OPEN ACCESS TEXTBOOK OF GENERAL SURGERY

ENDOCRINE DISORDERS

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INTRODUCTION

Certain endocrine disorders are managed surgically: the most common are disorders of the thyroid gland (see Chapter *Thyroid Gland*) and less commonly are those of the parathyroid gland, adrenal gland and certain rare islet cell lesions of the pancreas.

There are fundamental processes that all have in common: Clinical awareness and recognition, biochemical confirmation, anatomical localization, selection for surgery, surgical operation and the sequelae. Close co-operation between the surgeon and endocrinologist or physician provide optimal patient care.

This chapter will deal with surgical pathologies related to the parathyroid glands, the adrenal, endocrine tumours of the pancreas and GIT, as well as rare inherited syndromes

PARATHYROID GLANDS

Physiology

The major function of the parathyroid glands is to *maintain the body's calcium and phosphate levels within a very narrow range*, so that the nervous and muscular systems can function properly. The parathyroid glands do this by secreting parathyroid hormone.

PTH is a polypeptide containing 84 amino acids. It acts to increase the concentration of Ca^{2+} in the blood, whereas calcitonin (a hormone produced by the parafollicular cells (C cells) of the thyroid gland) acts to decrease Ca^{2+} concentration. PTH acts to increase the concentration of calcium in the blood by acting upon the PTH1 receptor (high levels in bone and kidney) and the PTH2 receptor (high levels in the central nervous system, pancreas, testis, and placenta).PTH ½ life is approximately 4 minutes.

PTH increases blood calcium levels by *stimulating osteoclasts* to break down bone and release calcium. PTH also *increases gastrointestinal calcium absorption* by activating vitamin D, and *promotes calcium conservation (reabsorption) by the kidneys*.

PTH also regulates serum phosphate concentrations via actions on the kidney.

Anatomy

There are typically 4 parathyroid glands; however, supernumerary glands and fewer than four glands have been reported. In the majority of cases the parathyroids are symmetrically located in the neck in close relationship to the posterior aspect of the thyroid (Fig1).

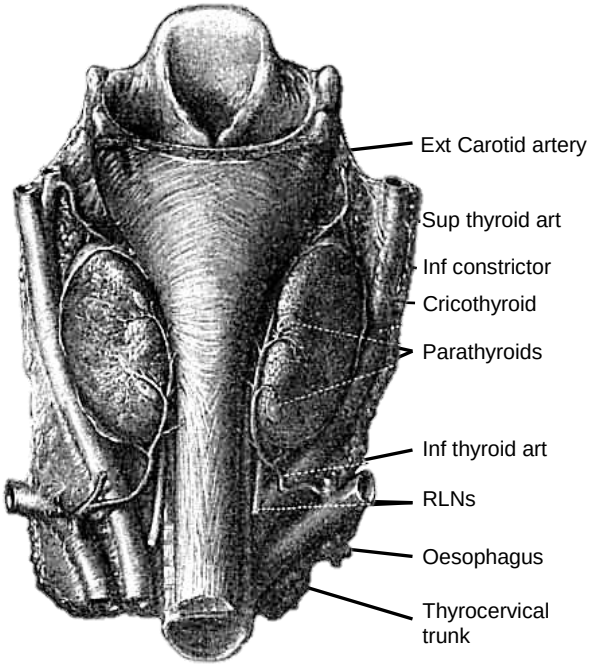


Figure 1: *Posterior view of the thyroid gland demonstrating parathyroids, the RLNs and the superior and inferior thyroid arteries*

Types of hyperparathyroidism

Hyperparathyroidism (HPT) is a condition of excess secretion of parathyroid hormone from the parathyroid glands.

PRIMARY HYPERPARATHYROIDISM

This is the most common form of hyperparathyroidism encountered. The disease is caused by abnormalities in the parathyroid glands. The usual pathology is of a *single adenoma.* The aetiology is not clear, and the cause of the adenoma is unknown. In a small proportion (approximately 5%) of cases all *4 glands have hyperplasia*. The latter may be associated with MEN syndrome, with a genetic mutation located on chromosome 11.

The ***excess secretion of parathyroid hormone (PTH***) results in ***hypercalcaemia***, and the consequent features of the disease.

PTH stimulates the osteoclast and promotes bone re-absorption, producing the characteristic bone changes, and releasing calcium, phosphate and alkaline phosphatase. The calcium and phosphate are presented in excess to the kidney and into the urine, which may result in stone formation. Although PTH promotes calcium absorption and phosphate loss in the renal tubule, the excess calcium "spills over". The hypercalcaemia may affect many organs including the brain.

Primary hyperparathyroidism is the *most common cause of hypercalcaemia in a non-hospital population*. In a hospital population, however, *malignant disease* makes up at least half the cases. In the past, certain calcium containing ulcer medications taken with milk ("milk alkali syndrome"), and excessive administration of cod liver oil and vitamin D (hypervitaminosis D) produced hyper-calcaemia: These are no longer encountered.

