Lecture n. 12

Adrenal Surgery

This chapter will cover diseases of the adrenal glands, which increasingly implicate surgery for the afflicted patient.

Primary hyperaldosteronism - Conn's Syndrome

In 1954 Jerome W. Conn first described the syndrome that now bears his name (*"Primary hyperaldosteronism, a new clinical syndrome"*).

The condition's pathophysiology is to be traced in by far the largest share of cases (85%) to an aldosterone-producing adrenocortical adenoma, most often solitary and unilateral rather than multiple of bilateral. The syndrome may be accompanied also by cortical hyperplasia without nodules or at times with diffuse micronodules, or by carcinoma. Onset varies according to published series, ranging from 20 to 60 years of age. The female-to-male ratio is 2/1.
This primary form of aldosteronism must be distinguished from the secondary form, which is due to an extra-adrenal stimulus, generally of a renal origin: *secondary hyperaldosteronism from hyperreninemia*.

From an anatomo-pathologic standpoint the lesion most frequently responsible for the syndrome is a cortical nodule usually smaller than 2.0 cm in diameter, round or oval in shape, bright yellow in color, well-defined compared to the adjacent cortical parenchyma but without a capsule. Histologically, it is typically made up of zona glomerulosa cells, at times zona fasciculata cells (but rarely both), arranged in nets or in cords. The nuclei are relatively small and vesicular, varying remarkably in shape and volume.

Symptoms include an array of manifestations, which to an untrained observer may seem to be unrelated. The patient is generally affected by mild to moderate - at times severe - systolic-diastolic arterial hypertension. In many cases this symptom, if modest, is underestimated or at most treated with antihypertensives. A range of additional disorders that are often overlooked - at least initially - provide the grounds for a correct diagnosis. Asthenia, adynamia and fatigue, an expression of the muscular weakness secondary to hypokalemia, are the earliest and most constant signs. The tandem hypertension/adynamia is pathognomonically telling. Thereafter, also in relation to the worsening of the endocrine disorder, headaches, muscle cramps,

paresthesia, paralysis and or intermittent tetanic episodes, polydipsia, and polyuria may develop in association or appear. In these latter conditions positivity to Chvostek's sign and to Trousseau's maneuver may be seen on physical examination.

The diagnosis may not be established, above all at outset. Generally speaking, hypertension is the finding that is first taken into account: the literature provides varying time lapses between the appearance of hypertension and the hyperaldosteronic state with its related symptoms. Adynamia, which manifests with a relatively rapid onset of intense exhaustion and severe muscular weakness, is usually the only noticeable symptom because it clearly worries the patient and leads him/her to the physician. If hypertension, even slight, is identified, a helpful diagnostic clue may be found in the association of these two elements.
At this point blood tests will reveal the underlying hypokalemia that accompanies hypernatremia, and it is at this stage that the diagnostic workup becomes more extensive: serum and urinary aldosterone levels are visibly raised (above all in the case of a adenoma), in contrast to suppressed renin activity (PRA). This latter finding is pivotal to distinguishing primary (low PRA value) from secondary (elevated PRA) hyperaldosteronism.

The diagnostic workup thus determines primary hyperaldosteronism. Ultrasound (US), and better still computed tomography (CT), confirm or dismiss the presence of an adrenal adenoma, which - as was pointed out earlier - is the most common cause. The adenoma is usually single; a micronodule is detectable only with CT scan. Other, more complex examinations (angiography, NP-59 iodocholesterol scintigraphy, adrenal venous sampling) are not routinely available and even outdated.

It is not uncommon, however, to diagnose Conn's syndrome without the above workup. In a number of our cases the adrenal adenoma was detected on US examination and thereafter the syndrome fully diagnosed with specific tests.

Because these are lessons on surgery, only those conditions that are resolvable by surgical intervention are taken into account. Other forms of the syndrome are remediable by medical therapy, but for information on these the reader is invited to refer to other sources.

Excision of the adenoma is the treatment of choice and generally guarantees a positive outcome.

Cushing's Syndrome

In 1932, Harvey W. Cushing, a neurosurgeon from Boston, first reported the syndrome that now bears his name, describing the condition as a pituitary pathology ("*pituitary basophilism*") deriving from a pituitary adenoma.

The syndrome may now be defined as an array of symptoms and signs resulting from excessive levels of glucocorticoids (hypercortisolism).

The pathophysiology of the condition may vary. Two fundamental forms are recognized: adrenocorticotropic hormone (ACTH)-dependent and ACTH-independent.
The former typically derive from an excess secretion of ACTH by the pituitary, most frequently depending on a basophil adenoma (Cushing's disease) and bilateral adrenal hyperplasia. Such a situation may also arise as a result of nonpituitary sources of ACTH, usually neoplasms in other sites, normally an apudoma.
The latter have an adrenal origin due to the presence of secreting tumors, usually adenomas or carcinomas, less frequently cortical hyperplasia (with or without nodules), with suppression of the hypothalamic-pituitary-adrenal (HPA) axis and functional autonomy of the adrenal cortex. Iatrogenic or otherwise exogenous forms belong to this category (prolonged and excessive administration of cortisone). This disease depends on adrenal lesions and affects above all females (adenoma: M/F ratio = 1:3; carcinoma: M/F = 1:2).

The ATCH-independent syndrome of adrenal origin is the focus of this discussion.

