Diseases of The Endocrine System:

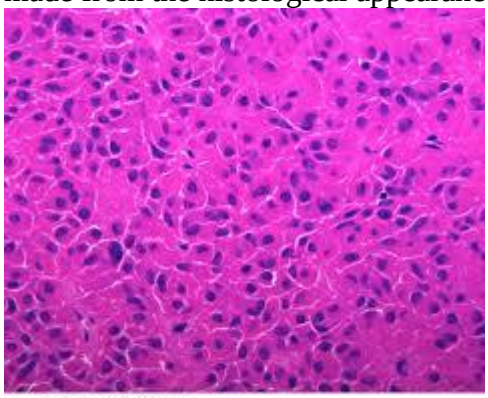
The Pituitary Gland:

Pituitary Adenomas:

Excess production of anterior pituitary hormones is most often caused by the presence of an adenoma. Other less common causes include:

1. Hyperplasias.
2. Carcinomas.
3. Non-pituitary tumours.
4. Certain hypothalamic disorders

Pituitary adenomas could also be non-functional, even causing hypopituitarism due to destruction of the adjacent pituitary gland tissue. Functional pituitary adenomas are usually composed of a single cell type and produce a single predominant hormone (e.g. prolactinomas, somatostatinomas, corticotroph cell adenomas). Adenomas exceeding 1 cm in diameter are called macroadenomas, and < 1 cm are called microadenomas. Grossly appearing as well circumscribed, soft lesions confined to the sells turcica, or extending superiorly into the suprasellar region compressing the optic chiasm. *Invasive adenomas* are seen usually invading the bone, dura and the brain, seen in 30% of cases. Microscopically, adenomas are composed of relatively uniform polygonal cells, arranged in sheets, cords, or papillæ. Mitotic activity is usually scanty. The functional status of the adenoma can not be reliably made from the histological appearance.



Densely granulated adenoma 40x

Hypopituitarism:

May occur with loss or absence of 75% or more of the anterior pituitary parenchyma. This may be congenital or acquired or due to hypothalamic tumours, usually accompanied by posterior pituitary dysfunction (diabetes insipidus). Most cases of hypopituitarism are caused by:

1. Non-secretory pituitary adenomas.

2. Ischæmic necrosis of the pituitary gland: The anterior pituitary tolerates ishæmia well; loss of up to half of the anterior pituitary parenchyma is without clinical consequences. Sheehan's syndrome is the most common form of ischæmic necrosis, developing after delivery, in patients with significant blood loss and shock. Pituitary necrosis may also be encountered in: DIC, sickle cell anæmia, elevated intracranial pressure, traumatic injury and shock.

3. Ablation by surgery or radiation.

4. Empty sella syndrome: caused by chronic herniation of the subarachnoid space into the sella turcica.

5. Inflammatory lesions.
6. Trauma.
7. Metastatic neoplasms.

The Thyroid Gland:

Hyperthyroidism:

Causes:

1. Diffuse hyperplasia of the thyroid (Grave's disease)
2. Iatrogenic.
3. Hyperfunctional multinodular goiter.
4. Follicular adenomas.
5. Thyroiditis.
6. TSH-releasing pituitary adenomas.
7. Ectopic thyroid tissue, in ovarian teratomas.

Hypothyroidism:

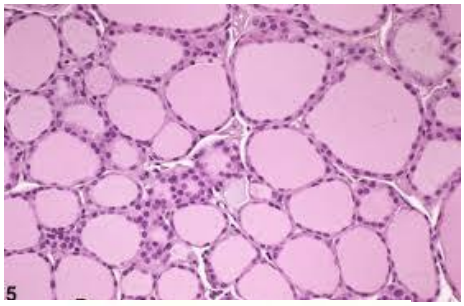
Causes:

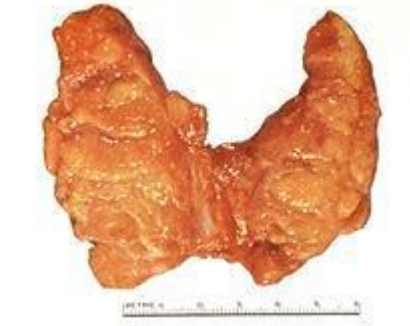
1. Thyroid ablation by surgery or radiation.
2. Hashimoto's thyroiditis.
3. Primary idiopathic hypothyroidism.
4. Iodine deficiency.
5. Dyshormonogenetic goiter.
6. Drugs: Lithium, iodide, p-aminosalicylic acid.
7. Thyroid dysgenesis.