Disorders of parathyroid glands
*Primary hyperpararthyroidism **
Long term Lithium Rx
Familial hypocalciuric hypercalcaemia
Malignancy
Haematological malignancy
Bone metastases
Paraneoplastic syndrome
Vit D disorders
Hypervitaminosis D
sarcoidosis
High bone turn over
Thyrotoxicosis
Long term bed rest
Thiazides
Vit A
Multiple myeloma
Renal disorders
Tertiary hyperparathyroidism
Milk-alkali syndrome
Aluminium intoxication

Table 1- *Causes of hypercalcaemia. 90% are caused by primary hyperparathyroidism or malignant disease*

Hypercalcaemia (>2.6 mmol/L) and its implications is frequently missed in clinical practice. Every case of hypercalcaemia requires a clinical explanation.

Clinical Features

The clinical presentations of primary hyperparathyroidism are often subtle, and may go unrecognized. Awareness of the condition is critical to the diagnosis.

It is not unusual for hypercalcaemia symptoms of hyperparathyroidism to be non-specific and vague and hence is often underestimated. Typical presentations include recurrent renal calculi, progressive bone density loss and occasionally pathological fractures, ill-defined musculo-skeletal complaints, neuro-cognitive impairment, and unexplained abdominal pain. *Bone, stones, groans and moans* is a helpful mnemonic to the effects of the disease.

In addition to these modes of presentation, *hypercalcaemic crisis* (dysequilibrium hypercalcaemia) may present as a fulminating emergency with rapidly rising calcium levels, polyuria and dehydration, and subsequent confusion, coma and death. This emergency requires major rehydration, hypocalcaemic drugs and urgent surgery.

• **Bones:** *Radiological and densitometric abnormalities* *Musculoskeletal pain/"fibromyalgia"/ "arthritis"* *Pathological fractures* *Von Recklinghausen disease*
• **Stones:** *Renal stones are common*
• **Groans:** *Abdominal pain from renal stones is common; Association with pancreatitis and peptic ulcer are questioned*.
• **Moans:** *Depression is common* *?Alzheimers* *Tiredness/ apathy* *Confusion in hypercalcaemic crisis* *Delirium*
• **Asymptomatic**: *A significant number present with incidental hypercalcaemia*

Table 2- *Clinical features of primary hyperparathyroidism*

Diagnosis

The diagnosis is made from the clinical features (eg: renal stones) and the biochemical confirmation. Many cases are asymptomatic, and the only clue to the diagnosis is unexplained hypercalcaemia. The diagnosis usually rests on two simple blood tests: elevations of the serum calcium and parathyroid hormone.

When, however, the biochemical diagnosis has been made and surgery is indicated, special localising studies are performed to guide the surgeon to the most likely site of the adenoma.

The most accurate of these is a *sestaMIBI scan*, performed by Nuclear Medicine.

Ultrasonography is a helpful adjunct in selected cases. CT scan, MRI, venous sampling are very seldom performed.

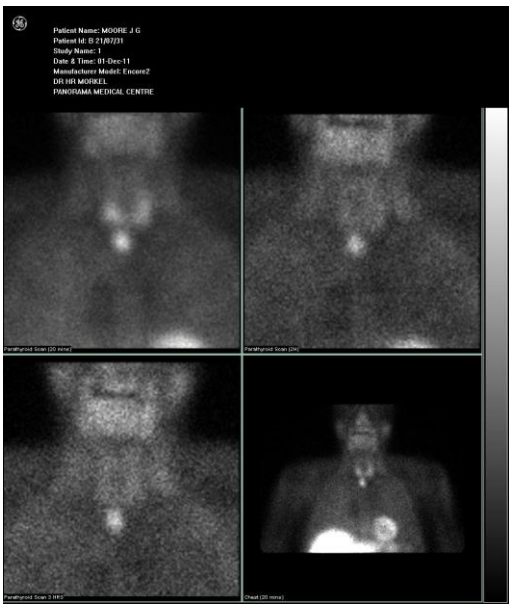


Figure 1- *Sestamibi scan showing a focus of parathyroid activity below the right pole of the thyroid gland, in keeping with an adenoma at that site*.

Pathology	Associations	Diagnostic tests
Primary hyperparathyroidism		
Adenoma (95%) Hyperplasia (5%)	Sporadic MEN syndrome	↑ sCa^{2+} ↑ sPTH normal PO^{4-} ↑ urineCa2+
Secondary hyperparathyroidism		
Hyperplasia	Renal failure GIT malabsorption	normal Ca^{2+} ↑ PTH ++++ ↑ PO^{4-}
Tertiary hyperparathyroidism		
Hyperplasia	Renal failure	↑ Ca^{2+} ↑ PTH ++++ ↑ PO^{4-}

Table 3- *diagnostic features of different types of hyperparathyroidism*

Treatment

Surgery is undertaken in most cases: the single adenoma is removed, or in the case of 4 gland hyperplasia, 3½ glands are removed. Asymptomatic patients are submitted to surgery unless they have a severe medical contra-indication as they may proceed to renal damage, osteopaenia or psychological abnormality in later life.