From an anatomo-pathologic standpoint the adenoma responsible for Cushing's syndrome is generally small, averaging no more than 3-4 cm. in diameter, weighing approximately 60 grams, well-defined or with a capsule, with a sectioned surface yellow or brown in color, but which may also be blackish due to pigmentation, and with the presence of cystic formations in larger lesions. A tumor that exceeds 100 grams must be viewed as potentially malignant.
Histologically, the adenoma is composed of clear zona fasciculata cells, grouped in cords or nets, and that may appear black in color due to lipofuscine impregnation. Under these conditions signs of atrophy in the surrounding parenchyma, as well as that in the contralateral gland, may be present. As was stated above, adrenal neoplasm responsible for Cushing syndrome and weighing more than 100 grams are in all likelihood carcinomas (the scarcity of histomorphologic features of these malignant lesions makes volume the differentiating pathognomomic factor). These lesions, moreover, may well reach 1000 grams or more; although they are often encapsulated, they nonetheless tend to invade adjacent structures and to metastasize via hematogenous routes (liver, lungs, etc.).

The clinical picture of the syndrome is characteristic. Almost all patients complain of asthenia (90%), muscular weakness, neuropsychological alterations, gonad dysfunctions; they may present regional obesity in the face (*moon facies*), the neck (*buffalo hump*), the torso or abdomen; by contrast, muscular atrophy of the limbs is strikingly evident. Skin features are also telling: facial plethora, acne, hirsutism in women, purple-reddish stretch marks (*purple striae*) on the abdomen, breasts and buttocks, easy bruising. Arterial hypertension, osteoporosis, hyperglycemia, increase

without variations in circadian rhythm of cortisol secretion and related urinary metabolites may also be present.

The diagnosis of ACTH-independent hypercortisolism of adrenal origin is based on a series of laboratory findings: increase in urinary free cortisol levels, abolition of the circadian rhythm of cortisol secretion, low levels of plasma corticotrophin (which is normal or high in ACTH-dependent forms), negative to the dexamethasone suppression test with CRH (Corticotropin-Releasing Hormone) stimulation, which is on the contrary present test in pituitary forms.
Imaging studies complete the picture of the features and location of the adrenal lesion.

Therapy is surgical and entails removal of the tumor. It may be a monolateral adrenalectomy, in the case of carcinoma excision may not be radical (debulking). Bilateral adrenalectomy may be indicated for an adrenal hyperplasia in some particular cases of ACTH-dependent Cushing's syndrome.

Surgical resection of the adrenal gland due to this disease always demands, even in cases of monolateral adrenalectomy (atrophy of the contralateral gland), painstaking monitoring and therapy delivered by a qualified endocrinologist.

Pheochromocytoma - medullary hyperfunction syndrome

Pheochromocytoma was first observed during an autopsy and subsequently described by F. Fränkel in 1886 (Virchows Arch 1886: 103, 244). This tumor derives from chromaffin cells that secrete excessive levels of catecholamine; 90% of lesions arise in the adrenal medulla, more rarely in extra-adrenal paraganglion tissues (organ of Zuckerkandl, pelvic, retroperitoneal and mediastinal paraganglion structures).
Pheochromocytoma is a relatively rare tumor (approximately 1-2/100,000) that occurs with equal frequency in males and females (with a slight preponderance in the latter). Adults are the most affected, but it does arise in pediatric age patients as well. In roughly 5% of cases, autosomally inherited, the tumor may present with other neuroendocrine disorders, above all MEN 2A and 2B.

From an anatomo-pathologic standpoint, the tumor is generally described as being encapsulated, no more than 3-5 cm in diameter; rarely is the lesion any larger and its weight is usually less than 100 grams. On cut section the tumor is yellow-pinkish in color, which darkens if exposed to light due to the formation of yellow-brown epinephrine and norepinephrine pigments; hemorrhagic and cystic areas are often

visible, especially in larger lesions. The surrounding medullary parenchyma may appear altered due to compression.
In 80% of cases the tumor affects only one gland, usually the right. In around 10% of cases it is bilateral; this feature increases in pediatric (25%) and in familial ((50%) forms. In 10% of cases the symptom of medullary hyperfunction is due to an extra-adrenal tumor.
Histologically a pheochromocytoma is composed of cells arranged in cords, alveoli or lobes; the cytoplasm is normally granular, slightly basophilic and may be vacuolized; plasmatic PAS-positive elements are frequent. Nuclei are round, oval or vesicular, and may be polymorphous, but this feature must not be viewed as being indicative of malignancy. The importance of the mitotic index in this context is the subject of debate. As with other endocrine tumors, the malignant form (pheochromoblastoma) is based fundamentally on the size of the lesion, extracapsular extent of growth, invasion of adjacent structures and obviously on the presence of distant metastases (by hematogenous routes).

Symptoms

Although arterial hypertension is believed to be the classic symptom of a pheochromocytoma, a closer examination of some etiopathogenetic features compels a rethinking of this conviction. A pheochromocytoma is a neuroendocrine tumor secreting above all epinephrine and norepinephrine, but also able - like most other similar tumors - to produce other vasoactive substances and peptides (e.g., dopamine, endotheline, somatostatin, vasoactive intestinal peptide [VIP], P substance, motiline). It follows that symptoms may vary according to the hormone produced, which, even if the hypertensive picture prevails, may itself be modified by the quality and level of catecholamine secretion. Indeed, the ratio of norepinephrine to epinephrine is rises above normal, which is usually 3/1 in favor of the latter. Because the two hormones' mechanisms differ, epinephrine acting on α- and β-receptors and norepinephrine only on α-adrenergic receptors, the hypertensive effect also differs. Consequently, paroxysmal hypertension will arise (nearly 70%) if epinephrine secretion is prevalent, while stable (permanent) hypertension will set in if norepinephrine is greater. In some patient series the latter form is prevalent.
A paroxysmal hypertensive crisis can suddenly and rapidly lead to extremely high systolic pressure levels, reaching higher than 300 mm Hg; crises may last from a few minutes to a few hours and arise for no apparent cause or subsequently to various stimuli (e.g., a coughing fit, consumption of some foods, defecation, frights, stress, strong emotions, medical tests, even slight traumas, etc.). The event itself is often accompanied by symptoms, including chills, horripilation (goose bumps), pallor, tremors, sweating, pulsing headache, tachyarrhythmia or tachycardia, precordial pain, anxiety (sense of doom), nausea and, at times, vomiting
The permanent hypertensive form does not differ from essential hypertension, with which it is often confused at onset, and in these cases traditional antihypertensive therapy becomes ineffective.

