Lecture no. 11

Hyperparathyroidism

Case No. 1

A 65-year-old male, without any noteworthy medical history. For some time he had been experiencing severe pyelo-ureteral colic (renal colic) first on the right, then on the left. Every so often he passed renal stones when urinating. These episodes recurred often. His general practitioner advised him to collect the stones he passed so that they could be examined. On the basis of the calculi composition an appropriate diet was prescribed. He was advised to drink plenty of water, especially oligomineral water. No positive result was achieved: the colic and passage of calculi persisted. The patient became a "producer of calculi". He ultimately consulted a urologist, who, after having performed a series of tests on the patient, referred him to a surgeon. Two specific blood tests enabled the urologist to correctly diagnose the disorder.

Similar cases did not have such a favorable outcome. The nephrolithiasis had been underestimated and, above all, not accurately assessed, thus giving rise to serious complications: pyelo-ureteral tract occlusion, hydronephrosis, nephrocalcinosis, etc. If the exact causal diagnosis had been made earlier, these complications would not have occurred: as mentioned above, two simple blood tests would have sufficed.

Case No. 2

A 50-year-old woman, a highly energetic teacher, had undergone thyroidectomy for goiter years earlier. For some time she had been experiencing strange symptoms: especially when she was in a hurry and wanted to increase her pace, her legs would suddenly give and she would fall. Indeed, one day she was nearly hit by a car while crossing a street at a crosswalk: walking quickly, she suddenly fell to the ground as a car approached. This phenomenon repeated itself on many occasions. Numerous visits to neurologists led to no appreciable results, at least not until one of consulting physicians opted to conduct a few blood tests, which identified the cause of the pathological signs.

Neurological syndromes with accompanying features (asthenia, sleepiness, memory loss, etc.), which can be invalidating in elderly persons, have been erroneously considered expressions of old age; as a consequence, patients often endure deplorable conditions, when a few specific and simple blood tests (as above) would have singled out the cause underlying the ailment and pointed to curative therapy.

Case No. 3

A 65-year-old woman long undergoing treatment for "osteoporosis". She complains of widespread bone and joint pain: very slight traumas - or even the absence of these - give rise to microfractures and violent invalidating pains. Treatment prescribed by the patient's family doctor for the osteoporosis led to no beneficial result. On the contrary, the patient's conditions worsened. At last, the consultation of a rheumatologist clarified the cause of the disorder on the grounds of the few usual blood tests alluded to above.

Other clinical pictures have been described as the manifestation of hyperparathyroidism, but the cases reported above are the most frequent examples of the affliction. As the name itself implies, the disorder entails an excessive secretion by the parathyroid glands; higher than normal serum calcium and parathyroid hormone (PTH) levels are the telltale signs of the condition.

Hypercalcemia is responsible for the syndromes, the most frequent onsets of which were alluded to above. Excessive serum calcium, however, may induce pathological signs that are difficult to interpret, such as those of a neuro-psychic nature, namely, asthenia, apathy, fatigue/weakness and sleepiness, as previously mentioned. The rare condition of acute hypercalcemia may lead to life-threatening conditions.
It is estimated that hypercalcemia is present in 3-5% of the population over 50 years of age and that in 90% of these subjects the condition is caused by hyperparathyroidism due to parathyroid adenoma, thereby making it an all but rare disorder: indeed, hyperparathyroidism carries a prevalence of 0.1% in the population (0.5% after 40 years of age), with peaks in frequency and intensity after 60 years of age.