The majority of parathyroid operations are simple, quick and very rewarding for both surgeon and patient. However on occasion parathyroid glands may be infuriatingly difficult to identify and may test the skill and patience of the most experienced endocrine surgeon. Parathyroidectomy is best performed by centers who are well versed with these complexities.

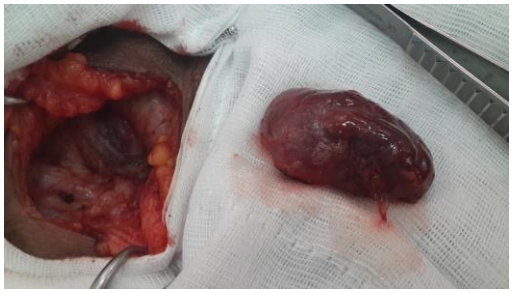


Figure 2- *Typical 3cm parathyroid adenoma adjacent to surgical site*.

SECONDARY HYPERPARATHYROIDISM

Secondary and tertiary hyperparathyroidism may arise in patients with chronic renal failure (or very rarely in GIT malabsorptive conditions) where phosphate retention and calcium deficiency secondarily stimulates the glands to secrete PTH in order to restore low normal calcium levels. This process chronically depletes the bone calcium stores. Patients usually have a ***normal serum calcium level***.

Calcium deficiency may develop during the course of chronic renal failure, particularly in patients on haemodialysis. Many mechanisms are responsible for this: decreased gut absorption (which is vitamin D mediated), decreased levels of vitamin D, due to absent renal hydroxylation of calciferol, and perhaps PTH resistance in bone. Phosphate retention and the falling calcium levels stimulate the parathyroid glands (hyperplasia), and the excessive levels of PTH then stimulate osteoclast activity causing osteopaenia.

The clinical picture is that of a patient in chronic renal failure who develops osteopaenia with elevated alkaline phosphatase and PTH levels. Other symptoms are pruritus, pathologic bone fractures, ectopic soft tissue calcification, severe vascular calcification, and bone pain or skin ulcers.

The surgical management is to *remove 3½ of the hyperplastic glands*. The fourth gland remainder may be left in situ or transplanted into the forearm for easy access should it be become overactive again.

TERTIARY HYPERPARATHYROIDISM

In some patients the process may become autonomous, typically after a successful renal transplant removes the hypocalcaemic stimulus; this is then labelled tertiary hyper-parathyroidism, and the patient becomes ***hypercalcaemia*** again, with the danger of renal calculi to the new transplanted kidney

ISLET TUMOURS OF THE PANCREAS *(see also chapter on pancreatic neoplasms)*

The pancreas consists of *exocrine* cells which secrete pancreatic enzymes into the duodenum and *endocrine* cells which produce hormones which are secreted into the blood. The latter are located in the pancreatic islets and may undergo neoplastic change becoming adenomas or carcinomas: the islet tumours of the pancreas.

The most common tumours are *gastrinomas and insulinomas*; glucogonomas and vipomas are excessively rare.

B cell - insulin insulinoma
A cell - glucagon glucagonoma
D cell - gastrin gastrinoma

Gastrinoma

The gastrin producing cells of the pancreas and duodenum - but not the antrum - may undergo neoplastic change and produce adenomas and carcinomas which *secrete gastrin*, with excessive acid production and the features of the disease.

The triad of recurrent peptic ulceration, marked acid secretion and an islet tumour defines the *Zollinger Ellison syndrome*. The diagnosis rests with the clinical suspicion of the condition and demonstration of elevated serum gastrin levels, together with raised acid secretion, particularly the basal (fasting) secretion.

The lesions are localised and staged by *CT scanning*, but surgical exploration is regarded as the most accurate method of localisation. Many lesions are located in the duodenal wall. Localised lesions without metastases are best treated by surgical removal; more advanced lesions may be managed by a proton pump inhibitor (if the tumour has been shown to be responsive and the patient compliant); in other cases a total gastrectomy, to abolish acid secretion, is undertaken.

- Recurrent ulcer
- Refractory ulcer
- Multiple ulcers
- Ulcers in unusual sites
- Ulcer and diarrhea
- Ulcer and MEN syndrome

Table 4- *features suggestive of Zollinger- Ellison Syndrome*

Insulinoma

An adenoma of the islet cells may secrete insulin autonomously and continuously. In normal people, after exercise or fasting, insulin secretion reduces; with insulinoma, however, the secretion continues, the blood levels of insulin being *inappropriate* for the glucose level (usually after an overnight fast) and the demonstration of an adenoma of the pancreas on CT scanning.