As already mentioned, the symptoms of a pheochromocytoma may be proteiform (hormonal). Asymptomatic forms are reported, however, that very ably disguise the severity of the condition, which may become evident as a hardly representative diseases or erupt in the most severe manifestations, above all cardiologic, during (for instance) surgical intervention. Even the so-called *tako-tsuba-like* syndrome has been described by some authors as a latent form of pheochromocytoma. A severe state of shock or of stress may in the presence of pheochromocytoma lead to sudden death. Still other forms resembling diabetic conditions due to glucose intolerance, pseudo-hyperthyroidistic forms, cardiopathic and neuropsychic manifestations, acute inflammatory states stimulating sepsis, etc., have also been reported.
Of course, a myriad of disease states may manifest in the event hormones different from catecholamine are secreted.
Because of all of the considerations cited above, pheochromocytoma must be viewed as a severe disease, a precursor over time of irreversible cardiac, renal, retinal and cerebral damage.

The diagnosis may be easily enough suspected when the symptoms are typical (paroxysmal hypertension). Greater skill is need in other, more unusual, circumstances. Levels in urine (increased) of vanillymandelic acid and/or their metabolites or free catecholamine leads in most cases (over 90%) to an accurate diagnosis. Plasma levels of catecholamine may also prove to be important.
When in doubt, other tests may be warranted, including suppression tests (using clonadine, phentolamine, prazosine); stimulation tests (glucagons, histamine) are less widely used given their inherent risk.
Morphologic diagnosis and localization are reached through:

- Ultrasonography
- CT scan
- Multilayer CT with contrast medium
- MRI
- Scintigraphic scan with I^{131}-labeled metaiodobenzylguanidina (MIBG)
- Other techniques, e.g., arteriography, venous sampling, entail increased risk.

The therapy of choice is surgery and requires caution in order to prevent hypertensive crises during the operation itself and possible hypotensive crises afterwards. This will be discussed in the section on adrenal surgery.

Adrenal Incidentaloma

With the advent and wide-spread use of imaging techniques, above all ultrasonography, the detection of generally nodular parenchymal formations without symptomatic or clinical signs has become increasingly more frequent. This is especially true for the liver, the kidney and, case in point, the adrenal gland. It has become commonplace to label such manifestations as incidentalomas.

The incidental detection (by US or CT scan) of an asymptomatic adrenal nodule clearly raises a number of questions.

The first and most immediate concerns the nature of the formation. From the published series it seems that roughly 10% are carcinomas, i.e., a minority. The second issue is what to do. The two questions are closely related. It was mentioned elsewhere in this lecture that for adrenal tumors, particularly cortical neoplasms, histological and even less so cytological examination do not in most instances allow an unequivocal diagnosis of malignancy, and that this is arrived at primarily through the lesion's dimensions. This observation firstly rules out FNA cytology and singles out the lesion's dimensions - clearly definable by US and even more so by CT scan - as the sole criteria to assess. It is evident that if the neoplasm is large, i.e., above 3-5 cm., no doubt exists as to the need for surgery. Smaller adrenal incidentalomas should be monitored by US (easier, less invasive, less costly) and their eventual increase in diameter accurately calculated. Fast growth - and/or reaching the above-mentioned critical dimension threshold - constitute indications for surgery.

Surgical Procedures

This lecture has presented adrenal gland disorders that necessitate total or partial adrenalectomy. The surgical experience of our group (Clinica Chirurgica, University of Genoa) regards anterior laparotomic or laparoscopic approach to the adrenal gland. The following will discuss only these procedures, drawing on accounts of our operative registers.

Anterior laparotomic approach

Midline or transverse laparotomy.

Right adrenal gland access

The right side of the transverse colon is displaced inferiorly; it is not always necessary to mobilize the hepatic flexure. Duodenal-pancreatic mobilization by Kocher's maneuver. Valve on the inferior surface of the liver and retraction cranially of the same. Exposure of the inferior vena cava. The

adrenal gland now becomes visible, and is often partially covered by the vena cava; displacement of its right edge medially is required to gain full vision of the adrenal gland. This maneuver exposes what is often an authentic *venous comb*, which from the medial edge of the gland flows into the vena cava. The largest of these veins is the *central adrenal vein* (also known as the principal or right adrenal vein), which may very well-developed at the expense of others (which in this case are thin or absent). Ligation of this venous hilum is the primary maneuver in the mobilization of the gland. Above all in the case of pheochromocytoma early ligation of the central vein allows subsequent mobilization maneuvers, averting the release into circulation of hormonal secretions due to possible compression from manipulation of the gland and thereby preventing perioperative hypertensive crises. At this point the medial margin of the gland is freed and can be distanced from the vena cava. Dissection may now proceed towards the superior pole of adrenal gland, which in some cases may be difficult to reach if the gland is located high up. From this stage on, every vessel - especially if thin - that comes into contact with the gland must be carefully handled and accurately ligated (laces, clips, harmonic scalpel) before interruption. Indeed, the arterial branches (superior, medial and inferior arteries) ramify and anastomose - precisely like small vessels - before penetrating the gland. It is now easy to detach loose periadrenal fibrous-adipose formations and to complete the adrenalectomy.