The parathyroid glands are internally secreting (endocrine) glands. There are usually 4 glands, sometimes 5 or 6, rarely 3. The parathyroid glands are small masses, 2-5 mm in diameter and no more than 30-40 mg in weight. They have a parenchymatous texture and are yellow to light-brown in color, similar to that of the suprarenal cortex. They are covered with a adipose sheath, which often proves helpful for their recognition. They are situated, two per side, posterior to the thyroid lobes; they are attached to the thyroid capsule and are often embedded in the thyroid parenchyma. The superior glands are situated near the superior thyroid pole, the inferior glands towards the inferior pole; it is possible, however, to find inferior parathyroid glands in the mediastinum: the thyrothymic ligament, the thymus, along the superior thyroid vessels, or even lower. The glands are vascularized from the anastomotic arch between the superior and inferior thyroid arteries: this anatomic feature demands that at least one of these arteries (the lower) is saved during thyroidectomy so as to preclude parathyroid necrosis.

Parathyroid hormone (PTH) is the hormone produced by these glands. Serum levels of PTH range fro 10 to 60 pg/ml, and the hormone acts by regulating calcium metabolism thereby maintaining plasma levels within normal levels (8.5-10 mg/dl). The hormone does this via a number of mechanisms: facilitating the reabsorption of calcium from bone matrix and from distal renal tubules (thus also limiting phosphate reabsorption by the proximal tubules) and by favoring its intestinal assimilation in synergy with vitamin D. Through this action of calcium homeostasis, PTH allows the correct function of numerous organic mechanisms: muscular contraction, mental status, bone metabolism and renal function.

Excess of PTH (hyperparathyroidism - HPT) occurs in three forms: primary, secondary and tertiary. Primary HPT is the focus of this lecture and, as already mentioned, is caused by parathyroid adenoma; secondary HPT is generally induced by a hypocalcemic state, itself due to various diseases, the most frequent of which is chronic renal failure (and the reason for the high incidence among dialysis patients); autonomous parathyroid function, induced by various events, most often following treated secondary HPT, leads to tertiary HPT.

Now let us turn to the cause of primary HPT, parathyroid adenoma. *Solitary adenoma*, meaning that it affects a single parathyroid gland, is a benign tumor 75-85% of the time. In some cases, however, the *solitary adenoma* may be surrounded by small satellite growths: this is a clue that the surgeon must bear in mind to avoid the risk of incomplete intervention. Much more infrequently (7-9% of cases) the adenoma may be double. Carcinoma is an exceptional finding in the patient series reported thus far. The possibility - in any case exceptional - of a primitive hyperplasia of the glandular complex causing a primary HPT is doubtful.
Parathyroid adenoma tends to localize more frequently in the inferior glands. It presents as a nodule, red-brown in color, roughly oval, but often irregular, in shape, well defined and encapsulated. It may present, especially in the largest lesions, hemorrhagic and cystic areas. In smaller adenomas a yellow-brown border of normal parenchyma may be visible, pushed towards

the periphery by the growth within the gland. The tumor's dimensions may range from 1 cm to more than 4 cm.
The microscopic structure (Figure 1) resembles that of endocrine tumors: fundamental cells not always organized in lobules or nodules, intersected by a delicate network of capillaries; a well-defined capsule is generally present, and outside of this, above all in smaller adenomas, the compressed and atrophic remains of original parathyroid parenchyma may be observed. As mentioned above, larger lesions may present hemorrhagic spaces and degenerative cystic formations, as well as areas of calcification.

As was illustrated in the introduction of this lecture, the symptoms of primary HPT may be varied and evasive, often leading the observer off track. The urological disturbances, skeletal manifestations, neuropsychiatric alterations, weakness, adynamia, muscular disorders, are syndromes - each manifesting singly and virtually never associated one to another - which at first observation are seemingly straightforward and obvious, but which can prompt inaccurate diagnostic conclusions. Faced with this clinical picture it is necessary to bear a primary HPT in mind and to implement two tests that dictate the proper diagnostic workup: serum calcium and intact PTH - PTH/I - levels (PTH/I, compared to other circulating portions of the molecule, such as the C-terminal or the N-terminal, expresses complete biological activity). Elevated levels of both PTH and calcium that these assays are able to reveal unequivocally indicate a primary HPT, which, in most cases, is due to a parathyroid adenoma.