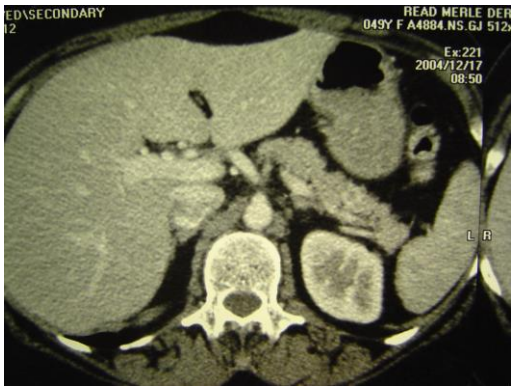
Causes of hypoglycaemia

- anti-diabetic drugs
- liver disease
- alcohol
- post gastrectomy dumping
- insulinoma

Other localizing tests include portal venous insulin sampling, and nuclear medicine imaging may help to locate the lesion for surgical excision.

Hypoglycaemia	*exercise or fasting*
Neuroglycopaenia	*weakness* *visual disturbance* *amnesia* *confusion* *convuslions*
Cathecholamine release	*sweating* *paliptations*

Table 4- *Suggestive features of insulinoma*



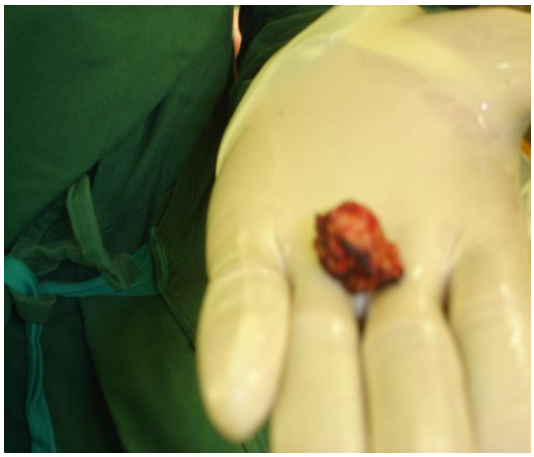


Fig 3- *Insulinoma are typically small tumours (<2cm) and identifications can be a challenge. CT shows a vascular blush along the body of the pancreas. The image is of the specimen*

MEN1 and MEN2

Certain endocrine neoplasms may occur concurrently or sequentially in the same individual, and the trait may be inherited. These groupings are called the *MEN (multiple endocrine neoplasia) syndrome*. The location of the insulin, calcitonin and Harvey ras oncogene on chromosome 11 might suggest a hereditary abnormal regulation at this site.

MEN 1 (Wermer's Syndrome)
Pituitary (*acromegaly/ prolactinoma*)
Pancreas (*insulinoma/ gastrinoma*)
Hyperparathyroidism
MEN 2a (Sipple Syndrome)
Medullary thyroid cancer
Phaeochromocytoma
Hyperparathyroidism
MEN 2b (mucosal neuroma syndrome)
Medullary thyroid cancer
Phaeochromocytoma
Marfanoid habitus
Mucosal neuromas

Individuals with any component should be tested for the others (eg: patients with gastrinoma should have growth hormone, prolactin and PTH measured; patients with phaeochromocytoma should be investigated for medullary thyroid carcinoma). Relatives of patients with the MEN syndrome should be screened for the disease.

ADRENAL GLANDS

Cortical function

The outer *zona glomerulosa* secretes the mineralo-corticoid, aldosterone. The inner *zona fascicularis* and *zona reticularis* together secrete glucocorticoids (cortisol and corticosterone), androgenic steroids and certain steroid precursors.

The hormones are secreted in response to external demand. Cortisol secretion is controlled by pituitary ACTH, the levels being maintained by a feed-back loop, which acts on both the pituitary and hypothalamus.

Aldosterone secretion is influenced by angiotensin (which is controlled by renin production), and by the concentration of plasma sodium and potassium. the sex hormones have a minimal role, the major role being taken by gonadal secretion.

Medullary function

The adrenal medulla secretes adrenaline, noradrenaline and dopamine, the noradrenaline precursor. Control is through the splanchnic nervous system. The urine may contain small amounts of these catecholamines, as well as their meta-metabolites, and vanillylmandelic acid (VMA). Medullary function may be assessed by urinary measurement of these.

Adrenaline stimulates alpha and beta adrenergic receptors, redistributing blood flow from the skin and splanchnic vessels to the heart, brain and muscles. Noradrenaline stimulates alpha receptors, causing generalised vasoconstriction and elevation of blood pressure.

Imaging the adrenal gland

The best images of the adrenal gland are obtained with a spiral CT scan. Excellent images are also obtained with MRI scanning, where the T2 weighted images show detailed adrenal anatomy. Complex adrenal problems are best referred to tertiary centres.

Ultrasonography is less satisfactory, but may be helpful in many cases.

Certain important adrenal lesions are only a few centimeters in diameter, and require detailed imaging.

SURGICAL DISEASES

CUSHING'S[1] SYNDROME

Cushing's syndrome refers to the clinical features found with an excess of adrenal cortical hormones. The pituitary-based variant was first described by the American neurosurgeon *Harvey Cushing*.