Left adrenal gland access

The transverse colon is displaced inferiorly. The greater gastric curve is skeletonized and the stomach turned over to the right. The adrenal gland is now visible. The principle vein emerges inferiorly and is often elongated to reach the renal vein; it is easily identifiable and is ligated and interrupted. The subsequent maneuvers are identical to those adopted for the right adrenal gland.

Laparoscopic Approach

Right adrenal gland access **(video no. 1)**

The patient is placed in a moderate lateral decubitus position with the left side down; the spine is slightly extended. Pneumoperitoneum of 12 mmHg is established using a Veress needle, at the junction of the anterior axillary and transverse umbilical muscles. Exploration of the abdominal cavity follows.
Four additional 10 mm trocars are introduced at the following positions: transverse umbilical line, 3-4 cm to the right of the umbilicus; xifo-umbilical line, 3-4 cm below the umbilicus; 3-4 cm medially to the prolongation of the midclavicular line in the subcostal region; right flank between the anterior and mid axillary lines.
The liver is displaced, and the vena cava and adrenal gland are visible. The right lateral margin of the vena cava is prepared, and the adrenal veins are ligated and interrupted.

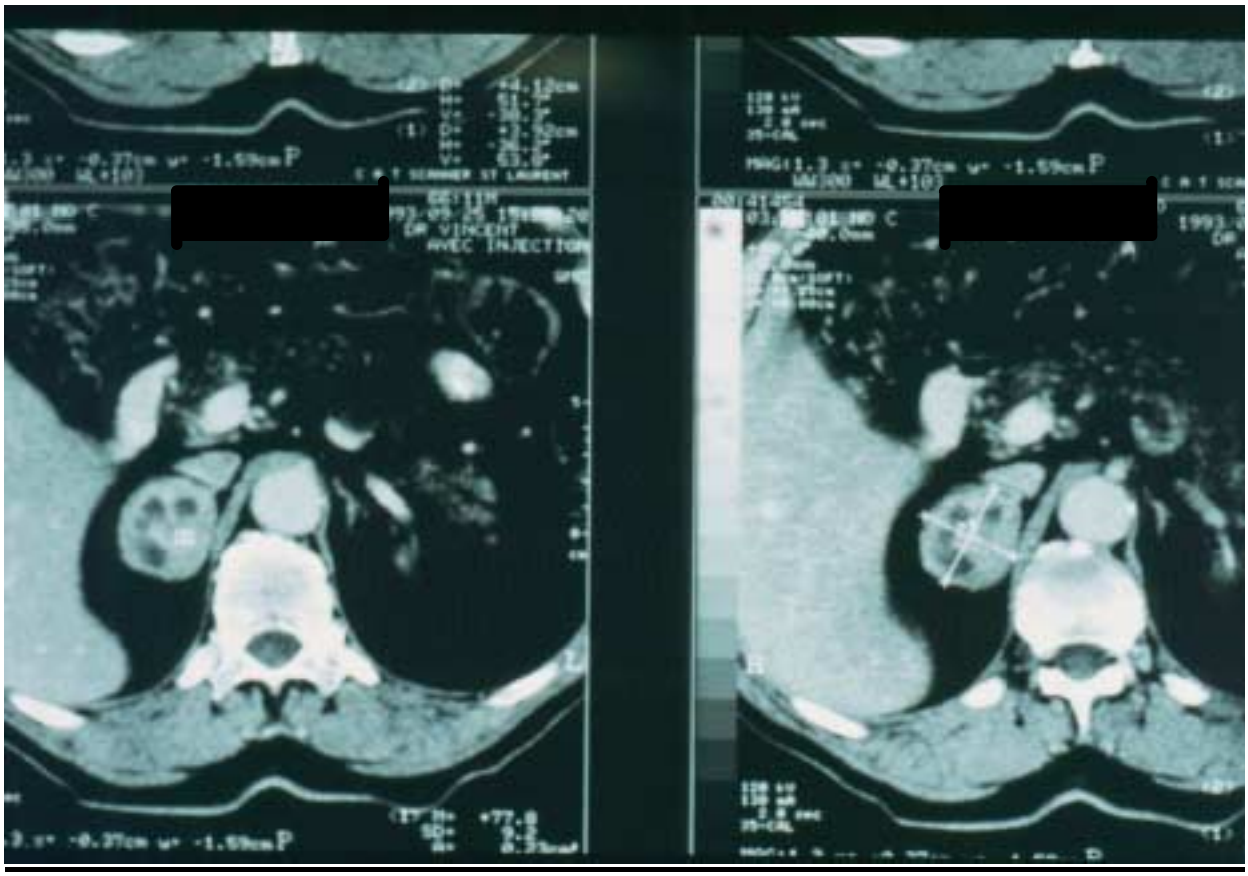
The arterial branches are ligated and interrupted. Mobilization of the gland is completed by freeing it from its fibrous-adipose capsule, particularly at the superior pole of the kidney. Removal in a bag. Inspection of hemostasis. Evacuation of the pneumoperitoneum. Suture of the accesses.

