dissected free and removed.[123,125]

Thoracoabdominal or lateral transthoracic approach are seldom used, but indicated for large neoplasms, particularly on the right side, where wide exposure for en bloc removal of contiguous structures or extensive lymph node dissection is desired. The incision is placed along the 10th rib, and pleural cavity is entered after resection of the rib. The diaphragm is incised and the retroperitoneal space is entered. The lung is retracted superiorly, and the liver anteriorly exposing the tumor.[123]

The choice between these methods is made according to the pathological lesion, size of the adrenal mass, location of the lesion, and patient morphology. The anterior approach is used if exploration of the entire peritoneal cavity to assess the extent of a malignant process is needed, or the disease is bilateral. The disadvantages are related to complications associated with major laparotomy: ileus, adhesions, hernias, pulmonary complications, and iatrogenic injuries to adjacent organs. The flank approach is better than the anterior or the posterior approach for obese patients, and if the tumor is too

large for the posterior approach. The posterior approach is easiest for the patient, with shorter operative time, smaller blood loss, and shorter hospital stay than in the anterior approach.[127] The flank approach is considered better than the anterior approach for the same reasons.[128]

Laparoscopic Adrenalectomy

Laparoscopic adrenalectomy was first described by Joseph Petelin (France) and Michael Gagner (U.S.A.) in 1992.[129,130] Since then, the technique has expanded and is now becoming the gold standard for adrenalectomy.[131,132] Prospective randomized studies to compare open and laparoscopic adrenalectomy have not been published, but several retrospective or nonrandomized studies show data suggesting that laparoscopic adrenalectomy is superior to open approaches when recovery, hospital stay and cost-effectiviness are compared.[129,133]

There are four principal techniques to perform videoscopic adrenalectomy: anterior transabdominal,[134] lateral transabdominal,[135] lateral extraperitoneal,[136] and posterior extraperitoneal technique.[137] The lateral transabdominal technique seems to be the technique of choice for most surgeons.[138] The anterior transabdominal approach is suitable for bilateral adrenalectomy, but the need for additional dissection and retraction of adjacent organs makes the operation more difficult and longer than the lateral transabdominal approach. In the extraperitoneal approaches, the anatomical landmarks for the location of the adrenal gland are not clearly visible and, furthermore, the working space is limited. There are, however, some potential advantages when using the retroperitoneal route.[139] The abdominal cavity is not entered and the need for dissection and retraction of adjacent organs is limited. In the posterior extraperitoneal approach both adrenals can be operated on without having to change the patient's position. Lateral transabdominal adrenalectomy and posterior extraperitoneal adrenalectomy have been compared, and the conclusion was that both approaches were effective and safe.The authors prefer the lateral approach for tumors larger than 6 cm and the posterior approach for bilateral tumors.[139] In a series of 69 posterior retroperitoneoscopic

adrenalectomies for benign tumors smaller than 8 cm in diameter the results are favourable with an operating time of 118 minutes for one-sided adrenalectomy and with few complications.[140] Today there is not enough data available to conclude which laparoscopic approach is optimal.

The technique of lateral transabdominal laparoscopic adrenalectomy is described in detail in the methods section, page 45.

The anterior transabdominal laparoscopic adrenalectomy is performed on the patient in the supine position, the surgeon usually standing between the legs, and 6 trocars are used. The operating table is turned to the right or to the left to remove the gland at each side. On the right side, the liver is retracted up and anteriorly, the peritoneum is incised lateral to the duodenum, and the adrenal gland and vein are dissected and clipped as in the lateral approach. On the left side, the splenic flexure of the colon is dissected free, and the spleen and the tail of the pancreas are mobilized.The adrenal gland is dissected free and the vein is clipped.[134] The procedure needs more dissection and retraction of adjacent organs than the lateral transperitoneal approach.[134]

The lateral extraperitoneal videoscopic adrenalectomy is performed on the patient in a semilateral position with the side of the tumor elevated. The retroperitoneal space is entered through an incision 5 cm below the costal margin at the dorsal axillary line, and first dissected with an finger. A balloon trocar is then inserted and inflated, and replaced after a few minutes with a blunt trocar, and the space is maintained with carbon dioxide inflation. Additional three trocars are inserted, one at the dorsal, and one at the ventral border of the created space, and one below the costal margin along the dorsal axillary line. Gerota's capsule is opened and the superior pole of the kidney is identified. The gland is dissected free as in transabdominal procedures.[141]

The posterior extraperitoneal operation is performed on the patient in a prone semi-jack-knife position. The retroperitoneal space is entered 2.5cm lateral to the 12th rib, and the balloon trocar is inserted aiming toward the costal-vertebral angle. After creation of pneumoretroperitoneum as described above, three additional trocars are inserted on a curved line, the medial one just below the 12th rib, one 1cm lateral to the 11th rib, and one between 9th and 10th ribs. The kidney is retracted downward from the medial trocar,

and dissection takes place from the two lateral trocars, the camera being positioned at the firts trocar. The dissection is started from the superior and anterior aspects of the gland at both sides, and the retraction of liver or spleen is not necessary. The gland is dissected free otherwise similarly to the other procedures.[137]

Laparoscopic adrenalectomy is indicated for all small and benign adrenal lesions,[142,143] including pheochromocytoma[76,144,145] and Cushing's syndrome.[134,146] It is considered contraindicated if the tumor is malignant, or when the tumor is large.[142]

Present Investigation

Aims of the Present Study

The purpose of the current clinical study was to examine adrenal insidentalomas, primary aldosteronism, and laparoscopic adrenalectomy for the treatment of benign adrenal disease.

The following points were particularly emphasized:

1. The nature of adrenal incidentalomas.

2. The natural course and criteria for operative treatment of the adrenal incidentalomas.

3. The effect of adrenalectomy for primary aldosteronism.

4. Lateral transperitoneal laparoscopic adrenalectomy for the treatment of benign adrenal tumors.

Patients and Methods

Patient demographics

Table 1. Patient demographics of publications I - V

Study	I	II	III	IV	V
Number of patients	36	27	29	12	38
Men:women	13:23	7:20	11:18	6:6	16:22
Mean age in years	56	59	48	51	52

Retrospective Study of 37 Operated Incidentalomas (I)

The retrospective study was based on 36 adult incidentaloma patients operated on at the Second Department of Surgery, Helsinki University Central Hospital during 1980-1989. All adrenal operations during that period (150 operations) were identified from the operating diaries and the case files were reviewed to identify incidentalomas. 36 patients were identified, one having a bilateral incidentaloma. Lesions were considered incidental if they were completely unexpected: prior to their radiologic discovery no symptoms, clinical signs, or laboratory findings suggested an adrenal pathology. The mean ages of the 23 women and 13 men were 59 years (range 31-85) and 51 years (18-71), respectively. In 21 patients the incidentalomas were primarily found in CT scans, 12 in US examinations, one during intravenous pyelography, and two in native roentgenography of the abdomen and back. In all except two cases the finding was verified by CT before the operation. The operations were conducted by 3 different surgeons, and anterior transperitoneal incision was used in 31 patients.

The patient demographics, results of preoperative radiologic and laboratory examinations, operative access, findings and intraoperative complications, postoperative complications, and the results of the pathologic examinations of the incidentalomas were

recorded. 30 patients had been tested for hormonal activity including the following examinations in most cases: serum potassium, serum cortisol at 0800 hours, 24-hour urine specimen for free cortisol, single-dose 1 mg overnight dexamethasone suppression test, and 24-hour urine specimen for metanephrines and VMA assays.
^{131}I-6β-iodomethylnorcholesterol or ^{75}Se-selenonorcholesterol scintigraphy had been performed during dexamethasone suppression in seven patients. MIBG scintigraphy had been done in three patients.

Follow-Up Study of 30 Nonoperatively Treated Incidentalomas (II)

At Helsinki University Central Hospital, from June 1981 through December 1992, 27 patients with nonoperatively treated incidentalomas were identified from the patient register of the Department of Endocrinology. 7 patients were male and 20 were female. The mean age of the patients at the time of the incidental discovery of the adrenal mass was 59 years (range 19-80 years). In 2 cases the incidentaloma was primarily found in an US examination, in 25 cases in a CT scan. If no malignant features in CT examination and no hormonal activity had been found, the patients had been controlled by CT or MRI. If the incidentaloma had not changed in size or appearance, the follow-up had been stopped. During 1997, the medical records and CT images were analyzed retrospectively, and the results of the hormonal investigations and the size and appearance of the incidentaloma were recorded. Nine patients had died before 1997. The death certificates were obtained from the national register and the cause of death was recorded. If a post-mortem examination had been carried out, the report was obtained and the findings were recorded. All the living patients were contacted and asked to participate in the follow-up program that had been approved by the ethical committee of Helsinki University Central Hospital. The program consisted of the history, physical examination, hormonal evaluation and MRI scan of the adrenal glands. The hormonal evaluation included 24 hour urine excretion of metanephrines and normetanephrines, 24-hour urine excretion of VMA and 1 mg overnight dexamethasone suppression test and serum potassium measurement.

The MRI examination was performed with a 1.5T superconducting imager (Siemens Magnetom Vision 1.5T, Siemens AG, Erlangen, Germany). A phased array local body coil was used in all the studies. The slices were acquired in the transaxial plane with 256 imaging matrix. Fast breath-hold sequences were utilized in order to reduce the imaging time and moving artifacts. The MR sequences protocol is shown in Table 2.