Most body systems may be affected, and the presentation may be subtle. The diagnosis is frequently missed by many doctors: the obese patient with depression, hyper-tension, amenorrhoea and diabetes may well have Cushing's Syndrome.

Central obesity *round face* *buffalo hump* *supraclavicular fat pads* *truncal obesity* *thin arms and legs*	90%
Weakness, proximal myopathy	80%
Hypertension	80%
Skin changes *thin skin, bruising* *acne, greasy skin* *hirsuitism, plethora* *abdominal striae, pigmentation* *infection*	70%
Psychiatric changes *mental slowing* *depression/ psychosis*	
Oligo / amenorrhoea / impotence	
Osteoporosis	
Thirst / polyuria	
Glucose intolerance	

Table 5- *Clinical features of Cushing's syndrome*

There are various causes of the syndrome, the most common being the administration of steroid therapy. In patients not on therapy, the most common cause in women is true Cushing's Disease (the problem being a pituitary adenoma), in men carcinoma of the bronchus (the problem being an ACTH secreting bronchial tumour), and in children the most frequent cause is an adrenal adenoma.

Steroid administration/ iatrogenic	common
Cushing's Disease (*pituitary*)	70%
Ectopic ACTH (*paraneoplastic*)	10%
Adrenal (*adenoma / carcinoma*)	20%

Table 6- *Causes of Cushing's Syndrome*

Screening for Cushing's syndrome

The differential diagnosis includes obesity, adult onset diabetes, essential hypertension and alcoholism.

Three 24 hour urinary samples should be taken and tested for cortisol. A 24 hour urinary cortisol level of more than 100µg is diagnostic of Cushing's syndrome. The episodic nature of cortisol secretion makes random blood cortisol levels unreliable. A low-dose dexamethasone test (1mg orally at 11pm, and measure plasma cortisol at 8am) will suppress plasma corstisol in normal individuals below 3µgms/100 ml and confirms the diagnosis.

[1] Harvey Cushing, Boston. 1869-1939.

Once the diagnosis of Cushing's syndrome has been made, one then proceeds to locate the site of the cause (Table 6).

Localizing the cause of Cushing's syndrome.

The key test is the *serum ACTH* level: suppressed levels indicate an adrenal level neoplasm, normal or slightly raised levels indicate a pituitary level adenoma, and markedly elevated levels indicate a non-endocrine ACTH secreting neoplasm.

The *high dose dexamethasone suppression test* (2mg 6hrly for 2 days) relies on the fact that autonomous neoplasms (cortical adenomas and non-endocrine tumours) will not respond to the external feed-back stimulus of dexamethasone, but that pituitary level Cushing's disease will.

Anatomical localization is best achieved by CT scanning of the pituitary and the adrenal glands. A skull radiograph may show an enlarged sella in 20% of cases of Cushing's syndrome.

Treatment

Cushing's disease is a disorder that mainly affects women between 20 and 50 years. The lesion is located at pituitary level and is usually a ***pituitary adenoma***, driven by CRF from the hypothalamus. It is managed by *transphenoidal resection of the tumou*r, which is successful in 80% of cases. *Radiotherapy* and medical therapy are adjuncts to this. Where pituitary surgery has failed, *bilateral adrenalectomy* with replacement therapy may be considered. *Nelson's syndrome* refers to the development of a pituitary adenoma due to lack of feed back in the absence of adrenal tissue.

Adrenal adenomas are managed by adrenalectomy, and a gradually reducing replacement therapy. ***Adrenal carcinomas*** are resected if possible, and the tumour bed irradiated.

Ectopic ACTH producing tumours (usually of the bronchus, but also the pancreas, thymus and at other sites) require control of the primary lesion. If this is not resectable, medical adrenalectomy with metyropone, aminoglutethamide and mitotone may be undertaken. The occurrence of Cushing's syndrome in a patient with an ACTH secreting malignancy is usually a terminal event in a patient dying from that malignancy. Frequently no medical action is taken.

PHAEOCHROMOCYTOMA

Phaeochromocytomas are tumours of the adrenal medulla, or more rarely (10%) the sympathetic tissue adjacent to the vertebral column, where they are called *paragangliomas*. The name comes from the Greek: *phaios* (dark), *chroma* (colour). They characteristically secrete adrenalin and noradrenaline, and untreated are invariably fatal. Approximately 10% are malignant, and 10% multifocal.

Phaeochromocytomas may be associated with the MEN 2 syndrome (medullary thyroid carcinoma and, hyperparathyroidism), as well as with neurofibromatosis and Von Hippel-Lindau syndrome.

Clinical features

These are analogous to a constant or intermittent infusion of adrenaline or noradrenaline. They can be easily missed and result in a fatal cardiovascular event, sometimes precipitated by surgery for other indications.

Investigations

Patients with *inappropriate* hypertension should be screened for surgically correctable diseases, including phaeochromocytoma. The most widely used biochemical test is urinary cathecolamine levels; the urine is best collected after an "attack".