Left adrenal gland access

Anterior **(video no. 2)**
The patient is placed in supine decubitus position. Four 10 mm trocars are introduced, two to the right of the xifo-umbilical line, two to the left slightly above the transverse umbilical line (see video no. 2). The greater gastric curve is skeletonized and the stomach turned over to the right. The adrenal gland is now visible and is prepared. The central adrenal vein emerges vertically below and is ligated and interrupted. Ligation and interruption of other vascular connections.

Lateral **(video no. 3)**
The patient is placed in a lateral decubitus position with the right side down. Access to the peritoneal cavity is achieved at the anterior axillary line, 3-4 cm above the transverse umbilical line. An additional three 10 mm trocars are introduced: subcostally slightly to the right of the first trocar; on the mid axillary line; and on the posterior axillary line. The splenocolic ligament is divided using a harmonic scalpel approximately 2 cm from the posterior splenic margin. Moving upwards, the posterior face of the gastric fundus is exposed. The tail of the pancreas and the spleen are bluntly detached from the adrenal gland, a maneuver which clearly reveals the mass detected by CT scan. The medial margin of the gland and related fibrovascular connections are freed. In particular, clips are used to ligate the medial adrenal artery. Working downwards, two vertical adrenal veins that form part of the inferior branch are freed. These are sectioned between clips, as is the inferior arterial branch. The gland descends with its anterior head in front of the superior pole of the kidney. The left renal vein clearly visible. The gland descends to a few cm from this vessel. Care must be taken to avoid the vasculature of the superior pole of the kidney. The gland, including the fibrous-adipose tissue surrounding it, is separated from the kidney. Finally, the superior diaphragmatic adrenal vessels are ligated and sectioned. The adrenal gland is removed in a bag.