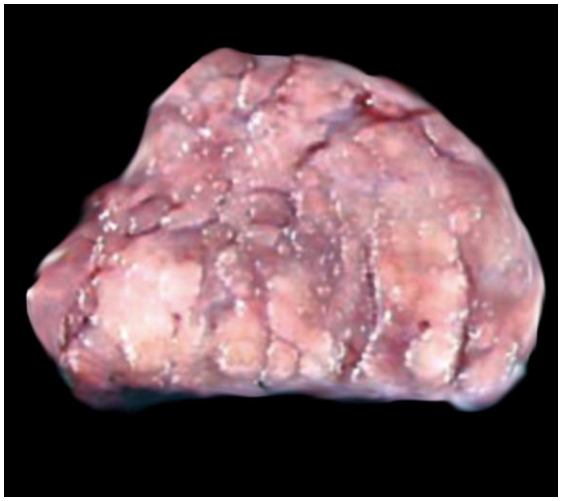
Cretinism refers to hypothyroidism developing in infancy or early childhood. Myxœdema refers to hypothyroidism developing in late childhood or elderly. Measurement of serum TSH is the most sensitive screening test of hypothyroidism.

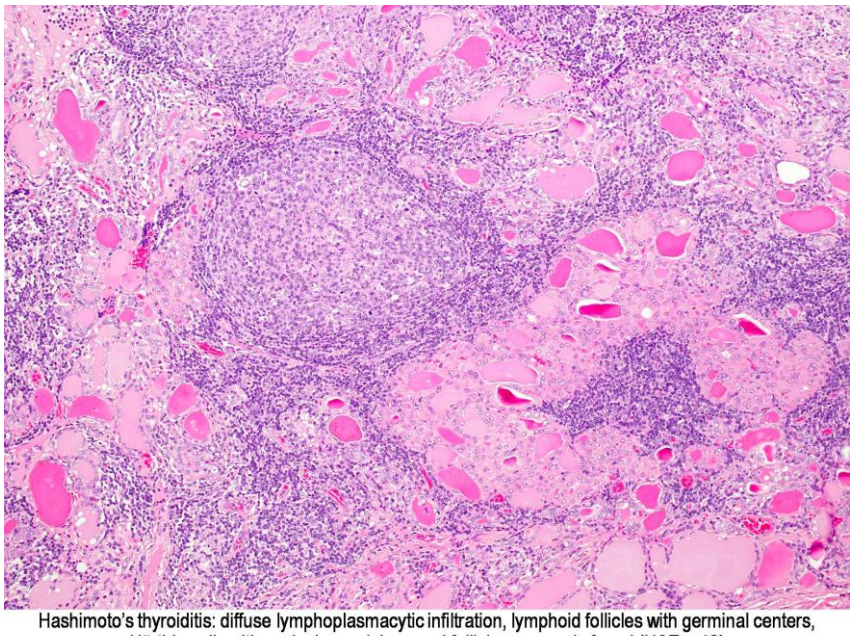
Chronic Lymphocytic (Hashimoto's) Thyroiditis:

- Is characterized by gradual hypothyroidism due to immunologic destruction of thyroid gland, most prevalent between 45-65 years of age, male to female ratio is 1:10, to 1:20. The pathogenesis is immune mediated by CD4+ cell interaction with thyroid antigens, CD8+ mediated cytotoxic cell death and binding of antithyroid antibodies followed by antibody-mediated cytotoxicity. Grossly the thyroid appears diffusely and symmetrically enlarged with pale grey-tan, firm cut surface(Cut surface resembles lymph nodes with tannish yellow color). Microscopically there is widespread mononuclear cell infiltration, with formation of lymphoid follicles showing germinal centers. The thyroid follicles are atrophic lined by epithelial cells having abundant eosinophilic cytoplasm called Hurthle cells or oxyphilic cells. Clinically it is characterized by painless enlargement of thyroid gland. There is a risk of development of non-Hodgkin's lymphoma in longstanding disease.