Where laboratory facilities are available, other urinary metabolites may also be measured, as well as serum catecholamines.

• Hypertension in the young
• Rapidly progressive hypertension
• Poorly controlled hypertension
• Paroxysmal attacks

Table 7- *features of phaeochromocytoma*

It is important to note that not all paheocromocytomas are hypertensive. Some patients are in fact prone to hypotension.

Localization of the tumour is best done with a *CT scan*. Radio-iodine labeled MIBG (meta-iodobenzylguanidine) will also show up the tumour location.. Paragangliomas along the abdominal vertebral column, as well as a lesion at the bifurcation of the abdominal aorta (organ of Zuckerkandl) may be sought.

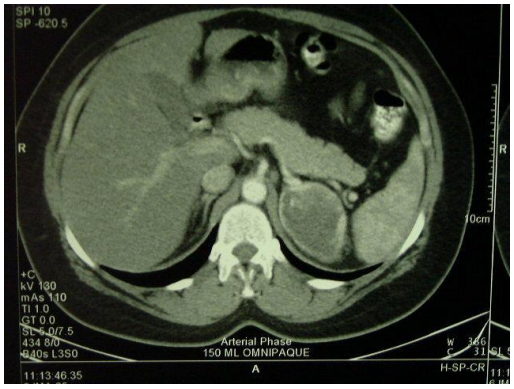


Fig 4- *CT image of a large left adrenal phaeochromocytoma*

Treatment

Patients with these tumours are best managed in major centres. An essential preparation is *alpha-blockade* using the drug phenoxybenzamine (starting at 10mg twice a day, and gradually increasing the dose) or prazocin; such blockade may take 10 days or more, and is judged adequate when there is postural hypotension, a slow pulse and nasal stuffiness.

The progressive loss of vasoconstriction leads to normovolaemia, and avoids dangerous hypotension due to loss of vasoconstriction after removal of the tumour. Intra-operative sodium nitroprusside or magnesium infusion may be required to avoid blood pressure swings during tumour handling.

CONN'S[2] SYNDROME

Conn's syndrome refers to the presence of an aldosterone secreting *adenoma of the adrenal* cortex ("aldosteronoma"), which has the exaggerated effect of an excess of *aldosterone action and causes hypertension and hypokalaemia*.

The condition is extremely rare, and should be suspected when hypertensive patients present with muscular weakness from hypokalaemia (K^+ <3 mg). Thiazide diuretics may also cause hypokalaemia in hypertensive patients, and should be stopped for two weeks before the potassium level is re-checked, and the diagnosis reconsidered. Patients with suspected Conn's syndrome should be referred to major centres for further investigation.

Sustained hypertension
Paroxysmal hypertension
"Adrenergic Attacks" *Headache/ palpitations/ blurring of vision/ sweating/ abdominal pain/ anxiety*
Major cardiovascular illness *pulmonary oedema/ stroke/ infarct*

Table 8- *inappropriate hypertension*

Investigation of Conn's syndrome

This requires confirmation of the following investigative steps:

- hypokalaemia, and excessive urinary potassium secretion.

[2] Jerome Conn, Ann Arbor. 1907-

- excessive aldosterone secretion by measuring blood and urinary levels. (ie *hyper-aldosteronism*)
- *primary hyperaldosteronism,* and exclusion of secondary variants by demonstrating *depressed renin* levels.
- Localization of the adenoma by CT scanning.

Approximately 50% of Conn's syndrome is caused by bilateral hyperplasia of the adrenal gland- this is treated medically only. The remainder are due a benign solitary adenoma, which should be sought and removed, since surgical removal of the adenoma leads to normotension in approximately 70% of cases, and reduction in antihypertensive therapy in the remainder.

Conn's syndrome constitutes one of several causes of hypertension, which may be corrected by surgical means. While hypertension is common, certain subsets of patients merit investigation, as the surgical correction of their problem is rewarding, leading to cure, and reduction in drug cost.

- coarctation of the aorta
- renovasular hypertension
- phaeochromocytoma
- Conn's syndrome
- Cushing's syndrome

Table 9- *Surgically correctable hypertension*

ADRENAL CARCINOMA

Adrenal carcinoma is a rare condition, where most patients present with advanced disease. Syndromes of hormone overproduction occur in about half the patients (Cushing's syndrome, hyperaldosteronism, virulisation), a palpable mass is present in 50% and 25% have hepatomegaly. Local invasion and metastases are common.

These patients have a poor prognosis, and the only hope of cure is resection of earlier, smaller, non-metastasizing lesions. Radiotherapy and chemotherapy yield disappointing results.

ADRENOGENITAL SYNDROME

There are various genetically determined enzyme defects, which impair adrenal steroid synthesis. This causes an increase in pituitary ACTH production and resultant adrenocortical hyperplasia, with inappropriate adrenal androgen secretion. The consequences depend on the sex and age of the patient.