Iconography



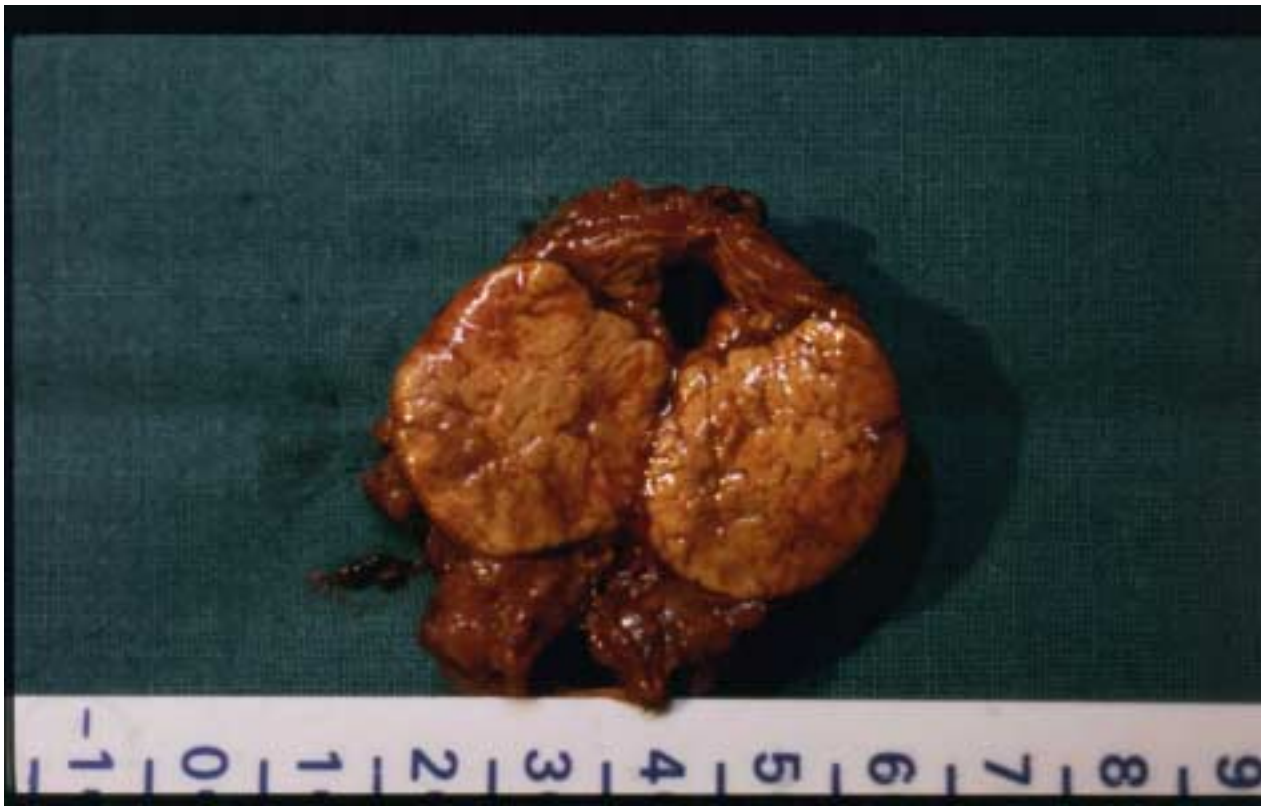


Fig. 1 - Right adrenal adenoma

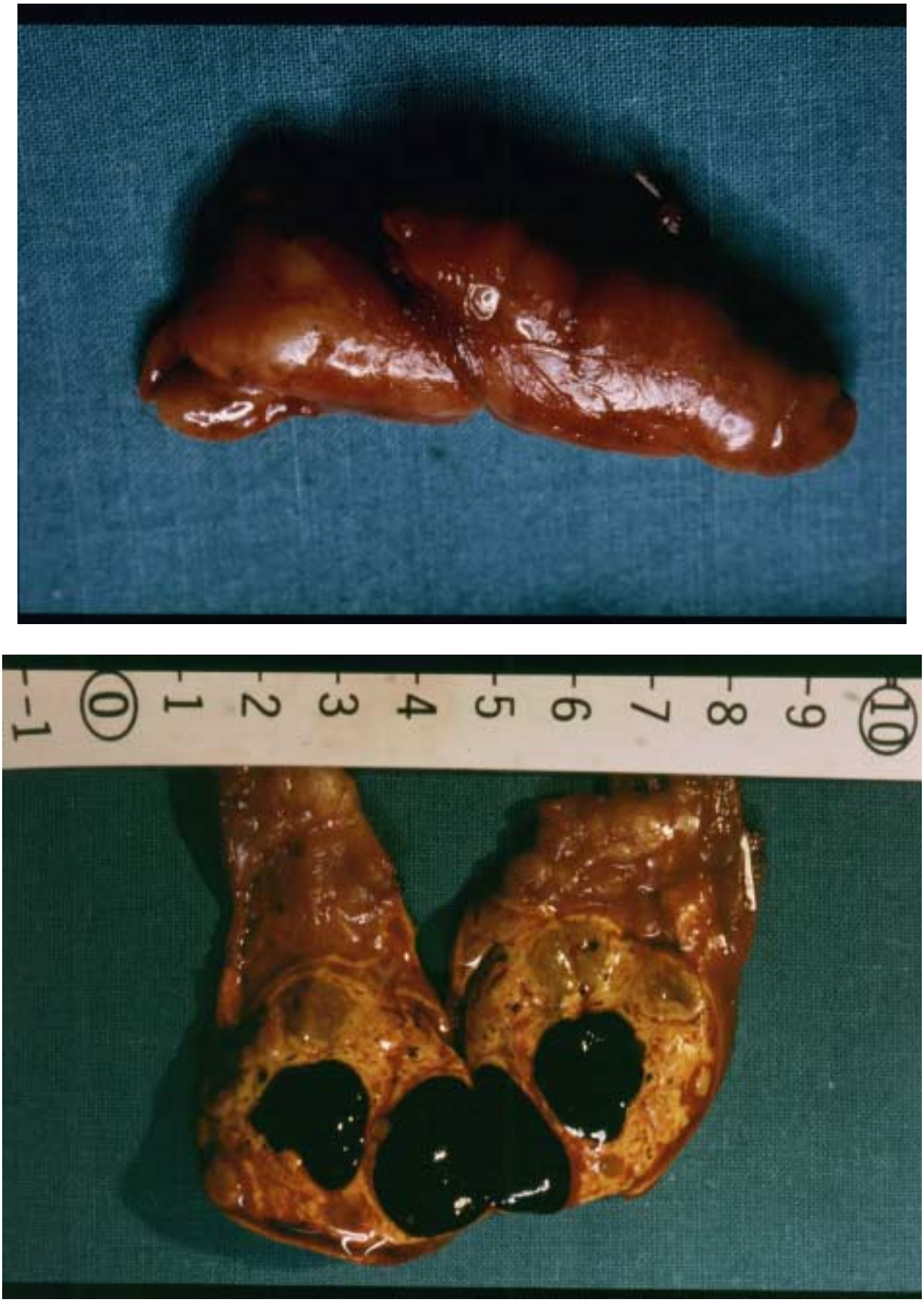


Fig. 2 - Cushing's syndrome -right adrenal adenoma - hemorrhagic areas on sectioning