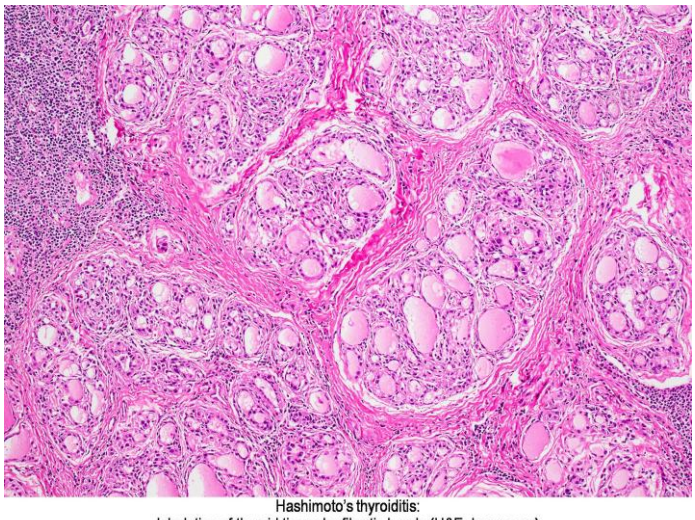








Hashimoto's thyroiditis: diffuse lymphoplasmacytic infiltration, lymphoid follicles with germinal centers, Hürthle cells with vesicular nuclei, normal follicles are rarely found (H&E, ×10)

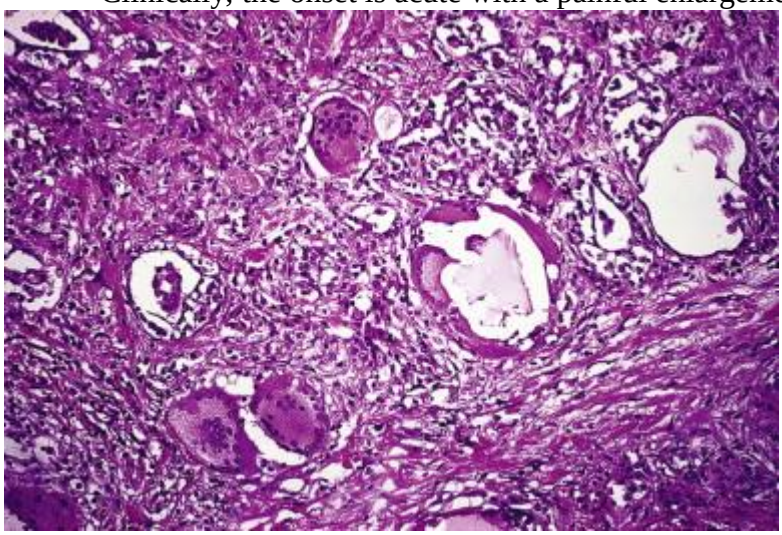


Hashimoto's thyroiditis:
lobulation of thyroid tissue by fibrotic bands (H&E, low power)

Subacute Granulomatous (de Quervian) Thyroiditis:

Is less common than Hashimoto's thyroiditis, most commonly seen between 30-50 years of age, more common in women. It is believed to be caused by viral infection or post-viral inflammatory process. Grossly the gland appears firm with intact capsule. Histologically there is disruption of the thyroid follicles with extravasation of colloid leading to neutrophilic infiltration, replaced later by lymphocytes, plasma cells and macrophages with granulomatous reaction. Healing occurs by resolution and fibrosis.

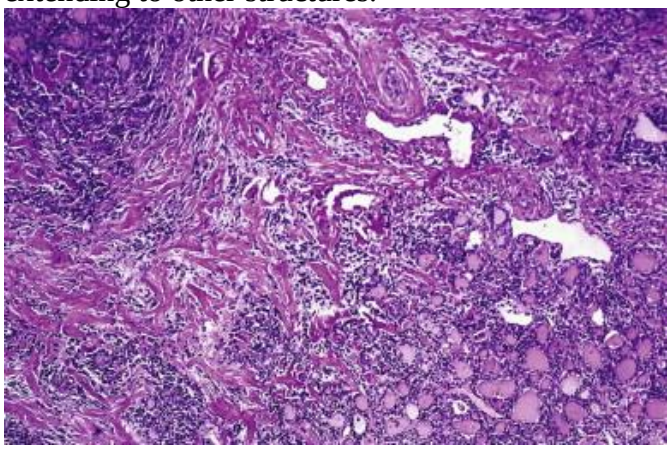
Clinically, the onset is acute with a painful enlargement of the thyroid.



Giant cells, inflammatory cells and destruction of thyroid follicles

Riedel's Thyroiditis:

Is a rare disorder of unknown ætiology, characterized by extensive fibrosis extending to other structures.