Infant girls have an enlarged clitoris, and varying fusion of the labial folds. Virilism supervenes with the development of pubic and facial hair; temporal alopecia, deepening of the voice, amenorrhoea and minimal breast development.

Young boys undergo precocious puberty, with excess muscle growth, but short stature ("infant Hercules").

The condition is treated with cortisol to suppress ACTH. Occasionally plastic surgical correction of genital abnormalities is required.

ADRENAL FEMINIZATION

Certain adrenal tumours secrete oestrogen and cause precocious puberty in females and feminization (gynaecomastia, testicular atrophy, loss of facial hair) in males. These tumours are usually malignant, and surgical removal is attempted. Recurrence and metastases are common.

INCIDENTALOMA

Diseases of the adrenal gland may be discovered incidentally at autopsy, surgery, or during imaging procedures (usually CT scanning) for other problems.

<u>Adrenal lesions found at autopsy</u>

Malignancy <1%
nodular hyperplasia, adenoma, adenolipoma, cyst, myolipoma, metastases phaeochromocytoma, cortical carcinoma, ganglion neuroma.

Such lesions have been called "incidentalomas". The vast majority are benign, silent and do not affect the patient's life. The discovery of such a lesion requires a balanced approach: if here are features that may suggest a phaeochromocytoma, appropriate investigations should be done. If the lesion is more than 5cms in diameter, an adrenal carcinoma should be excluded.

ADRENAL INSUFFICIENCY

Addison's[3] disease bears the name of the British physician who described it in 1855. The causes include destruction of the gland by Tuberculosis, auto-immune adrenalitis, and metastatic disease. Tuberculosis is the most common cause where this disease is prevalent. The increasing prevalence of AIDS has seen an increase of this condition. Metastatic disease from breast and bronchial cancer, as well as melanoma find adrenal insufficiency a terminal event in these diseases.

Clinical and investigative features

Features are variable and result from mineralocorticoid and glucocorticoid insufficiency. These are fever, nausea, vomiting, severe hypotension and lethargy. Chronic symptoms are more subtle and include fatigue, weight loss, anorexia, nausea, vomiting, abdominal pain and diarrhoea.

Laboratory findings include hyponatraemia, hyperkalaemia, hypoglycaemia and renal failure. There may be eosinophilia, and adrenal calcification may be visible on a radiograph. Low serum levels of cortisol, together with high ACTH levels are diagnostic.

[3] Thomas Addison, London. 1793-1860

Management

The management of an adrenal crisis may be necessary before laboratory confirmation is made. Immediate administration of 4mg dexamethasone, together with intravenous administration of normal saline may be necessary.

Chronic states require glucocorticoid and mineralocorticoid supplementation. (See: *Replacement therapy.*)

OTHER DISEASES

Ganglioneuroma

These are well encapsulated benign tumours, which arise from ganglion cells. Their growth is progressive and slow, reaching a large size. Surgical removal is indicated.

Neuroblastoma

This is one of the most common malignant tumours found in infancy and childhood. Most arise in the adrenal gland, but some may arise at other sympathetic nervous system sites, such as the mediastinum and retroperitoneum. About 75% of these tumours secrete catecholamines. Haematogenous spread occurs to the brain, bone, lung and liver.

Half of the cases occur before the age of two years and most before the age of 10 years. The presenting feature may be a mass in the loin, or in some cases, with metastatic disease.

Investigation includes CT scanning, and estimation of urinary VMA. A metastatic screen of investigations would examine the lung, brain and liver. The treatment is a combined modality one: after surgical removal of the primary, the tumour bed is irradiated, and adjuvant chemotherapy administered (cyclophosphamide, vincristine).

Surgical approaches to the adrenal glands

The investigation and management of diseases of the adrenal gland is complex, difficult and requires special facilities and expertise. Patients with suspected adrenal disorders which require surgery should be referred to specialist centres.

The confirmation of diagnosis requires many special investigations, and relies on biochemical facilities and CT scanning. Where a definite diagnosis has been made, certain preparations must be made prior to surgery: patients with a phaeochromocytoma must have mandatory therapeutic alpha-blockade (phenoxybenzamine) for approximately 10 days, and patients with Conn's and Cushing's syndromes require potassium supplementation.

There are various surgical approaches to the adrenal gland, which are dictated by the disease and the preference of the surgeon.

Adrenalectomy is best performed by *laproscopic* means, unless the neoplasm is large (>8cm) or previous surgery renders access problematic.

Larger neoplasms require laparotomy or occasionally thoraco-abdominal procedures.