Table 2. MR sequence protocol

Sequence	weighing	Fs	TR	TE	FA	Acq	Time	SL	No	Gap
2d true fisp	T2	no	5	2,5	70	1	12	5	11	0,5
fast spin echo	T2	yes	3300	138	180	1	17	4	19	0,4
2d gradient echo	T1	no	138	4,1	80	1	22	4	18	0
2d gradient echo	T1	yes	85	4,1	80	1	16	5	9	0.2

Fs = fat saturation; TR = repetition time in msec; TE = echo time in msec; FA = flip angle; Acq = number of acquisitions; Time = duration of the sequence in sec; SL = slice thickness in mm; No = number of slices; Gap = gap between sections in mm.

Fat suppressed T1 weighted axial images were acquired before, and 25 sec and 55 sec after the injection of an iv. bolus of gadolium diethyltriaminepentaacetic acid (DTPA) (Magnevist^{R}, Schering AG, Berlin, Germany; dose 0.1 g/kg). The imaging was continued with slices in coronal plane. The duration of the whole imaging procedure was about 20 minutes.

The MR images were reviewed by a blinded observer experienced in abdominal MR imaging. The visualization of the adrenal glands was assessed. The size of existing adrenal tumor was measured and compared with the data of earlier CT studies . The T1 and T2 signal intensity of the tumor as well as the contrast enhancement of the lesion were compared with normal adrenal tissue.

Follow-Up Study of 29 Patients Operated for Primary Aldosteronism (III)

At Helsinki University Central Hospital, from January 1979 through December 1993, 29 patients with primary aldosteronism were operated on. Eighteen patients were women (62%) and 11 were men. The mean age was 48 years, range 29-71 years. Primary aldosteronism was suspected in hypertensive patients with hypokalemia, inappropriately high urinary excretion of potassium (>30 mmol/24h) and suppressed plasma renin activity together with normal or high serum aldosterone level. The distinction between unilateral neoplasia and bilateral hyperplasia was made using CT (n=29), ^{131}I-6-β-iodomethyl norcholesterol scan (n=13) with dexamethasone suppression, and postural test during volume load (n=18). Patient charts were reviewed retrospectively and the relevant data was collected. The follow-up data was obtained from the patient charts and by letter and, if necessary, by a telephone call to the patient and to the patient's primary physician. One patient had died and the cause of death was verified from the national register of death causes. If recent blood pressure and serum potassium measurements were not available, the patient was instructed to obtain them and the values were recorded. The patient was re-examined if any indication of persistent hyperaldosteronism was present (CT and postural test during volume load).

Prospective Series of 12 Consecutive Laparoscopic Adrenalectomies for Primary Aldosteronism (IV)

This prospective series from July 1995 until November 1997 consists of twelve consecutive laparoscopic adrenalectomies for primary hyperaldosteronism operated on at Helsinki University Central Hospital by one surgeon, and includes first eight laparoscopic adrenalectomies at our institution. There were six women and six men with a mean age of 51 years (range 38-64 years). Demographic data, operative time, blood loss, operative complications, pre- and postoperative hemoglobin value, need of narcotic analgesics, hospital stay, convalescence time, postoperative complications and outcome

were recorded. The laparoscopic operation is described in detail below.

Prospective Series of 40 First Laparoscopic Adrenalectomies at Helsinki University Central Hospital (V)

The data on forty consecutive laparoscopic adrenal procedures at Helsinki University Central Hospital from July 1995 until February 1999 was prospectively collected and the patients were followed up for adequacy of the resection. There were 22 women and 16 men with a mean age of 52 years (range 25-83 years). Demographic data, operative time, blood loss, operative complications, pre- and postoperative hemoglobin value, need for narcotic analgesics, hospital stay, convalescence time, postoperative complications and outcome were recorded. The laparoscopic operation is described in detail below.

The Operative Tehnique of the Lateral Transperitoneal Laparoscopic Adrenalectomy (IV and V)

Lateral transperitoneal approach was used in all cases and in bilateral operations the patient was repositioned during the operation. The operative technique is mostly the same as described earlier by Gagner *et al.*[135,142]

The patient was positioned in lateral decubitus position with the side of the pathological gland up. The upper arm was extended and suspended. The operating table was extended at the waist to open the space between the costal margin and the iliac crest. A 10 - 20^{o} reverse Trendelenburg position was used. The surgeon and assistant were standing facing the anterior surface of the abdomen. The monitor was placed behind the patient's shoulder on the opposite side. The instrument nurse stood on the opposite side to the surgeon. 12-15 mmHg carbon dioxide pneumoperitoneum and 3 or 4 10/12mm troacars below the costal margin were used. The 10mm 30^{o} laparoscope and, in case four trocars were used on the left side, grasping forceps were held by the assistant. A mechanical arm was used to hold the liver retractor during right adrenalectomy. Dissection was carried out using ultrasonic coagulating shears (Harmonic Scalpel®, UltraCision Inc. Smithfield,

RI, U.S.A.) except with the first 9 patients on which scissors and hook with cautery were used.

On the left side, the peritoneal attachments of the splenic flexure of colon were cut, if necessary, to expose the space between the spleen and the upper pole of the kidney. The peritoneum (splenorenal ligament) between spleen and kidney was opened beginning from the medial border of spleen towards the diaphragm laterally, leaving a 1-2cm peritoneal cuff towards the spleen. The spleen was not mobilized. At this point the adrenal gland was usually identified superior and medial to the kidney by the typical bright yellow colour of adrenal tissue. If the gland was not visible, retroperitoneal fat was dissected between the upper pole of the kidney and the spleen to expose it. At this stage, care was taken not to injure the tail of the pancreas. During the dissection the gland was manipulated by grasping preferably the perinephric fat. If the gland had to be grasped we used an atraumatic bowel grasper. The dissection was started from the inferior and superior borders of the gland. The adrenal vein could be divided early in the operation if necessary, but usually it was easier to divide it at a later stage of the operation when the gland had been mobilized. The adrenal vein is situated at the inferior medial corner of the gland and is usually the only structure that has to be divided between titanium clips applying two clips on the patient's side and one on the adrenal's side. Occasionally, an accessory vein at the inferior border of the gland could be found and was divided between clips. Once the gland was free, it was placed in a plastic bag and removed in one piece via one of the trocar sites by spreading the muscular layer with a finger or enlarging the incision, depending on the size of the tumor.

On the right side, the right lobe of the liver was lifted with a fan-shaped retractor and the triangular ligament was devided exposing the adrenal gland and the vena cava. Usually the inferior border of the adrenal was dissected first. The medial border was freed next along the lateral edge of the vena cava and the adrenal vein was identified and clipped. The superior portion was then dissected free. An accessory adrenal vein is sometimes found at the upper border of the gland and must be searched for and divided between clips if encountered. All other vessels could be coagulated by the ultrasonic shears.

In bilateral adrenalectomy, the same operative methods were used and the patient was

repositioned and redraped between the two operations.

Protocols of the Endocrinologic Tests

Single-dose 1 mg overnight dexamethasone suppression test: 1mg dexamethasone was administered orally at 2300 h, and serum cortisol was measured at 0800 h the next morning.[147]

Postural test during volume load: Serum aldosterone and PRA were measured at 0800 h recumbent and after four hours walk at 1200 h during volume load. Volume load was accomplished by administering 16g NaCl/day orally for three days, or by infusing 2000 ml of physiologic NaCl during four hours just before the test.[49]

Statistics

Study I and II were descriptive. In study III paired t-test was used in comparison of pre- and postoperative blood pressures and serum potassium levels. McNemars test was used in comparison of preoperative with postoperative symptoms. Conventional regression analysis was used to find out if the duration of hypertension was associated with the level of postoperative blood pressure. In study IV the differences in operative time were tested with Mann-Whitney two-sample rank sum test. In Study V statistical analysis was performed with an unpaired Student's t-test.

In all studies p-values less than 0.05 were considered significant.

Results

Retrospective Study of 37 Operated Incidentalomas (I)

The incidentaloma was unilateral in 35 cases and bilateral in one. Clinical data of 36 incidentaloma patients is presented in Table 3. The size of the lesions was mean 3.9 cm (range 1 to 16 cm). A total of 19 cortical adenomas were discovered. Six patients had multiple nodules (nodular hyperplasia), one of them bilaterally. Four pheochromocytomas without signs of malignancy were diagnosed. Two patients had ganglioneurinomas, two had organized hematoma, one intraadrenal lipoma, one myelolipoma, and one a calcified cyst. The cortical adenomas ranged in size from 1 to 16 cm (mean 3.5 cm). Only 2 of these 19 adenomas were 5 cm or larger, whereas 10 of the 17 other incidentalomas were 5 cm or more in size.

Table 3. Clinical data of 36 incidentaloma patients.

Diagnosis	n	Hormonal activity	Mean age (years)	Sex men:women	Mean size (cm)
Inactive adenoma	16		55	5:11	2,8
Hormonally active adenoma	3	2 cortisol 1 androgen	63	0:3	7,3
Nodular hyperplasia	6		51	2:4	3,0
Pheochromocytoma	4	catechol-amines	41	4:0	6,5
Ggl. neurinoma	2		37	0:2	7,0
Hematoma	2		61	1:1	5,5
Myelolipoma	1		60	1:0	5,0
Lipoma	1		45	0:1	14,0
Cyst	1		57	0:1	6,0
Total	**36**		**56**	**13:23**	**3,9**

Hormonal evaluation had been done in 30 patients, and 7 incidentalomas were hormonally active. Elevated values of cortisol production were found in two patients; each had a cortical adenoma, 2 cm and 4 cm in size. One patient had elevated androgen values related to a histologically benign adenoma, 16 cm in diameter. The VMA and metanephrines were elevated in three patients, and marginally elevated in one patient. Hormonal evaluation had not been done in one of the pheochromocytoma patients. A 4-cm mass found in the region of the left adrenal gland near the tail of the pancreas was falsely interpreted as a pancreatic tumor. No α-blockade was used, but the surgery was uneventful. The patient with marginally elevated values did not have a pheochromocytoma; he had macronodular cortical hyperplasia without other hormonal changes. In further five patients the hormonal evaluation had not been done, because the patients were operated on for another disease, and the incidentalomas were not thought to have any clinical significance.