Grave's Disease:

Is the most common cause of endogenous hyperthyroidism, characterized by:

1. Thyrotoxicosis caused by diffuse enlargement of hyperfuctional thyroid.
2. Infiltrative ophthalmopathy, resulting in exophthalmous.
3. Localized infiltrative dermopathy designated as pretibial myxœdema.

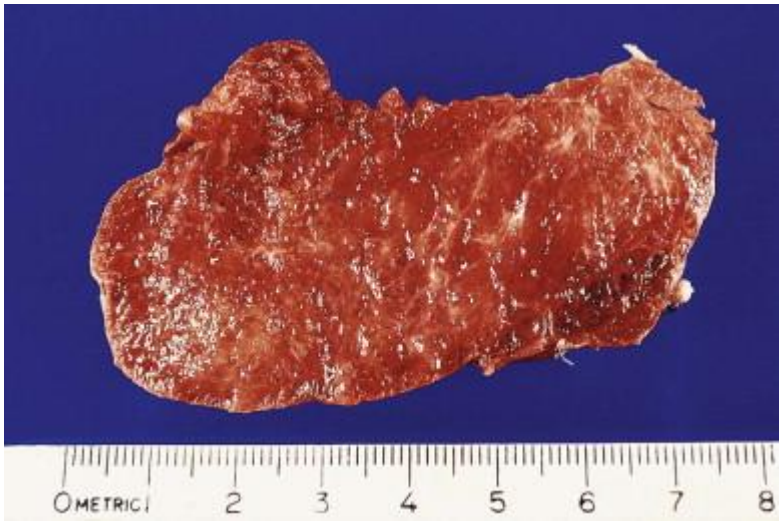
The peak incidence is between 20-40 years. Male to female ratio is 1:7, with a genetic predisposition. It is an autoimmune disorder with a variety of antibodies including:

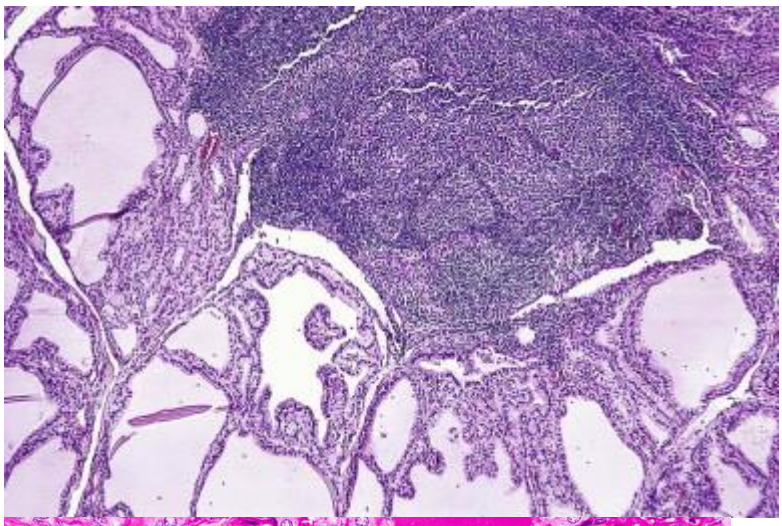
1. Thyroid stimulating IgG: Binds to TSH receptor and mimics the action of TSH.
2. Thyroid growth stimulating Igs. (TGIs): implicated in the proliferation of thyroid follicular cells.
3. TSH-binding inhibitor Igs (TBII): Prevent TSH from binding normally to its receptor, preventing TSH from action.

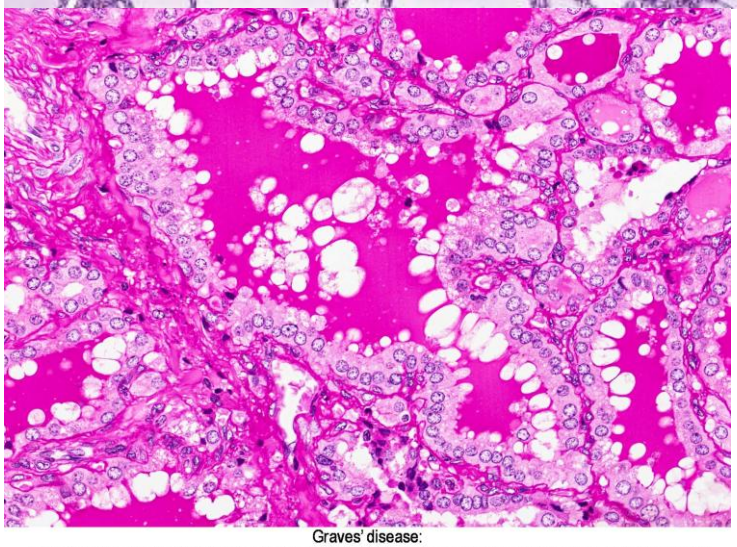
Grave's ophthlamopathy is caused by increased volume of retrobulbar tissue by: 1. Infiltration by mononuclear cells mainly T cells. 2. Œdema of extraoccular muscles. 3. Accumulation of extracellular matrix components. 4. Increased number of adipocytes.