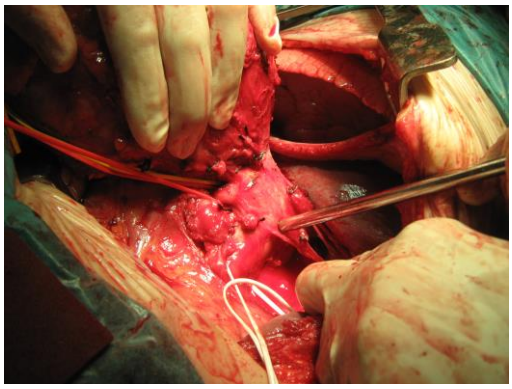


Fig5- R*emoval of a large phaeochromocytoma via a right thoraco-abdominal incision*

Replacement therapy

Replacement therapy is required after bilateral adrenalectomy, or unilateral adrenalectomy for an adrenocortical adenoma. Post operative hydrocortisone sodium succinate (100mg 8hourly intramuscularly) is given until the patient is able to take oral medication. Thereafter the oral dose is tapered down to hydrocortisone 100mg daily in divided doses and fludrocortisone 0.1mg daily. Correct dosage is monitored by serum electrolytes, blood pressure and patient well being.

CARCINOID TUMOURS AND CARCINOID SYNDROME

Carcinoids are an indolent type of neuroendocrine tumor, originating in the *cells of the neuroendocrine system.* They are found anywhere in the GIT, particularly the ileum; carcinoid tumors are the most common malignancy of the appendix, but can also occur in the lung, thymus and ovary. They have the capacity to metastasize and secrete metabolic products- if these bypass the metabolic filter of the liver, as occurs in cases with liver metastases, they have systemic effect and cause a constellation of symptoms typical of a "carcinoid syndrome".

Presentation

Most carcinoids are asymptomatic and are **discovered incidentally** upon surgery for unrelated reasons.

About 10% of carcinoids secrete excessive levels of a range of hormones, most notably serotonin (5-hydroxy-trptophan) and cause a systemic syndrome characterized by flushing, severe diarrhea, wheezing, abdominal cramping and peripheral edema. This constellation of symptoms is called ***carcinoid syndrome***. Episodic flushing is the clinical hallmark of the carcinoid syndrome, and occurs in 85 percent of

patients. The typical flush associated with midgut carcinoids begins suddenly and lasts 20 to 30 seconds. It primarily involves the face, neck and upper chest, which become red to violaceous or purple, and is associated with a mild burning sensation. Severe flushes are accompanied by a fall in blood pressure and rise in pulse rate.

Occasionally they may **bleed** or **obstruct** the small bowel. In the appendix they may precipitate an attack of ***acute appendicitis***.

Approximately 40% of patients develop ***carcinoid heart disease*** is characterized by plaque-like deposits of fibrous tissue. The valves and endocardium of the right side of the heart are most often affected, because inactivation of humoral substances by the lung protects the left heart.

Physiologic	*menopause* *anxiety* *anaphylaxis*
Drugs	*alcohol* *diltiazem* *levo-dopa*
Metabolic	*carcinoid* *phaeochromocytoma* *medullary thyroid carcinoma* *renal cell carcinoma* *endocrine pancreatic tumours*

Table 10- *Causes of flushing*

Diagnosis

Non-functioning tumours are either diagnosed incidentally, or a result of local symptoms of GIT bleeding or bowel obstruction.

When the carcinoid syndrome is suspected, as in other endocrine syndromes, biochemical and endocrine investigations are used to confirm the syndrome, and then imaging tests are done to identify the site of the neoplasm.

The most useful initial diagnostic test for the carcinoid syndrome is to measure *24-hour urinary excretion of 5-hydroxyindoleacetic acid (HIAA), which is the end product of serotonin metabolism*. This test has a sensitivity and specificity of 90 percent for the carcinoid syndrome but requires strict avoidance of foods containing serotonin and tryptophan as well as certain drugs for three days prior to the urine collection. Measurement of urinary 5-HIAA excretion is generally not useful in foregut (gastroduodenal, bronchial) carcinoids, which seldom secrete serotonin and aromatic amino acid decarboxylase.

Serum chromogranin A (CgA) is not a useful screening test for carcinoid syndrome but a normal CgA would mitigate against the presence of a carcinoid tumor.

Once the biochemical diagnosis of the carcinoid syndrome is confirmed, usually by an elevated 24-hour excretion of 5 HIAA, the tumor must be localized. Two techniques, abdominal *computed tomography (CT) and somatostatin receptor scintigraphy (SRS)* have a complementary role.

Treatment

Non-functional carcinoids are resected if large and symptomatic. Small mucosal carcinoids in the stomach can be safely left untreated.

Patients with the *carcinoid syndrome however are complex and challenging and require multi-disciplinary management.*

More than 90 percent of patients with the carcinoid syndrome have metastatic disease, typically involving the liver. Exceptions are bronchial and ovarian carcinoids, which can release hormones directly into the systemic circulation, thereby producing symptoms without metastases.

Carcinoid symptoms are best managed by *somatostatin analog drugs such as octreotide*. These drugs

are however not freely available, and access may be a problem.

Patients with resectable liver metastases should undergo *hepatic resection.* The value of cytoreductive or debulking surgery in symptomatic patients with more advanced unresectable liver metastases is more controversial, and decisions must be individualized. Chemotherapy is of little benefit and is generally not indicated.