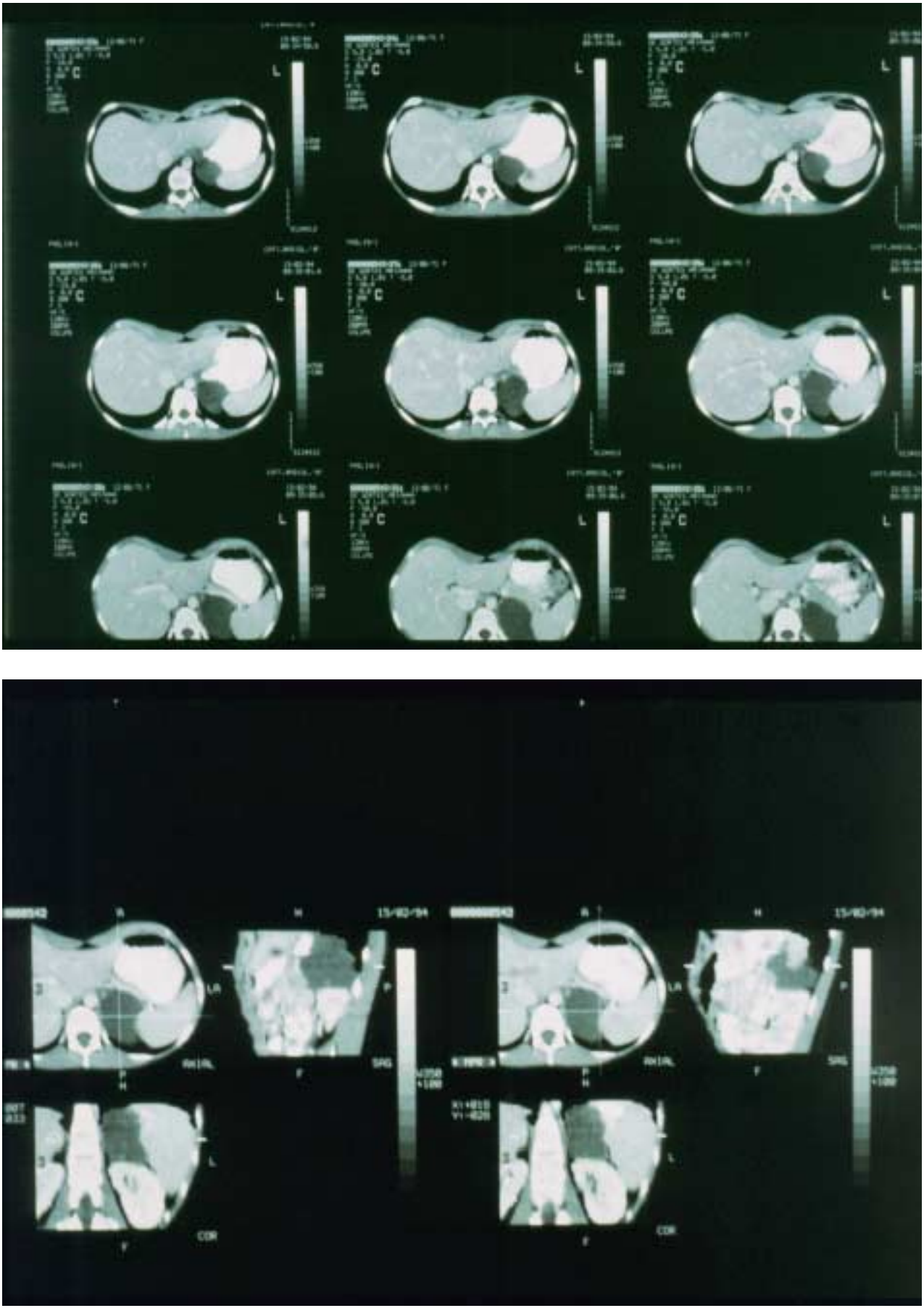


Fig. 3 - Left adrenal gland cystic neoplasm - CT scan

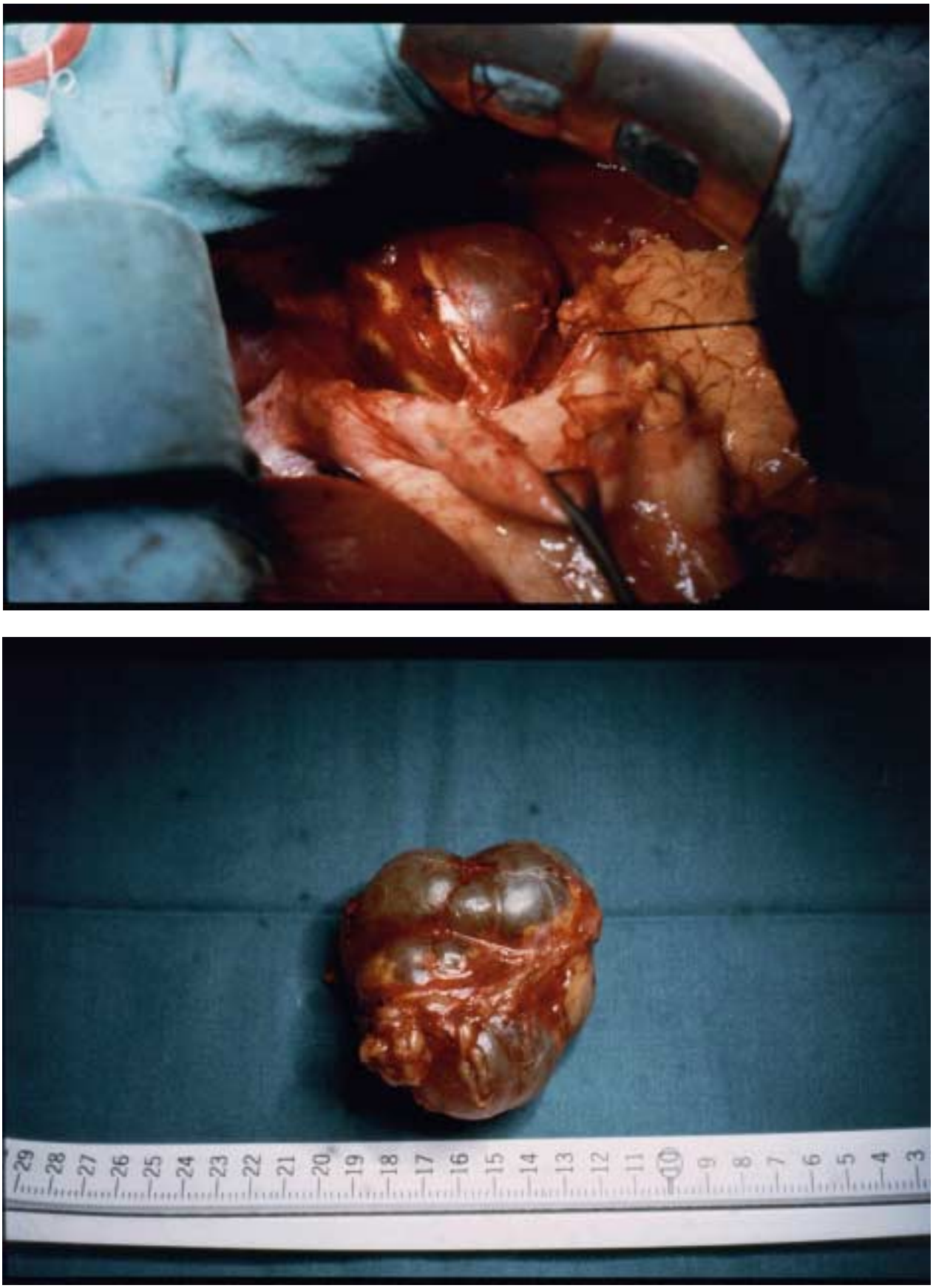


Fig. 4 - Left adrenal gland cystic neoplasm