At this point the diagnosis of parathyroid adenoma and the site of the tumor (or tumors) need to be confirmed. The most reliable examination for this purpose, with a more-than 90% success rate, is scintigraphy with *sestamibi*, which brought important improvements to and now replaces the thallium-technetium subtraction method. Ultrasonography with extra-sensitive probes is also a key diagnostic tool, unless the adenomas are localized mediastinally. (As is well known, the thorax is not easily explored via ultrasonography.) Only when this is the suspected site, for example on the basis of scintigraphic findings, should the workup include CT or MRI.
Normally, specimens of parathyroid tumor are not possible with tradition maneuvers based on physical signs, except in some cases in which the adenoma is particularly large or is placed such that palpation is possible. Usually, moreover, the palpatory sample corresponds at first instance to a thyroid tumefaction, whose definitive diagnosis can be achieved only by the means described above.

Surgical removal of adenoma (or adenomas) immediately resolves primary HPT and all of its manifestations, beginning with the hypercalcemia.
Up until a few years ago it was necessary to guarantee the identification and intraoperative anatomic control of all of the parathyroid glands, with the intraoperative subsequent histological confirmation of adenoma, and therefore required ample cervicotomic access, and despite these expedients the postoperative management of HPT unfortunately still remained. Today, however, the above-mentioned preoperative means of detection and localization, and the possibility to know perioperatively in only a few minutes the level of PTH with the rapid PTH method (*), surgical intervention can be performed with a targeted operation, i.e., directed at the adenoma itself through minimally invasive techniques, which in select cases and carried out by skilled teams may be videoscopic or video-assisted.

(*) Scheme no. 16 on this website in Synoptic Table no. 5 - Hyperparathyroidism - illustrates the rapid drop in serum PTH levels with the removal of the adenoma, which thus sanctions the conclusion of the operation.

However:

- when preoperative data are not entirely straightforward;
- when faced with the management of large adenomas, above all if localized inferiorly and especially if encroachment of the superior mediastinum is suspected;
- when the parathyroid disease is associated with other conditions in the region, e.g., goiter, autoimmune thyroid disorders, etc.;
- when surgery must be performed on an already operated neck (previous surgery of the parathyroid glands or the thyroid gland, etc.);
- finally, when the surgeon is more skilled with traditional maneuvers than with minimally invasive techniques, which are not always easy to perform and often harbor greater risk for the patient under the above conditions,

the most expedient approach is Kocher's classic anterior cervical access, which affords the optimal exploration of all regional components and best protects the important structures. We must, in fact, bear in mind (and recall what was emphasized with other sites, namely, the thyroid gland) that, as with all intervention on the neck, parathyroid gland surgery, too, is susceptible to complications: intra- and/or postoperative hemorrhage, or lesions of important vascular and nervous structures, the most serious of which is injury to the inferior recurrent laryngeal nerve with resulting respiratory and speech problems. These issues are clearly aggravated in cases - thankfully seldom - of mediastinal parathyroid adenomas, whose ablation requires the skilled hand of a thoracic surgeon.

In closing, it must be borne in mind that parathyroid adenoma may fall into any of one multiple endocrine neoplasia (MEN) syndromes:
Type I, if associated with pituitary and pancreatic neuroendocrine adenoma;
Type IIA, if associated with medullary thyroid carcinoma and pheochromocytoma;
Type IIB, if associated with medullary thyroid carcinoma, pheochromocytoma, multiple mucous neuromas, ganglioneuromatosis of the digestive tract and marfanoid features