Iodonorcholesterol scintigraphy had been carried out to detect possible cortical hyperfunction in 6 patients; all showed uptake (one bilaterally). Only one of these patients had hypercortisolism; she had a cortical adenoma. The patient with bilateral uptake had bilateral nodular hyperplasia, the other patients had unilateral nodular hyperplasia or cortical adenomas. Selenonorcholesterol scintigraphy was carried out and it was negative in one patient.

MIBG scintigraphy had been carried out on three hypertensive patients; all were negative, and none of these patients had a pheochromocytoma.

One patient having a pancreatic carcinoma and an adrenal mass died of bleeding after pancreaticoduodenectomy, but operative mortality related to adrenalectomy was 0%. One patient had splenectomy done, because of an intraoperative lesion of the spleen. Two patients had postoperative wound infection. One patient was slightly hypotensive during the first postoperative day for an unknown reason, but he recovered spontaneously and had no further complications.

Follow-Up Study of 30 Nonoperatively Treated Incidentalomas (II)

Twenty-seven patients had an incidentally discovered adrenal mass, 3 a bilateral incidentaloma. The mean size of the incidentalomas was 2.5 cm, (range 1.5-4 cm), eight were 3 cm or larger. Hormonal evaluation had been negative in all cases. The mean follow-up time was 85 months (range 23-196 months).

Nine patients had died before this follow-up program started. The mean age at death was 73 years. The cause of death was acute myocardial infarct in 3 cases, ventricular arrhythmia after aortic and mitral valve reconstruction, pulmonary oedema caused by cardiac failure, thrombosis of femoral vein and pulmonary embolism, acute cerebrovascular infarct, bolus suffocation related to multi-infarction dementia, and lung carcinoma with cerebral metastases. In death certificates and available medical records nothing suggested that these deaths would be related to the incidentalomas. An autopsy had been carried out on 4 patients. In 3 cases the incidentaloma had been documented: 2 cortical adenomas and one myelolipoma were found. No change in the size of the incidentalomas could be noticed.

Sixteen patients attended the follow-up program. None of the patients had any symptoms related to the incidentaloma. Two patients did not want to be re-examined, but stated that they were asymptomatic. The results of the hormonal tests were normal. MRI could not find any adrenal pathology in 4 patients, although the visualization of the adrenal glands was considered excellent. In one of these cases the incidentaloma had cystic appearance and had been emptied with aspiration. One adrenal gland was horizontally positioned and this had caused the misinterpretation of adrenal tumor in the original CT examinations. In 2 cases the incidentalomas had diminished in size already during the original one-year follow-up and had been considered adrenal hematomas. The sizes of 7 incidentalomas had not changed. 5 incidentalomas were larger and 3 incidentalomas were smaller than at the time of detection. The change was from 4 to 10 mm.

When compared with the MR signal of normal adrenal tissue, the T1 and T2 signals of the observed tumors were isointense in all except one case. This particular tumor appeared homogeneously hyper intense in T2 weighted images. The lesion showed no

contrast enhancement. Such a tumor correlates well with a simple cyst. All the other adrenal tumors demonstrated a minor rim enhancement of the lesion 25 sec after the contrast injection. The following slices, 55 sec after the injection, showed a slight and equalized enhancement of the tumor analogous to the surrounding normal adrenal tissue.

Follow-Up Study of 29 Patients Operated on for Primary Aldosteronism (III)

All 29 operated patients were hypertensive, and all but one had a low serum potassium level. The mean serum potassium was 2.9 mmol/L (range 2.2-3.6). The hypertension was generally not in good control. The mean duration of hypertension at the time of the operation was 105 months (range 1-360). The finding that primarily had led to the suspicion of primary aldosteronism was poorly controlled hypertension with low serum potassium in most cases.

The postural test during volume load could be reliably interpreted in 18 cases. There was a clear decline in plasma aldosterone level, suggesting adenoma, from 8 a.m./recumbent to 12 p.m./supine in 16 cases. 15 of these cases were adenomas, and one was an adenoma with micronodular hyperplasia. The result was inconclusive in one patient having an adenoma, and the plasma aldosterone level increased, suggesting hyperplasia, in one patient having an adenoma.

The CT scan was carried out and had correctly localized the adenoma in every case. Twenty-five patients had a unilateral solitary adenoma with otherwise normal adrenal histology. The mean size of the adenomas was 15 mm (range 8-32). Fourteen adenomas were on the left side, and eleven on the right. One patient had an aldosterone producing cortical carcinoma, 11 cm in diameter, with no lymph node involvement or distant metastases. One patient had macronodular hyperplasia. The largest nodule, 10 mm in size, was seen in CT; the contralateral gland was normal in CT and in laparotomy. Two patients had an encapsulated adenoma, 15 and 25 mm in diameter, but also micronodular hyperplasia. In one of these cases a hormonal analysis of cultured adrenal cells had been carried out, and only the adenoma cells were found to produce aldosterone. The cells of micronodular hyperplasia were inactive.

There was no mortality, or major operative or postoperative complications. The serum potassium level was normalized in all patients during the first postoperative week. The mean blood pressure levels at the time of discharge were significantly lower than preoperatively, 140/90 and 183/113 mmHg, respectively ($p>0.001$). Only three patients had a diastolic blood pressure over 100 mmHg, although the effect could be partly due to perioperative antihypertensive treatment.

One patient had died during the follow-up period, 21 months postoperatively, owing to cholangiocarcinoma with distant metastases. The patient operated on for the adrenocortical carcinoma had mild medicated hypertension and no signs of recidivist disease at the end of the follow-up study. However, pulmonary metastases occurred later and the patient died 74 months postoperatively. The mean follow-up time for the living patients with benign disease was 76 months (range 9-154), and the effect of the operation on hypertension was estimated by the patient and her or his doctor at the end of the follow-up. The hypertension was cured in 11 cases (41%). In 10 cases (37%) the hypertension after the operation was mild and responded well to medication. In the remaining 6 cases (22%) the blood pressure values did not respond to the operation, although the hypertension is better controlled by the medication. The duration of preoperative hypertension did predict the outcome of surgery.

In two patients with solitary adenomas the serum potassium level dropped below normal during the follow-up, but no signs of persistent hyperaldosteronism could be found.

Prospective Series of 12 Consecutive Laparoscopic Adrenalectomies for Primary Aldosteronism (IV)

All patients had a cortical adenoma, with a mean size of 14 mm (range 8 - 27 mm). The adenoma was on the right adrenal gland in five and on the left gland in seven patients. The mean weight of the patients was 83 kg (range 52 - 117 kg) and the body mass index (BMI) was in average 29 kg/m^2 (range 19 - 39 kg/m^2). One patient having a right-sided adenoma had previously been operated on for cholecystitis from an upper midline incision. No other upper abdominal surgery had been performed. The mean operating

time was 126 minutes (range 60 - 265 minutes). The mean operating time for the first 6 patients was 159 minutes and for the last 6 patients 93 minutes. This difference was statistically significant (p=0.015, median difference 43 min., CI_{95} of median difference = 5 -145 min.). The operations of male and obese patients lasted somewhat longer than those of female or normal weight patients, but these differences were not significant. The mean intraoperative blood loss was 100 mL (range 0-800 mL). No intraoperative complications were encountered, and no conversions were necessary.

The duration of narcotic analgesia was in average 1.7 days (range 1-4 days). The mean decrease in hemoglobin value was 12.2 g/L (range -3 - 41 g/L). The average length of hospital stay was 3.4 days (range 2 - 5 days) and the length of sick leave was on average 13.2 days (range 8 - 18 days). All patients became normokalemic after the operation. Two patients had postoperative complications, both having pain at the trocar wound region. They were treated with non-steroid anti-inflammatory drugs and the pain resolved within 2 weeks postoperatively. On follow-up (mean 12.5 months, range 2-28 months) 4 patients were normotensive without medication, 8 patients were on antihypertensive drugs, but in all cases the medication had been reduced from the preoperative level.

Prospective Study of 40 First Laparoscopic Adrenalectomies at Helsinki University Central Hospital (V)

The indications for the operation were suspected aldosterone producing adenoma (20), pheochromocytoma (9), Cushing's adenoma (3), Cushing's disease (1), adrenocortical hyperplasia with hypercortisolism caused by ectopic ACTH production (1) and incidentally discovered hormonally inactive adrenal tumor (4). Two of the Conn's adenomas had been detected as incidentalomas. One of the suspected Cushing's adenomas turned out to be a low-grade cortical carcinoma. One suspected pheochromocytoma turned out to be a hematoma. The four hormonally inactive incidentalomas were: 1 hematoma, 1 cyst, 1 inactive cortical hyperplasia, and 1 inactive

cortical adenoma.

The mean size of the tumors was 2.6 cm (range 0.8-8 cm). Sixteen lesions were on the right side, 24 on the left side; in two patients both adrenals were removed. The mean weight of the patients was 81 kg (range 27-121 kg) and the BMI was on average 28 kg/m^2 (range 17-31 kg/m^2).

The mean operating time was 121 minutes (range 53-360 min.). The operating time was significantly longer in male patients than in female patients, 156 min. and 105 min., respectively ($p<0.001$). The mean BMI of male patients was 29.5 and of female patients 26.5. The difference is not statistically significant. The mean operating time for patients with BMI >30 (n=12) was 126 minutes and for patients with BMI <30 120 minutes. The mean operating time for tumors 4cm in size or more was 132 min (n=10) and for tumors less than 4cm in size 118 min. The mean operating time for left-sided tumors was 125 min and for right-sided tumors 116 min The size of the tumor, BMI, or side of the tumor did not have significant effect on the operative time. The mean operating time for the last 20 operations (112 min) was shorter than for the first 20 operations (131 min), but the difference was not significant. The estimated intraoperative bleeding was on average 80 mL (range 0-800 mL).