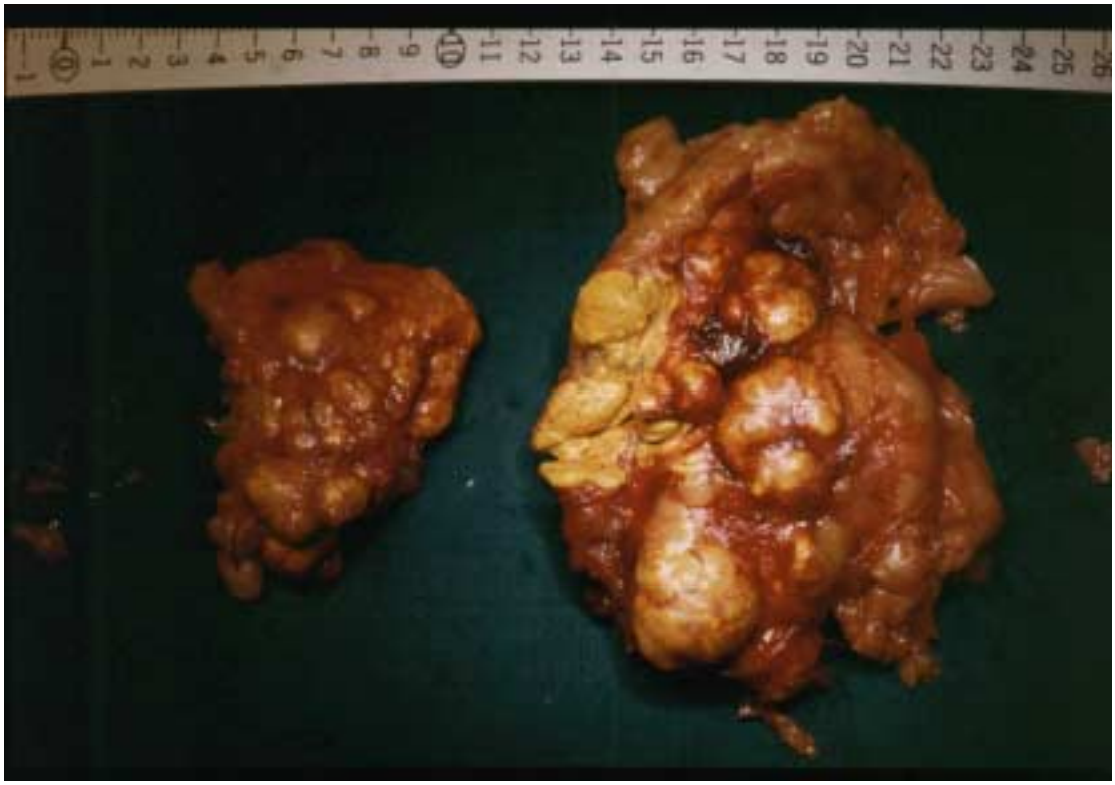


Fig. 5 - Bilateral adrenal gland neoplasm

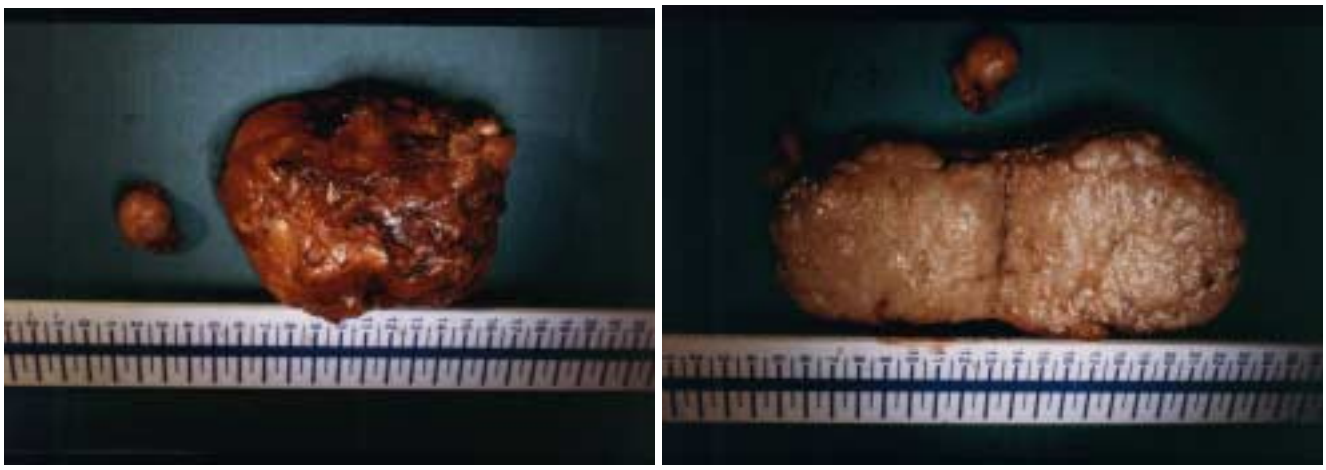


Fig. 6 - Adrenal gland metastases from previous existing lung carcinoma

---