Figures and Legends

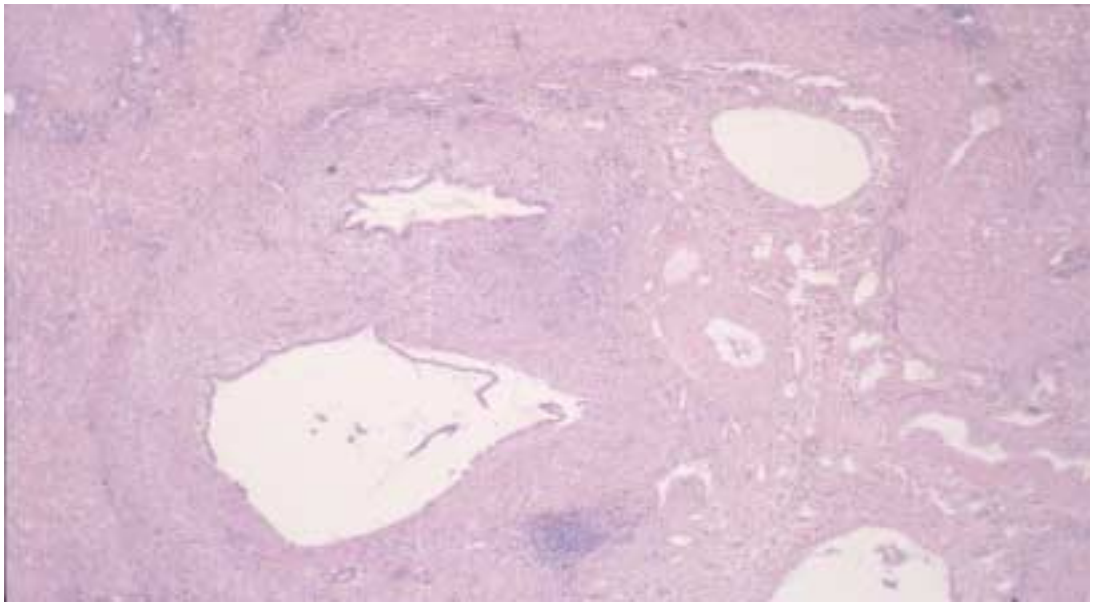