Four of the eight pheochromocytoma patients had transient elevations in blood pressure during the procedure, but they were easily controlled with medication. There was no marked hypotension during the operation or postoperatively.

Usually the adrenal gland could be dissected free without damage to the adrenal tissue. Sometimes small tears of the border of the normal adrenal tissue were noticed. The tumor itself was never grasped and every gland could be resected and positioned in to the plastic bag without damage to the tumor tissue.

Conversion to laparotomy was done in one case (2.4%). This obese woman (BMI 35 kg/m^2) had hypercortisolism and bilateral adrenocortical hyperplasia caused by ectopic ACTH syndrome. She had undergone right hemicolectomy for a colon carcinoma. After the left adrenal had been successfully removed laparoscopically, an attempt to perform laparoscopic procedure on the right side was done in spite of an extremely enlarged liver and postoperative adhesions. It turned out to be technically impossible and the

operation was converted to laparotomy through a subcostal incision.

The median postoperative hospital stay was 3 days (mean 3.6 days, range 2-12 days). All patients were able to start oral intake during the first postoperative day. The patients needed narcotic analgesics on average 1.8 days (range 0-8 days) postoperatively. The median postoperative sick leave was 17 days (mean 21.2 days, range 8-55 days).

There was no mortality nor reoperations. Seven patients had postoperative complications (18 %). One patient had transient postoperative dyspnea. A small pulmonary embolus was found in a CT scan and was treated with anticoagulation. This patient was the one converted to laparotomy and therefore had the longest operative time in the series. The patient was also extremely obese. One patient developed a pneumothorax treated with pleural suction for 4 days. Two postoperative bleedings at the operative site required red blood cell transfusions. Two patients had prolonged pain at a trocar wound. One patient had a urinary tract infection, and was treated with antibiotics.

The duration of follow-up was on average 5 months (range 1-28 months). All patients were considered to have responded as expected to the adrenalectomy, and no evidence of a recurrent tumor or any symptoms of hormonal activity were observed.

After the first eight laparoscopic operations had been successfully done, we decided to operate all small benign adrenal tumors laparoscopically. After this point, 9 patients were treated by conventional open adrenalectomy at our hospital. Data on conventional open operations performed was collected, but it was not possible to compare these two different groups of patients.

Discussion

Most of the adrenal tumors are not operated on, because hormone overproduction or signs of malignancy are not presented. However, every adrenal mass must be thoroughly evaluated. Incidentalomas are unexpectedly discovered adrenal tumors found in radiologic examinations carried out for symptoms not related to adrenal pathophysiology. Hypersecretion of adrenocortical hormones with distinct clinical syndromes and the clinical behavior of pheochromocytoma are classical entities in endocrinology.

During this decade, many new diagnostic methods have been taken in clinical use, and the introduction of minimally invasive surgery has allowed laparoscopic methods to rapidly replace open operations. Approximately 30% of adrenal operations in Finland are performed in Helsinki University Central Hospital. This clinical study gives additional information on the management of adrenal incidentalomas, results of surgery for primary aldosteronism, and the novel method laparoscopic adrenalectomy.

Patients and Methods

The patients of the present study consisted of five different groups. In the retrospective study of operated incidentalomas (I), 36 patients were identified from the operating diaries. All operated incidentalomas from a ten-year period from 1980 to 1989 are included. Although the number of patients is limited, the series is one of the largest series of operated incidentalomas published. Most published series consist of incidentalomas left to watchful management, and therefore the pathological diagnosis of the incidentalomas is not known. In the follow-up study of 27 patients with incidentaloma (II), the list of patients was achieved from the patient records of the Department of Endocrinology, and consisted of all patients recorded as having an incidentaloma at the department. The total number of incidentalomas recognized in

radiologic examinations during the same period is not known, but it should be considerably higher.[95] However, if the sample is biased, we expect that the most interesting cases have been referred to the Department of Endocrinology. The number of the patients is rather small, but it was not possible to enlarge the patient group in this follow-up program including several laboratory examinations and MRI due to the considerable cost of the program.

The follow-up study of operated primary aldosteronism patients (III) consisted of all patients operated on this diagnosis identified from the operating diaries. The patients left to conservative therapy were not included. The accuracy of the diagnostic workout and results of the surgical therapy can only be evaluated from this basis; we do not know if potentially curable adenoma patients were left to the conservative treatment.

The number of patients operated on adrenal pathology at our institution has varied from 8 to 21 patients per year. The limited number of patients and the heterogeneity of the underlying pathology makes it very difficult to run prospective series and even impossible to randomize patients to different groups of treatment. Therefore, the number of patients in the prospective series of laparoscopic adrenalectomy for primary aldosteronism (IV) was small, and it was not possible to make a comparison to open adrenalectomy. The number of patients in the prospective series of all laparoscopic adrenalectomies at our institution (V) is also limited, but only few series with a considerably larger number of patients have been reported.[140,142] Furthermore, through late 1997 a total of less than 600 cases of laparoscopic adrenalectomy were reported in the world literature.[132] We chose the lateral transperitoneal laparoscopic access, because it is a well-documented and widely used method.[138,143]

Incidentalomas of the Adrenal Gland (I and II)

The prevalence of asymptomatic adrenal masses is considerable, and they are incidentally detected in CT and other imaging studies at an increasing rate. Although the mortality and morbidity of modern adrenal surgery is low, surgery is not indicated if the tumor is benign and hormonally inactive.[99]

Our series of 37 operated incidentalomas and also other reports show that the frequency of hormonal activity of incidentalomas is not rare. In the present series (I) 7 tumors (19%) were hormonally active: 4 pheochromocytomas, 2 cortisol-producing adenomas, and one androgen-producing adenoma. Basic hormonal testing of all incidentalomas is therefore indicated. The recommendations for this evaluation vary, but should include tests for pheochromocytoma, hypercortisolism and in hypertensive patients also for hyperaldosteronism.

Primary or metastatic malignancy must be excluded next. Primary adrenocortical carcinoma is a rare tumor, and usually large at detection. Therefore large incidentalomas (over 3 to 6 centimeters in diameter) are recommended to be operated. If features of malignancy are encountered in CT or MRI examination, operative treatment is indicated. However, no single examination can reliably separate benign from malignant lesions. Iodocholesterol scintigraphy and in selected cases fine needle aspiration biopsy may give further information. In our series no malignancies were encountered, preoperative imaging studies were negative for malignancy, and all operations for hormonally inactive lesions independent of their size were unnecessary.

The natural course of incidentalomas has not been clear. Few follow-up studies have been done so far.[110] The present series (II) shows that during the 7-year follow-up none of the 30 incidentalomas became hormonally active or turned out to be malignant. The change in the size of the incidentalomas was small. These results further confirm that small hormonally inactive incidentalomas can be observed safely.

Adrenalectomy for Primary Aldosteronism (III)

The prevalence of primary hyperaldosteronism among hypertensive patients is less than 1%, but being a potentially curable cause of hypertension it must be suspected in any patient with hypertension and hypokalemia.

The diagnosis is in most cases suspected when the combination of hypertension and hypokalemia is found. Other clinical symptoms, such as headache, weakness, and fatigue only occasionally are the primary clue to the diagnosis. In the present series, these

symptoms were cited as the leading indication for hormonal analysis in only two cases. After screening tests and confirmation of the diagnosis, the main issues are to differentiate APA from IHA, and to localize adenomas. This series shows that CT scan is reliable if suggestive of adenoma. However, we do not know if some adenomas were missed and classified as being IHA. The most accurate test to differentiate APA from IHA is selective venous sampling for aldosterone measurement. We have not used this method because the technique is invasive and difficult. When appropriate, the suspicion of APA can be confirmed with postural test. In this series it was accurate in 89%, and in collected literature its accuracy was 75%.[148] Iodocholesterol scintigraphy or MRI can also be used for the localization of adenomas, but they are not better than CT.

The treatment of APA is adrenalectomy. IHA is best treated by aldosterone antagonists. The long-term cure rate of hypertension in APA patients treated by adrenalectomy in the collected literature was 69%.[53] In this series with a mean follow-up time of more than 6 years, 41% of patients were normotensive without medication, 37% had a mild hypertension well controlled by mild medication, and in 22% the blood pressure levels had not decreased from the preoperative values, but the hypertension was better controlled by medication. In this series the duration of hypertension predicted the outcome to some extent.

Laparoscopic Adrenalectomy (IV and V)

Laparoscopic adrenalectomy has been widely used for small benign adrenal tumors during the last 5 years, and it is becoming the gold standard for adrenalectomy.[101] It has not been possible to compared conventional and laparoscopic adrenalecomy in prospective randomized series due to the rarity of adrenal operations even in large centers. However, several studies have compared laparoscopic adrenalectomy with historical series of conventional operations, and the enhanced recovery, shorter hospital stay, and cost-effectiviness of the laparoscopic adrenalectomy have been well documented.[131,149-152] In the present series of 40 laparoscopic adrenalectomies, the operative time of 121 minutes is similar to the operative time raported for open

adrenalectomies.[153] The intraoperative blood loss, postoperative need for narcotic analgesics, postoperative hospital stay and the length of sick leave in our series, are shorter than reported for conventional open operations.[152,154] In our study there was no mortality, and the complication rate of 18% is in concordance with earlier experiences in laparoscopic adrenalectomy,[131,151] and when compared with conventional adrenalectomies, the complication rate is similar,[151] or lower.[131] The comparison of complications between laparoscopic and open adrenalectomy for primary hyperaldosteronism in this study is not possible. There seems to be no complications in the open adrenalectomy group, but this is most probably explained by the retrospective method of the study. The follow-up results of laparoscopic adrenalectomy for primary aldosteronism regarding normokalemia and postoperative need for antihypertensive drugs were similar to the results of the conventional operation (III).

Due to the rarity of adrenal tumors, primary diagnostic evaluation and adrenal surgery should be concentrated in a small country like Finland. In university hospitals there are enough facilities and knowledge to use modern mini-invasive techniques with well-documented enhanced recovery, shorter hospital stay, and cost-effectiveness. Laparoscopic adrenalectomy is the operative method for choice when operating on small benign adrenal tumors.[155] In centers not familiar with laparoscopic adrenalectomy conventional posterior and lumbar approaches may be used.[48]

Conclusions

On the basis of the present study, the following conclusions can be drawn:

1. Most of the incidentally detected adrenal tumors are hormonally inactive adenomas or other nonfunctioning benign tumors. However, hormonally active incidentalomas are not rare, and all incidentaloma patients should be examined with basic hormonal tests.

2. The growth tendency of nonfunctional incidentalomas is limited, and operative treatment of small incidentalomas is not indicated if the incidentaloma is hormonally inactive, shows no signs of malignancy in imaging studies, and does not grow in follow-up.

3. The results of operative treatment for primary aldosteronism are favourable, and the diagnostic procedures used could rule out IHA.

4. Lateral transperitoneal laparoscopic adrenalectomy seems to be a safe and effective minimally invasive approach, and it should therefore be considered the standard surgical procedure for benign adrenal tumors.

Summary

Incidental discovery of adrenal mass in radiologic examinations is common. Vast majority of these so-called incidentalomas are hormonally inactive benign adenomas, or other benign tumors not requiring surgery. Some incidentalomas have hormonal activity that has to be ruled out by basic hormonal testing in every incidentaloma patient. Primary adrenal malignancy is extremely rare, but has to be ruled out. The large size of the tumor, malignant appearance in radiologic examinations, and growth during follow-up are related to malignancy and indicate operative treatment. Small hormonally inactive incidentalomas that have a benign appearance in radiologic examinations and do not grow during follow-up can be observed safely. The natural course of these incidentalomas seems silent, and operative therapy becomes seldom indicated.

Primary aldosteronism is a rare cause of hypertension. When caused by aldosterone-producing neoplasia the operative treatment is indicated. Medical treatment with aldosterone antagonists seems better in most cases of hyperplasia. The diagnosis should be suspected when hypokalemia is found in a patient with hypertension. The choice of therapy is based on distinguishing unilateral from bilateral adrenal disease. Selective adrenal venous catheterization with sampling for aldosterone measurement is the most accurate test differentiating unilateral and bilateral disease. However, the technique is invasive and difficult, and not used at our institution. Hormonal tests and CT are usually accurate, and in our series all operated patients had a correctly diagnosed unilateral disease. Operative therapy reverses the hypokalemia and frequently cures the hypertension in cases of adenoma.

During the last five years, the laparoscopic adrenalectomy has become a new gold standard in adrenal surgery for small benign tumors. The first laparoscopic adrenalectomy in Finland was carried in 1995 at our institution, and today we have performed more than 40 adrenalectomies laparoscopically. This method seems to have the general advantages of minimally invasive surgery, the complication rate is low and conversion is seldom necessary. During this study, laparoscopic adrenalectomy has

become the standard operation for small benign adrenal tumors in Helsinki University Central Hospital.

References

1. Eustachius, B. Opuscula Anatomica de Renum structura, Efficio et Administratione. Venice: V.V. Lucchino; 1564. Cited by: Hiatt,J.R., Hiatt,N. The Conquest of Addison's Disease. Am. J. Surg. *174*:280, 1997

2. Welbourn, R. B. Anonymous The history of endocrine surgery. New York: Praeger; 1990:147-210.

3. Cuvier, G. L. C. Lecons d'anatomie comparee, Paris: Baudonin, 1800-1805. Cited by: Mihai,R., Farndon,J.R: Surgical Embryology and Anatomy of the Adrenal Glands. In: Clark, O. H.; Duh, Q. eds. Textbook of Endocrine Surgery. Philadelphia: W.B. Saunders; 1997:447-459.

4. Addison, T. On the constitutional and local effects of disease of the suprarenal capsules, London: Samuel Highley, 1855. Cited by: Mihai.R., Farndon,J.R: Surgical Embryology and Anatomy of the adrenal Glands. In: Clark, O. H.; Duh, Q. eds. Textbook of Endocrine Surgery. Philadelphia: W.B. Saunders; 1997:447-459.

5. Mihai, R.; Farndon, J. R. Surgical Embryology and Anatomy of the Adrenal Glands. In: Clark, O. H.; Duh, Q. eds. Textbook of Endocrine Surgery. Philadelphia: W.B. Saunders; 1997:447-459.

6. Cushing, H. Clinical states produced by disorders of the hypophysis cerebri. In: Anonymous The pituitary body and its disorders. Philadelphia: JB Lippincott; 1912:

7. Conn, J.W. Presidential address: Part I. Painting background, Part II, Primary aldosteronism, a new clinical syndrome. J. Lab. Clin. Med. *45*:3, 1955

8. Orchard, T., Grant, C.S., van Heerden, J.A., Weaver, A. Pheochromocytoma - continuing evolution of surgical therapy. Surgery *114*:1153, 1993

9. Whalen, R.K., Althausen, A.F., Daniels, G.H. Extra-adrenal pheochromocytoma. J. Urol. *147*:1, 1992

10. Coupland, R. E. Observations on the size distribution of chromaffine granules and on the identity of adrenaline- and noradrenaline-storing chromaffine cells in vertebrates and man. In: Heller, H.; Lederis, K. eds. Subcellular organization and function in endocrine tissues - Proceedings of a symposium held at the University of Bristol. Society for Endocrinology memoirs, vol 19. Bristol, England: Society for Endocrinology; 1971:611-635.

11. Ober, W.B. Emil Zuckerkandl and his delightful little organ. Path. Ann. *18*:103, 1983

12. Stenstrom, G., Svardsudd, K. Pheochromocytoma in Sweden 1958-1981, An Analysis of the National Cancer Registry Data. Acta Med. Scand. *220*:225, 1986

13. Williams, P. L.; Warwick, R. W.; Dyson, M.; Bannister, L. H. eds. Gray's anatomy. New York: Churchill Livingstone; 1989:1468-1472.

14. Waldayer, A.; Mayet, A. eds. Anatomie des Menschen. Berlin: de Gruyter; 1976:257-264.

15. Monkhouse, W.S., Khalique, A. The adrenal and renal veins of man and their connections with azygos veins. J. Anat. *146*:105, 1986

16. Bloom, W.; Fawcett, D. W. Adrenal Glands and Paraganglia. In: Anonymous A Textbook of Histology. 1975:540-555.

17. Ganong, W. F. The Adrenal Medulla & Adrenal Cortex. In: Anonymous Review of Medical Physiology. 1987:270-300.

18. Gröndal, S.; Hamberger, B. Adrenal Physiology. In: Clark, O. H.; Duh, Q. eds. Textbook of Endocrine Surgery. Philadelphia: W.B. Saunders; 1997:461-465.

19. Orth, D. N.; Kovacs, W. J. The Adrenal Cortex. In: Wilson, J. D.; Foster, D. W.; Kronenberg, H. M.; Larsen, P. R. eds. Williams Textbook of Endocrinology. Philadelphia: W.B. Saunders; 1998:517-664.

20. Young, J. B.; Landsberg, L. Catecholamines and the Adrenal Medulla. In: Wilson, J. D.; Foster, D. W.; Kronenberg, H. M.; Larsen, P. R. eds. Williams Textbook of Endocrinology. Philadelphia: W.B. Saunders; 1998:665-728.

21. Oelkers, W. Adrenal insufficiency [see comments]. [Review] [43 refs]. N. Engl. J. Med. *335*:1206, 1996

22. Carey, R.M. The changing clinical spectrum of adrenal insufficiency [editorial] [see comments]. Ann. Int. Med. *127*:1103, 1997

23. Brosnan, C.M., Gowing, N.F. Addison's disease [see comments]. BMJ *312*:1085, 1996

24. Doherty, G.M., Nieman, L.K., Cutler, G.B., Jr., Chrousos, G.P., Norton, JA. Time to recovery of the hypothalamic-pituitary-adrenal axis after curative resection of adrenal tumors in patients with Cushing's syndrome. Surgery *108*:1085, 1990

25. Daitch, J.A., Goldfarb, D.A., Novick, A.C. Cleveland Clinic experience with adrenal Cushing's syndrome. J. Urol. *158*:2051, 1997

26. Välimäki, M., Pelkonen, R., Porkka, L., Sivula, A., Kahri, A. Long-term results of adrenal surgery in patients with Cushing's syndrome due to adrenocortical adenoma. Clin. Endocrinol. *20*:229, 1984

27. Favia, G.; Lumachi, F. Cushing's Syndrome. In: Clark, O. H.; Duh, Q. eds. Textbook of Endocrine Surgery. Philadelphia1: W.B. Saunders; 1997:497-505.