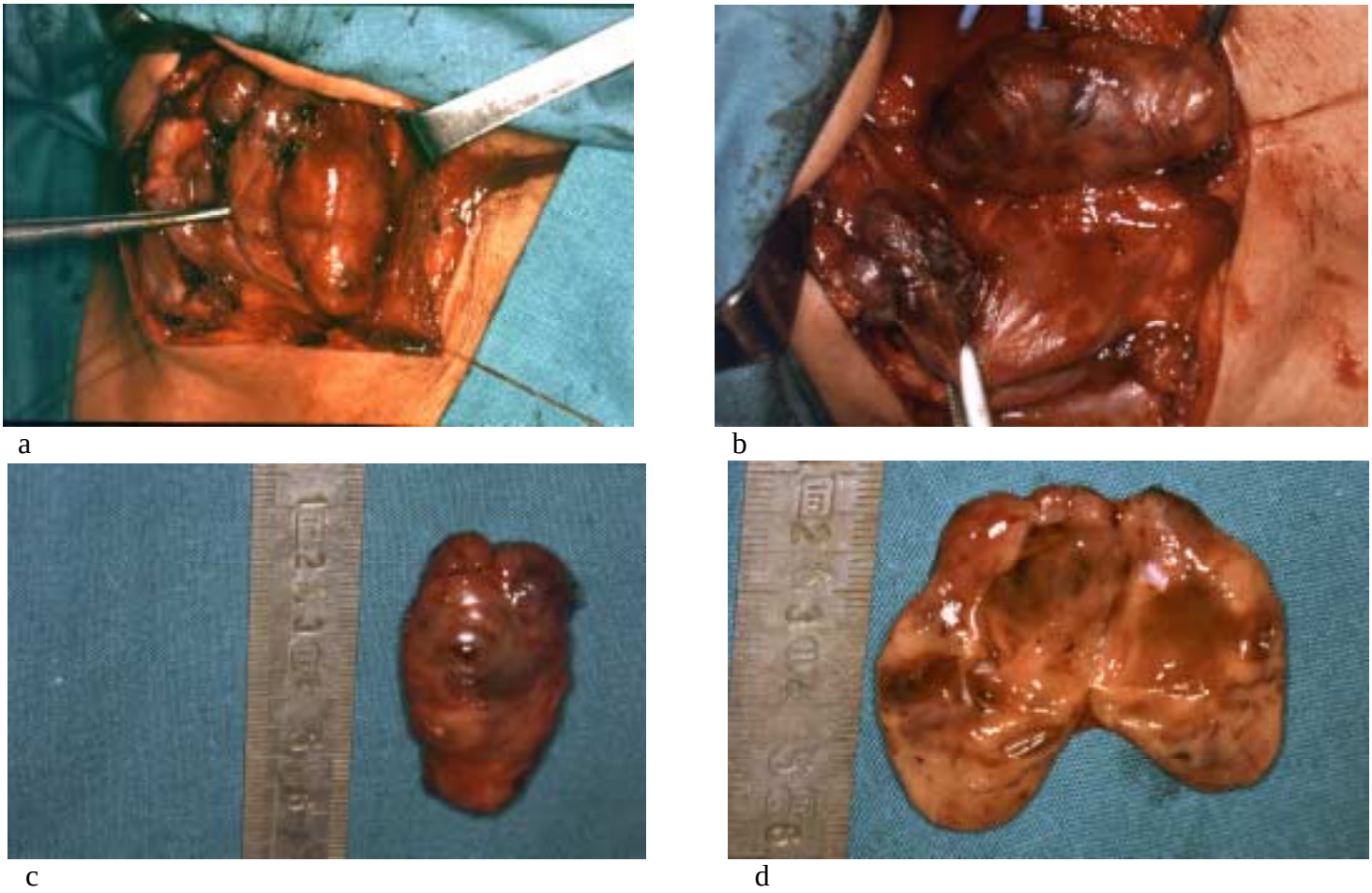