28. van Heerden, J.A., Young, W.F., Jr., Grant, C.S., Carpenter, P.C. Adrenal surgery for hypercortisolism--surgical aspects. Surgery *117*:466, 1995

29. Corcuff, J.B., Tabarin, A., Rashedi, M., Duclos, M., Roger, P., Ducassou, D. Overnight urinary free cortisol determination: a screening test for the diagnosis of Cushing's syndrome. Clin. Endocrinol. *48*:503, 1998

30. Newell-Price, J., Trainer, P., Besser, M., Grossman, A. The diagnosis and differential diagnosis of Cushing's syndrome and pseudo-Cushing's states. [Review] [286 refs]. Endocr. Rev. *19*:647, 1998

31. Brouwers Smalbraak, G.J., Vasen, H.F., Struyvenberg, A., Nieuwenhuijzen Kruseman, A.C., Helsloot, M.H., Lips, C.J. Multiple endocrine neoplasia type 2A (MEN-2A): natural history, screening, and central registration. Neth. J. Med. *29*:111, 1986

32. Fernandez-Real, J.M., Ricart-Engel, W., Simo, R. Pre-clinical Cushing's syndrome: report of three cases and literature review. [Review] [26 refs]. Horm. Res. *41*:230, 1994

33. Chidiac, R.M., Aron, D.C. Incidentalomas. A disease of modern technology. [Review] [155 refs]. Endocrinol. Metabol. Clin. North Am. *26*:233, 1997

34. Berwaerts, J.J., Verhelst, J.A., Verhaert, G.C., Verhaegen, A.A., Abs, R.E. Corticotropin-dependent Cushing's syndrome in older people: presentation of five cases and therapeutical use of ketoconazole. [Review] [30 refs]. J. Am. Geriatr. Soc. *46*:880, 1998

35. Chapuis, Y., Pitre, J., Conti, F., Abboud, B., Pras Jude, N., Luton, J.P. Role and operative risk of bilateral adrenalectomy in hypercortisolism. World J. Surg. *20*:775, 1996

36. O'Riordain, D.S., Farley, D.R., Young, W.F., Jr., Grant, C.S., van, Heerden, J.A. Long-term outcome of bilateral adrenalectomy in patients with Cushing's syndrome. Surgery *116*:1088, 1994

37. Plotz, C.M., Knowlton, A.I., Ragan, C. The natural history of Cushing's syndrome. Am. J. Med. *13*:597, 1952

38. Imai, T., Funahashi, H., Tanaka, Y., Tobinaga, J., Wada, M., Morita-Matsuyama, T., Ohiso, Y., Takagi, H. Adrenalectomy for Treatment of Cushing Syndrome: Results in 122 Patients and Long-Term Follow-up Studies. World J. Surg. *20*:781, 1996

39. Berglund, G., Andersson, O., Wilhelmsen, L. Prevalence of primary and secondary hypertension: Studies in a random population sample. BMJ *2*:554, 1976

40. Scoggins, B.A., Coghlan, J.P. Primary hyperaldosteronism. Pharmacol. Ther. *9*:367, 1980

41. Irony, I., Kater, C.E., Biglieri, D.G., Shackleton, C.H.L. Correctable subsets of primary aldosteronism. Primary adrenal hyperplasia and renin responsive adenoma. Am. J. Hypertens. *3*:576, 1990

42. Abdelhamid, S., Muller-Lobeck, H., Pahl, S., Remberger, K., Bonhof, J.A., Walb, D., Rockel, A. Prevalence of adrenal and extra-adrenal Conn syndrome in hypertensive patients. Arch. Int. Med. *156*:1190, 1996

43. Obara, T., Ito, Y., Okamoto, T., Kanaji, Y., Yamashita, T., Aiba, M, Fujimoto, Y. Risk factors associated with postoperative persistent hypertension in patients with primary aldosteronism. Surgery *112*:987, 1992

44. Granberg, P.O., Adamsson, U., Hamberger, B., Lins, P.E. Surgical treatment of primary aldosteronism. Ann. Chir. Gynaecol. *72*:171, 1983

45. Giebink, E.S., Gotlin, R.W., Biglieri, E.G., Katz, F.H. A kindred with familial glucocorticoid suppressible aldosteronism. J. Clin. Endocrinol. Metab. *36*:715, 1973

46. Gordon, R.D., Stowasser, M., Tunny, T.J., Klemm, S.A., Rutherford, J.C. High incidence of primary aldosteronism in 199 patients referred with hypertension. Clin. Exp. Pharmacol. Physiol. *21*:315, 1994

47. Brown, M.A., Cramp, H.A., Zammit, V.C., Whitworth, J.A. Primary hyperaldosteronism: a missed diagnosis in 'essential hypertensives'? Austr. N. Z. J.Med. *26*:533, 1996

48. Obara, T.; Ito, Y.; Fujimoto, Y. Hyperaldosteronism. In: Clark, O. H.; Duh, Q. eds. Textbook of Endocrine Surgery. Philadelphia: W.B.Saunders Company; 1997:487-488.

49. Vaughan, N.J.A., Jowett, T.P., Slater, J.D.H., Wiggins, R.C., Lightman, S.L., Ma, J.T.C., Payne, N.N. The diagnosis of primary hyperaldosteronism. Lancet *1(8212)*:120, 1981

50. Doppman, J.L., Gill, J.R.J. Hyperaldosteronism: Sampling the Adrenal Veins. Radiology *198*:309, 1996

51. Ikeda, D.M., Francis, I.R., Glazer, G.M., Amendola, M.A., Gross, M.D., Aisen, A.M. The detection of adrenal tumors and hyperplasia in patients with primary aldosteronism: comparison of scintigraphy, CT, and MR imaging. Am. J. Roentgenol. *153*:301, 1989

52. Doppman, J.L., Gill, J.R.J., Miller, D.L., Chang, R., Gupta, R., Friedman, T.C., Choyke, P.L., Feuerstein, I.M., Dwyer, A.J., Jicha, D.L., Walther, M.M., Norton, J.A., Linehan, W.M. Distinction between Hyperaldosteronism Due to Bilateral Hyperplasia and Unilateral Aldosteronoma: Reliability of CT. Radiology *184*:677, 1992

53. Young, W.F., Hogan, M.J., Klee, G.G., Grant, C.S., van Heerden, J.A. Primary aldosteronism: diagnosis and treatment. Mayo Clin. Proc. *65*:96, 1990

54. Folkow, B. Physiological aspects of primary hypertension. Physiol. Rev. *62*:347, 1982

55. Hughes, I.A. Congenital adrenal hyperplasia--a continuum of disorders. Lancet *352*:752, 1998

56. Silva, I.N., Kater, C.E., Cunha, C.F., Viana, M.B. Randomised controlled trial of growth effect of hydrocortisone in congenital adrenal hyperplasia. Arch. Dis. Childh. *77*:214, 1997

57. Sciarra, F., Tosti-Croce, C., Toscano, V. Androgen-secreting adrenal tumors. [Review] [40 refs]. Minerva Endocrinol. *20*:63, 1995

58. Lanigan, D., Choa, R.G., Evans, J. A feminizing adrenocortical carcinoma presenting with gynaecomastia. Postgrad. Med. J. *69*:481, 1993

59. Beard, C.M., Sheps, S.G., Kurland, L.T., Carney, J.A., Lie, J.T. Occurrence of pheochromocytoma in Rochester, Minnesota, 1950 through 1979. Mayo Clin. Proc. *58*:802, 1983

60. Sutton, M.G., Sheps, S.G., Lie, J.T. Prevalence of clinically unsuspected pheochromocytoma. Review of a 50-year autopsy series. Mayo. Clin. Proc. *56*:354, 1981

61. Beatty, O.L., Russell, C.F., Kennedy, L., Hadden, D.R., Kennedy, T.L., Atkinson, A.B. Phaeochromocytoma in Northern Ireland: a 21 year review. [Review] [41 refs]. Eur. J. Surg. *162*:695, 1996

62. Geoghegan, J.G., Emberton, M., Bloom, S.R., Lynn, J.A. Changing trends in the management of phaeochromocytoma. Br. J. Surg. *85*:117, 1998

63. Grant, C. S. Pheochromocytoma. In: Clark, O. H.; Duh, Q. eds. Textbook of Endocrine Surgery. Philadelphia: W.B. Saunders; 1997:513-522.

64. Heaney, A.P., O'Rourke, D., Arthur, K., Beatty, O.L., Russell, C.F., Sloan, J.M., Hamilton, P., Atkinson, A.B. Flow cytometric analysis does not reliably differentiate benign from malignant phaeochromocytoma [see comments]. Clin. Endocrinol. *44*:233, 1996

65. Pommier, R.F., Vetto, J.T., Billingsly, K., Woltering, E.A., Brennan, M.F. Comparison of adrenal and extraadrenal pheochromocytomas. Surgery *114*:1160, 1993

66. Lairmore, T.C., Ball, D.W., Baylin, S.B., Wells, S.A.J. Management of pheochromocytomas in patients with multiple endocrine neoplasia type 2 syndromes. Ann. Surg. *217*:595, 1993

67. van Heerden, J.A., Sizemore, G.W., Carney, J.A., Grant, C.S., ReMine, W.H., Sheps, S.G. Surgical management of the adrenal glands in the multiple endocrine neoplasia type II syndrome. World J. Surg. *8*:612, 1984

68. Neumann, H.P., Berger, D.P., Sigmund, G., Blum, U., Schmidt, D., Parmer, R.J., Volk, B., Kirste, G. Pheochromocytomas, multiple endocrine neoplasia type 2, and von Hippel-Lindau disease [see comments] [published erratum appears in N Engl J Med 1994 Dec 1;331(22):1535]. N. Engl. J. Med. *329*:1531, 1993

69. Latif, F., Tory, K., Gnarra, J., Yao, M., Duh, F.M., Orcutt, M.L., Stackhouse, T., Kuzmin, I., Modi, W., Geil, L., et al. Identification of the von Hippel-Lindau disease tumor suppressor gene [see comments]. Science *260*:1317, 1993

70. Martin, R.L., Goldblatt, J., Walpole, I.R. Efficacy of gene testing for von Hippel-Lindau disease. Med. J. Austr. *169*:422, 1998

71. Sheps, S.G., Jiang, N.S., Klee, G.G. Diagnostic evaluation of pheochromocytoma. [Review] [43 refs]. Endocrinol. Metabol. Clin. North Am.*17*:397, 1988

72. Peppercorn, P.D., Reznek, R.H. State-of-the-art CT and MRI of the adrenal gland. Eur. Radiol. *7*:822, 1997

73. Quint, L.E., Glazer, G.M., Francis, I.R., Shapiro, B., Chenevert, T.L. Pheochromocytoma and paraganglioma: comparison of MR imaging with CT and I-131 MIBG scintigraphy. Radiology. *165*:89, 1987

74. Casanova, S., Rosenberg Bourgin, M., Farkas, D., Calmettes, C., Feingold, N., Heshmati, H.M., Cohen, R., Conte Devolx, B., Guillausseau, P.J., Houdent, C., et al: Phaeochromocytoma in multiple endocrine neoplasia type 2 A: survey of 100 cases. Clin. Endocrinol. Oxf. *38*:531, 1993

75. Sand, J., Salmi, J., Saaristo, J., Auvinen, O. Preoperative treatment and survival of patients with pheochromocytomas. Ann. Chir. Gynaecol. *86*:230, 1997

76. Gagner, M., Breton, G., Pharand, D., Pomp, A. Is laparoscopic adrenalectomy indicated for pheochromocytomas? Surgery *120*:1076, 1996

77. Mornex, R., Badet, C., Peyrin, L. Malignant pheochromocytoma: a series of 14 cases observed between 1966 and 1990. J. Endocrinol. Invest. *15*:643, 1992

78. Schlumberger, M., Gicquel, C., Lumbroso, J., Tenenbaum, F., Comoy, E., Bosq, J., Fonseca, E., Ghillani, P.P., Aubert, B., Travagli, J.P., et al: Malignant pheochromocytoma: clinical, biological, histologic and therapeutic data in a series of 20 patients with distant metastases. J. Endocrinol. Invest. *15*:631, 1992

79. Finnish Cancer Registry. 1996. (Unpublished)

80. Icard, P., Chapuis, Y., Andreassian, B., Bernard, A., Proye, C. Adrenocortical carcinoma in surgically treated patients: a retrospective study on 156 cases by the French Association of Endocrine Surgery. Surgery *112*:972, 1992

81. Proye, C. A.; Pattou, F. N. Adrenocortical Carcinoma: Nonfunctioning and Functioning. In: Clark, O. H.; Duh, Q. eds. Textbook of Endocrine Surgery. Philadelphia: W.B. Saunders; 1997:490-496.

82. Khafagi, F.A., Gross, G.M., Shapiro, B., Glazer, G.M., Francis, I., Thompson, N.W. Clinical significance of the large adrenal mass. Br. J. Surg. *78*:828, 1991

83. Dunnick, N.R., Heaston, D., Halvorsen, R., Moore, A.V., Korobkin, M. CT appearance of adrenal cortical carcinoma. J. Comput. Assist. Tomogr. *6*:978, 1982

84. Katz, R.L., Patel, S., Mackay, B., Zornoza, J. Fine Needle Aspiration Cytology of the Adrenal Gland. Acta Cytol. *28*:269, 1984

85. Hosaka, Y., Rainwater, L.M., Grant, C.S., Young, W.F., Jr., Farrow, G.M., van Heerden, J.A., Lieber, M.M. Adrenocortical carcinoma: Nuclear deoxyribonucleic acid ploidy studied by flow cytometry. Surgery *102*:1027, 1987

86. Gicquel, C., Leblond-Francillard, M., Bertagna, X., Louvel, A., Chapuis, Y., Luton, J.P., Girard, F., Le Bouc, Y. Clonal analysis of human adrenocortical carcinomas and secreting adenomas. Clin. Endocrinol. *40*:465, 1994

87. Gicquel, C., Raffin-Sanson, M.L., Gaston, V., Bertagna, X., Plouin, P.F., Schlumberger, M., Louvel, A., Luton, J.P., Le Bouc, Y. Structural and functional abnormalities at 11p15 are associated with the malignant phenotype in sporadic adrenocortical tumors: study on a series of 82 tumors. J. Clin. Endocrinol. Metabol. *82*:2559, 1997

88. MacFarlane, D.A. Cancer of the adrenal cortex: The natural history, prognosis, and treatment in fifty-five cases. Ann. R. Coll. Surg. Engl. *23*:155, 1958

89. Haak, H.R., Hermans, J., van de Velde, C.J., Lentjes, E.G., Goslings, B.M., Fleuren, GJ, Krans, H.M. Optimal treatment of adrenocortical carcinoma with mitotane: results in a consecutive series of 96 patients [see comments]. Br. J. Canc. *69*:947, 1994

90. Decker, R.A., Elson, P., Hogan, T.F., Citrin, D.L., Westring, D.W., Banerjee, T.K., Gilchrist, K.W., Horton, J. Eastern Cooperative Oncology Group study 1879: mitotane and adriamycin in patients with advanced adrenocortical carcinoma. Surgery *110*:1006, 1991

91. Berruti, A., Terzolo, M., Pia, A., Angeli, A., Dogliotti, L. Mitotane associated with etoposide, doxorubicin, and cisplatin in the treatment of advanced adrenocortical carcinoma. Italian Group for the Study of Adrenal Cancer. Cancer *83*:2194, 1998

92. Fallo, F., Pilon, C., Barzon, L., Pistorello, M., Pagotto, U., Altavilla, G., Boscaro, M., Sonino, N. Paclitaxel is an effective antiproliferative agent on the human NCI-H295 adrenocortical carcinoma cell line. Chemotherapy *44*:129, 1998

93. Prinz, R.A., Brooks, M.H., Churchill, R., Graner, J.L., Lawrence, A.M., Paloyan, E., Sparagana, M. Incidental asymptomatic adrenal masses detected by computed tomographic scanning. Is operation required? JAMA. *248*:701, 1982

94. Glazer, H.S., Weyman, P.J., Sagel, S.S., Levitt, R.G., McClennan, B.L. Nonfunctioning adrenal masses: incidental discovery on computed tomography. Am. J. Roentgenol. *139*:81, 1982

95. Abecassis, M., McLoughlin, M.J., Langer, B., Kudlow, J.E. Serendipitous adrenal masses: prevalence, significance, and management. Am. J. Surg. *149*:783, 1985

96. Belldegrun, A., Hussain, S., Seltzer, S.E., Loughlin, K.R., Gittes, R.F., Richie, J.P. Incidentally discovered mass of the adrenal gland. Surg. Gynecol. Obstet. *163*:203, 1986

97. Russi, S., Blumenthal, H.T. Small Adenomas of the Adrenal Cortex in Hypertension and Diabetes. Arch. Int. Med. *76*:284, 1945

98. Russell, R.P., Masi, A.T., Richter, E.D. Adrenal Cortical Adenomas and Hypertension. Medicine *51*:211, 1972

99. Kloos, R.T., Gross, M.D., Francis, I.R., Korobkin, M., Shapiro, B. Incidentally discovered adrenal masses. [Review] [253 refs]. Endocr. Rev. *16*:460, 1995

100. Bitter, D.A., Ross, D.S. Incidentally discovered adrenal masses. Am. J. Surg. *158*:159, 1989

101. Caplan, R.H., Kisken, W.A., Huiras, C.M. Incidentally discovered adrenal masses. Minn. Med. *74*:23, 1991

102. Aso, Y., Homma, Y. A survey on incidental adrenal tumors in Japan. J. Urol. *147*:1478, 1992

103. Gohring, U., Ziegler, R., Buhr, H. [When should incidentalomas of the adrenal gland be surgically treated?]. Chirurg. *61*:304, 1990

104. Reincke, M., Nieke, J., Krestin, G.P., Saeger, W., Allolio, B., Winkelmann, W. Preclinical Cushing's syndrome in adrenal "incidentalomas": comparison with adrenal Cushing's syndrome. J. Clin. Endocrinol. Metab. *75*:826, 1992

105. Ross, N.S., Aron, D.C. Hormonal evaluation of the patient with an incidentally discovered adrenal mass. N. Engl. J. Med. *323*:1401, 1990

106. Copeland, P.M. The incidentally discovered adrenal mass. Ann. Surg. *199*:116, 1984

107. Thompson, N.W., Cheung, P.S. Diagnosis and treatment of functioning and nonfunctioning adrenocortical neoplasms including incidentalomas. Surg. Clin. North Am. *67*:423, 1987

108. Ahren, B., Werner, S. [Adrenal incidentalomas are a diagnostic dilemma. New guidelines for investigation and treatment. Medical Research Council]. [Swedish]. Lakartidningen *93*:3041, 1996

109. Saxe, A. Invited commentary. World J. Surg. *20*:792, 1996

110. Barry, M.K., van Heerden, J.A., Farley, D.R., Grant, C.S., Thompson, G.B., Ilstrup, D.M. Can Adrenal Incidentalomas Be Safely Observed? World J. Surg. *22*:599, 1998

111. Woods, W.G. Unravelling mysteries of neuroblastoma [comment]. Lancet *352*:667, 1998

112. Alspaugh, C.D., Zanolli, M. Blue nodules in a newborn. Neuroblastoma. Arch. Dermatol. *133*:775, 1977

113. Han, M., Burnett, A.L., Fishman, E.K., Marshall, F.F. The natural history and treatment of adrenal myelolipoma. J. Urol. *157*:1213, 1997

114. Guerreiro, S., Hofmockel, G., Dammrich, J., Frohmuller, H. [Lipoma of the adrenal gland. Case report and review of the literature]. [Review] [79 refs] [German]. Urologe - Ausgabe A *37*:526, 1998

115. Reiher, F., Steinbach, F., Buhtz, P., Kasper, H.U., Samland, D., Allhoff, E.P. Epithelial cyst of the adrenal gland: an unusual cause of recurrent flank pain. J. Urol. *157*:2238, 1997

116. Ohsawa, M., Tomita, Y., Hashimoto, M., Yasunaga, Y., Kanno, H., Aozasa, K. Malignant lymphoma of the adrenal gland: its possible correlation with the Epstein-Barr virus. Mod. Pathol *9*:534, 1996

117. Howe, J.R., Norton, J.A., Wells, S.A.J. Prevalence of pheochromocytoma and hyperparathyroidism in multiple endocrine neoplasia type 2A: results of long-term follow-up. Surgery *114*:1070, 1993

118. Gagel, R. F. Multiple Endocrine Neoplasia. In: Wilson, J. D.; Foster, D. W.; Kronenberg, H. M.; Larsen, P. R. eds. Williams Textbook of Endocrinology. Philadelphia: W.B. Saunders; 1998:1627-1650.