Fig. 1 - Panoramic histological picture of parathyroid adenoma



a b c d

Fig. 2 - large parathyroid adenoma: a) to the left, the left thyroid lobe is displaced medially to reveal the adenoma; b) the adenoma removed and isolated from the thyroid gland; c) the tumor measures 5-6 cm: hemorrhagic areas appear on the surface; d) analysis reveals regressive and hemorrhagic phenomena.

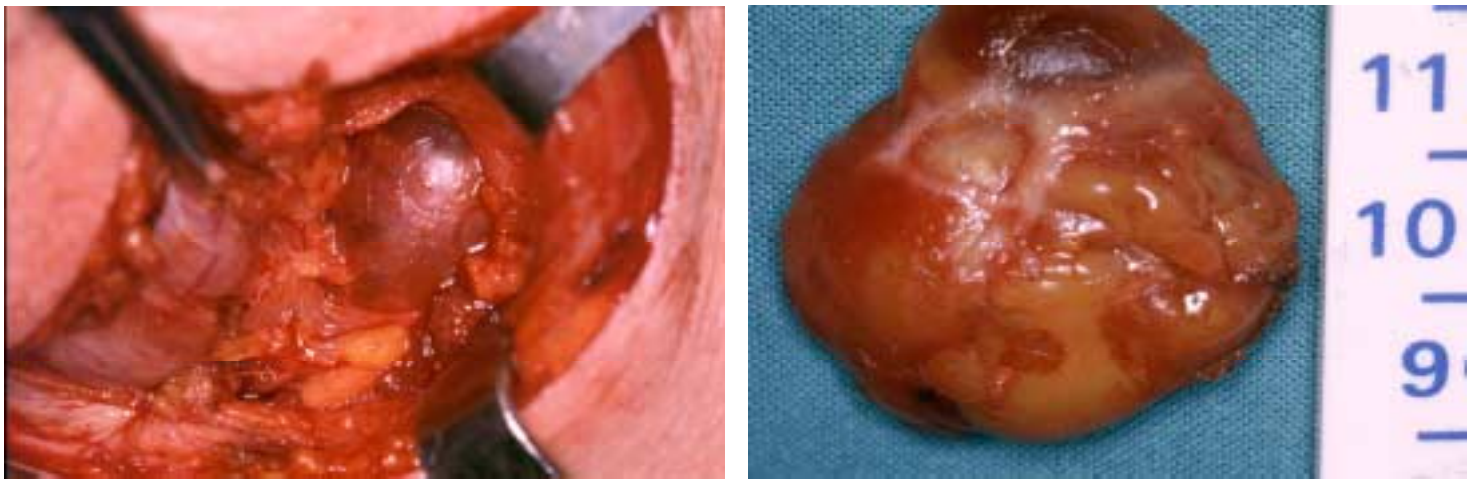
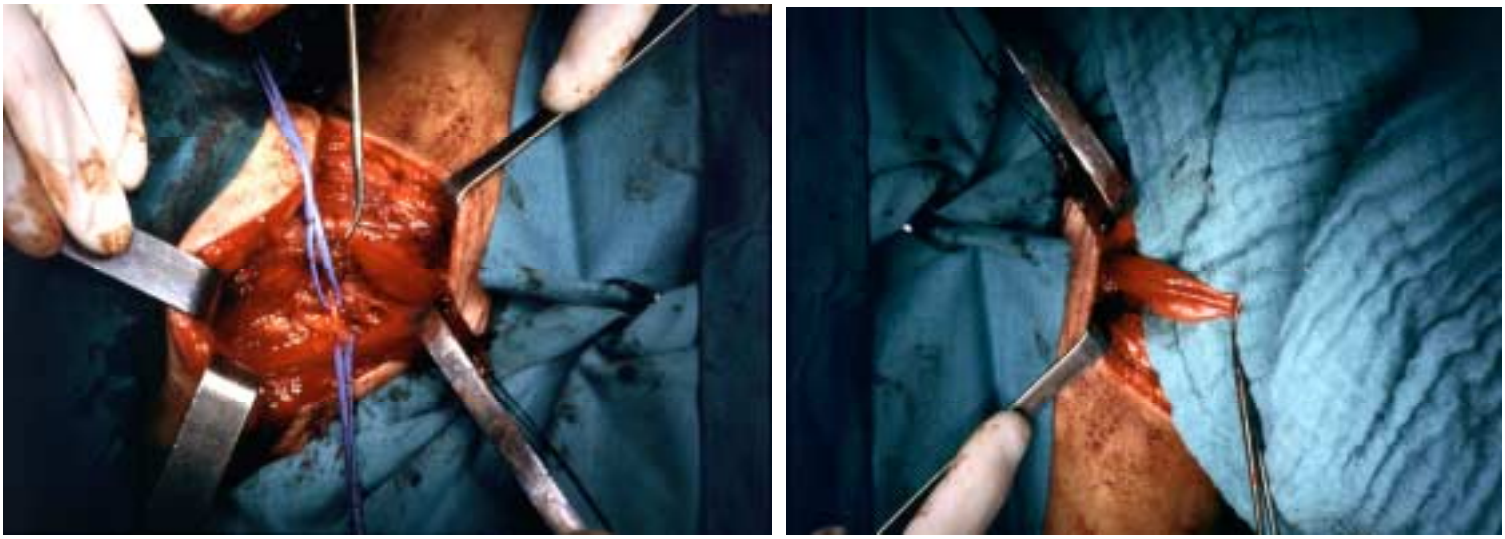
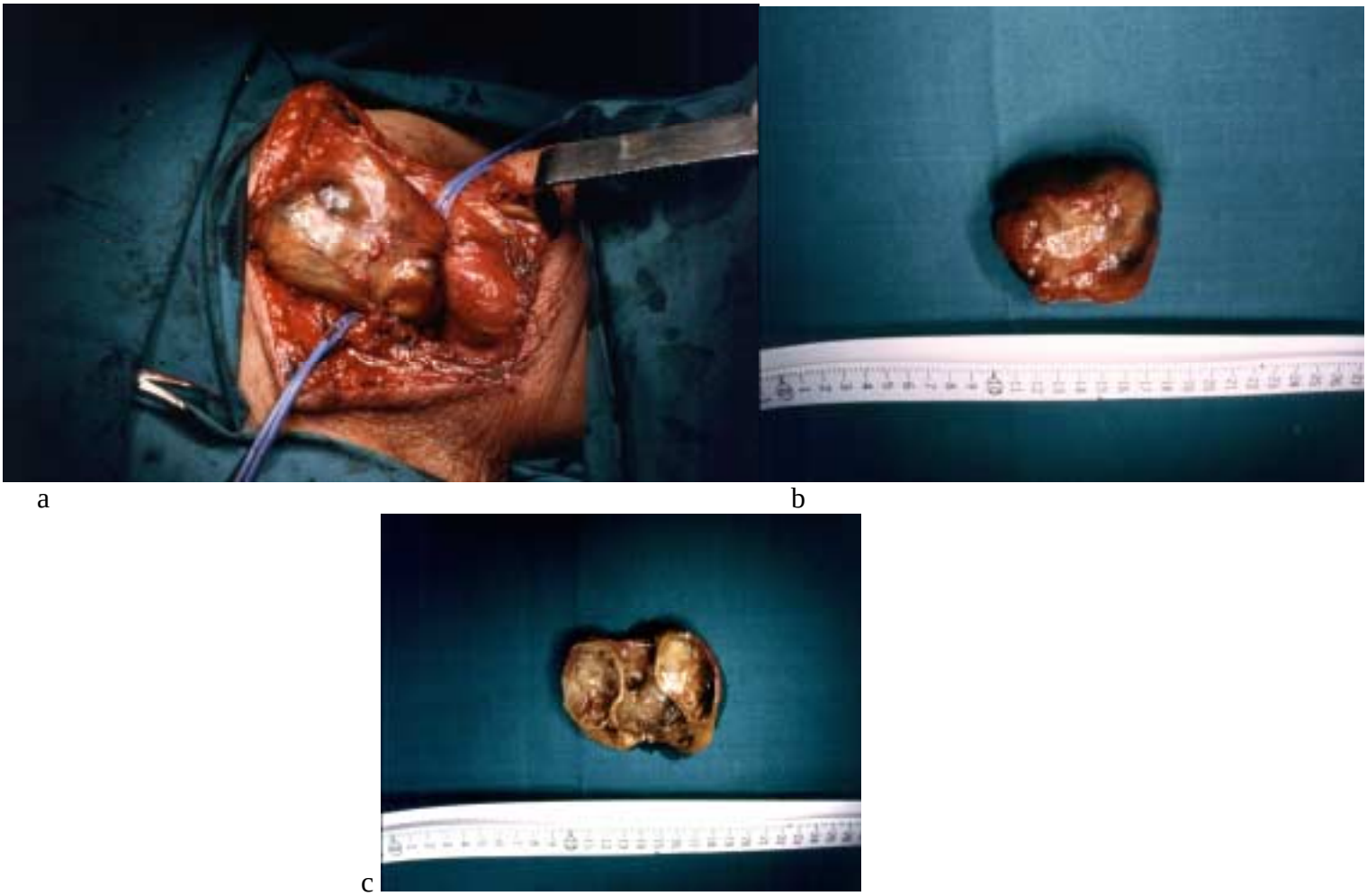


Fig. 3 - Another large adenoma



a b

Fig. 4 - an unusual case of an elongated adenoma.
a) the forceps grasp the superior pole of the adenoma; the upper loop passes under the right inferior thyroid artery; the lower loop under the right inferior recurrent laryngeal nerve; b) the adenoma about to be removed.



a b c

Fig. 5 - Large (7 cm) cystic parathyroid adenoma. a) the right lobe of the thyroid gland is medialized towards the right of the image; the two loops show, respectively, the inferior thyroid artery (to the right) and the recurrent nerve (to the left); b) -c) the large node, which when sectioned presents extensive cystic cavities.