119. Gagel, R.F., Levy, M.L., Donovan, D.T., Alford, B.R., Wheeler, T., Tschen, J.A. Multiple endocrine neoplasia type 2a associated with cutaneous lichen amyloidosis [see comments]. Ann. Int. Med. *111*:802, 1989

120. Verdy, M.B., Cadotte, M., Schurch, W., Sturtridge, W.C., Cantin, J., Weber, A.M., Lacroix, A., Forster-Gibson, C. A French Canadian family with multiple endocrine neoplasia type 2 syndromes. Henry Ford Hosp. Med. J. *32*:251, 1984

121. Goretzki, P.E., Hoppner, W., Dotzenrath, C., Clark, O.H., Simon, D., Cupisti, K., Schulte, H., Roher, H.D. Genetic and biochemical screening for endocrine disease. World J. Surg. *22*:1202, 1998

122. Eng, C., Clayton, D., Schuffenecker, I., Lenoir, G., Cote, G., Gagel, R.F., van, Amstel, H.K., Lips, C.J., Nishisho, I., Takai, S.I., Marsh, D.J., Robinson, B.G., Frank-Raue, K., Raue, F., Xue, F., Noll, W.W., Romei, C., Pacini, F., Fink, M., Niederle, B., Zedenius, J., Nordenskjold, M., Komminoth, P., Hendy, G.N., Mulligan, LM, et al. The relationship between specific RET proto-oncogene mutations and disease phenotype in multiple endocrine neoplasia type 2. International RET mutation consortium analysis. JAMA *276*:1575, 1996

123. Prinz, R. A.; Falimirski, M. E. Operative Approaches to the Adrenal Gland. In: Clark, O. H.; Duh, Q. eds. Textbook of Endocrine Surgery. Philadelphia: W.B. Saunders Company; 1997:529-534.

124. Prinz, R.A. Mobilization of the Right Lobe of the Liver for Right Adrenalectomy. Am. J. Surg. *159*:336, 1990

125. Novick, A.C. Surgery for primary hyperaldosteronism. Urol. Clin. North Am. *16*:535, 1989

126. Sand, J., Saaristo, J., Nordback, I., Auvinen, O. Posterior Approach for Adrenal Surgery: Experiences with 59 Patients. Ann. Chir. Gynaecol. *86*:234, 1997

127. Russell, C.F., Hamberger, B., van Heerden, J.A., Edis, A.J., Ilstrup, D.M. Adrenalectomy: anterior or posterior approach? Am. J. Surg. *144*:322, 1982

128. Irvin, G.L., Fishman, L.M., Sher, J.A., Yeung, L.K., Irani, H. Pheochromocytoma. Lateral versus anterior operative approach. Ann. Surg. *209*:774, 1989

129. Schell, S.R., Talamini, M.A., Udelsman, R. Laparoscopic adrenalectomy for nonmalignant disease: improved safety, morbidity, and cost-effectiveness. Surg. Endosc. *13*:30, 1999

130. Gagner, M., Lacroix, A., Bolte, E. Laparoscopic adrenalectomy in Cushing's syndrome and pheochromocytoma [letter]. N. Engl. J. Med. *327*:1033, 1992

131. Jacobs, J.K., Goldstein, R.E., Geer, R.J. Laparoscopic adrenalectomy. A new standard of care. Ann. Surg. *225*:495, 1997

132. Smith, C.D., Weber, C.J., Amerson, J.R. Laparoscopic adrenalectomy: New Gold Standard. World J. Surg. *23*:389, 1999

133. Horgan, S., Sinanan, M., Helton, W.S., Pellegrini, C.A. Use of laparoscopic techniques improves outcome from adrenalectomy. Am. J. Surg. *173*:371, 1997

134. Fernandez Cruz, L., Saenz, A., Benarroch, G., Sabater, L., Taura, P. Total bilateral laparoscopic adrenalectomy in patients with Cushing's syndrome and multiple endocrine neoplasia (IIa). Surg. Endosc. *11*:103, 1997

135. Gagner, M., Lacroix, A., Prinz, R.A., Bolte, E., Albala, D., Potvin, C., Hamet, P., Kuchel, O., Querin, S., Pomp, A. Early experience with laparoscopic approach for adrenalectomy. Surgery *114*:1120, 1993

136. Kelly, M., Jorgensen, J., Magarey, C., Delbridge, L. Extraperitoneal 'laparoscopic' adrenalectomy. Aust. N. Z. J. Surg. *64*:498, 1994

137. Mercan, S., Seven, R., Ozarmagan, S., Tezelman, S. Endoscopic retroperitoneal adrenalectomy. Surgery *118*:1071, 1995

138. van Heerden, J.A. Endocrine surgery. [Review] [32 refs]. J. Am. Coll. Surg. *186*:141, 1998

139. Duh, Q.Y., Siperstein, A.E., Clark, O.H., Schecter, W.P., Horn, J.K., Harrison, M.R., Hunt, T.K., Way, L.W. Laparoscopic Adrenalectomy. Comparison of the Lateral and Posterior Approaches. Arch. Surg. *131*:870, 1996

140. Walz, M.K., Peitgen, K., Saller, B., Giebler, R.M., Lederbogen, S., Nimtz, K., Mann, K., Eigler, F.W. Subtotal Adrenalectomy by the Posterior Retroperitoneoscopic Approach. World J. Surg. *22*:621, 1998

141. Parrilla, P., Lijan, A.J., Rodriguez, J.M., Robles, R., Illana, J. Initial experience with endoscopic retroperitoneal adrenalectomy [short note]. Br. J. Surg. *83*:987, 1996

142. Gagner, M., Pomp, A., Heniford, B.T., Pharand, D., Lacroix, A. Laparoscopic Adrenalectomy. Lessons Learned From 100 Consecutive Procedures. Ann. Surg. *226*:238, 1997

143. Fernandez Cruz, L. Laparoscopic adrenal surgery. Br. J Surg. *83*:721, 1996

144. Janetschek, G., Finkenstedt, G., Gasser, R., Waibel, U.G., Peschel, R., Bartsch, G., Neumann, H.P. Laparoscopic surgery for pheochromocytoma: adrenalectomy, partial resection, excision of paragangliomas. J. Urol. *160*:330, 1998

145. Mobius, E., Nies, C., Rothmund, M. Surgical treatment of pheochromocytomas: laparoscopic or conventional? Surg. Endosc. *13*:35, 1999

146. Ferrer, F.A., MacGillivray, D.C., Malchoff, C.D., Albala, D.M., Shichman, S.J. Bilateral laparoscopic adrenalectomy for adrenocorticotropic dependent Cushing's syndrome. Journal of Urology *157*:16, 1997

147. Nugent, C.A., Nichols, T., Tyler, F.H. Diagnosis of Cushing's syndrome - single dose dexamethasone. Arch. Int. Med. *116*:172, 1965

148. Granberg, P.O., Adamson, U., Cohn, K.H., Hamberger, B., Lins, P.E. The management of patients with primary aldosteronism. World J Surg. *6*:757, 1982

149. Terachi, T., Matsuda, T., Terai, A., Ogawa, O., Kakehi, Y., Kawakita, M., Shichiri, Y, Mikami, O., Takeuchi, H., Okada, Y., Yoshida, O. Transperitoneal laparoscopic adrenalectomy: experience in 100 patients. J. Endourol. *11*:361, 1997

150. Staren, E.D., Prinz, R.A. Adrenalectomy in the era of laparoscopy. Surgery *120*:706, 1996

151. Linos, D.A., Stylopoulos, N., Raptis, S.A. Adrenaloma: a call for more aggressive management. World J. Surg. *20*:788, 1996

152. Brunt, L.M., Doherty, G.M., Norton, J.A., Soper, N.J., Quasebarth, M.A., Moley, J.F. Laparoscopic adrenalectomy compared to open adrenalectomy for benign adrenal neoplasms. J. Am. Coll. Surg. *183*:1, 1996

153. Proye, C.A., Huart, J.Y., Cuvillier, X.D., Assez, N.M., Gambardella, B., Carnaille, B.M. Safety of the posterior approach in adrenal surgery: experience in 105 cases. Surgery *114*:1126, 1993

154. Linos, D.A., Stylopoulos, N., Boukis, M., Souvatzoglou, A., Raptis, S., Papadimitriou, J. Anterior, posterior, or laparoscopic approach for the management of adrenal diseases? Am. J. Surg. *173*:120, 1997

155. Gagner, M. Laparoscopic Adrenalectomy. In: Clark, O. H.; Duh, Q. eds. Textbook of Endocrine Surgery. Philadelphia: W.B.Saunders Company; 1997:535-545.