Some times Hashimoto's thyroiditis precedes Grave's disease in a condition known as hashitoxicosis.

Grossly, the thyroid is diffusely enlarged. Microscopically, the thyroid is hypertrophic and hyperplastic, with tall columnar lining follicular cells, often with pseudopapillary structures.







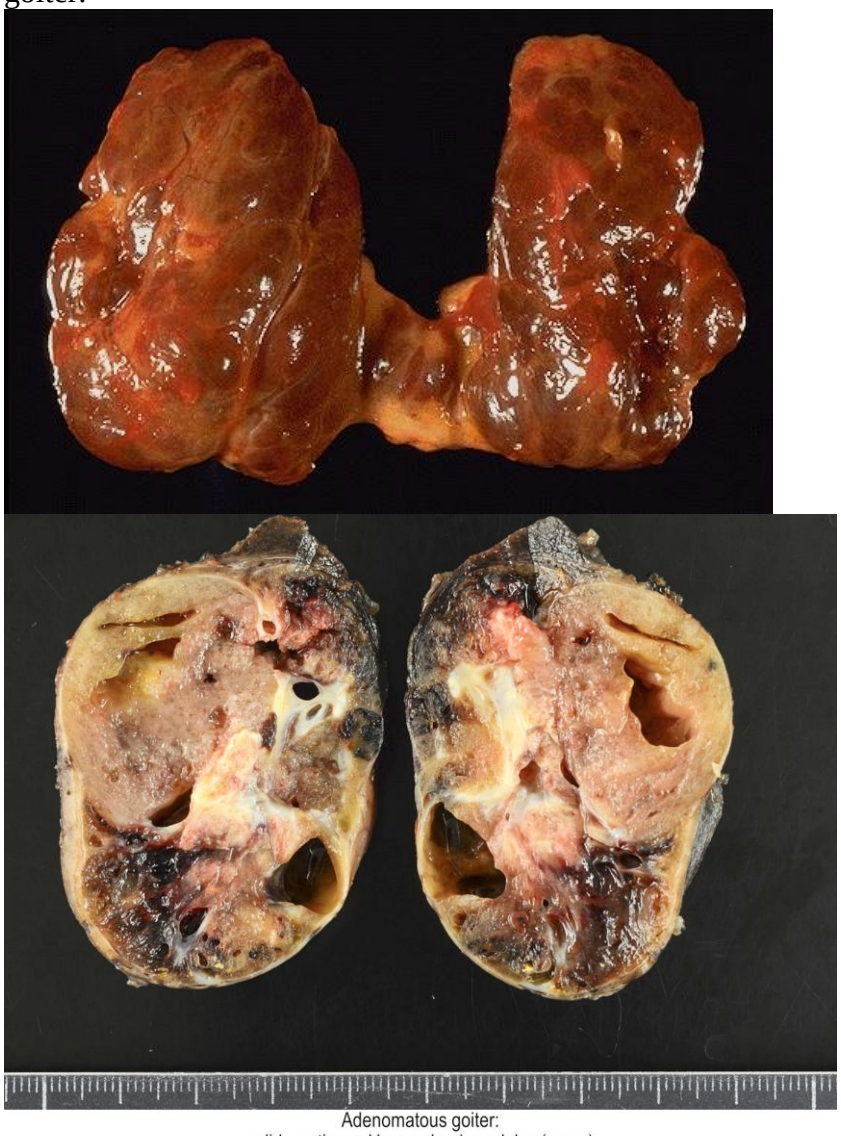
Graves' disease:
active tall epithelium with light vacuolated cytoplasm, numerous colloid resorption droplets (PAS-D, ×40)

Multinodular Goiter:

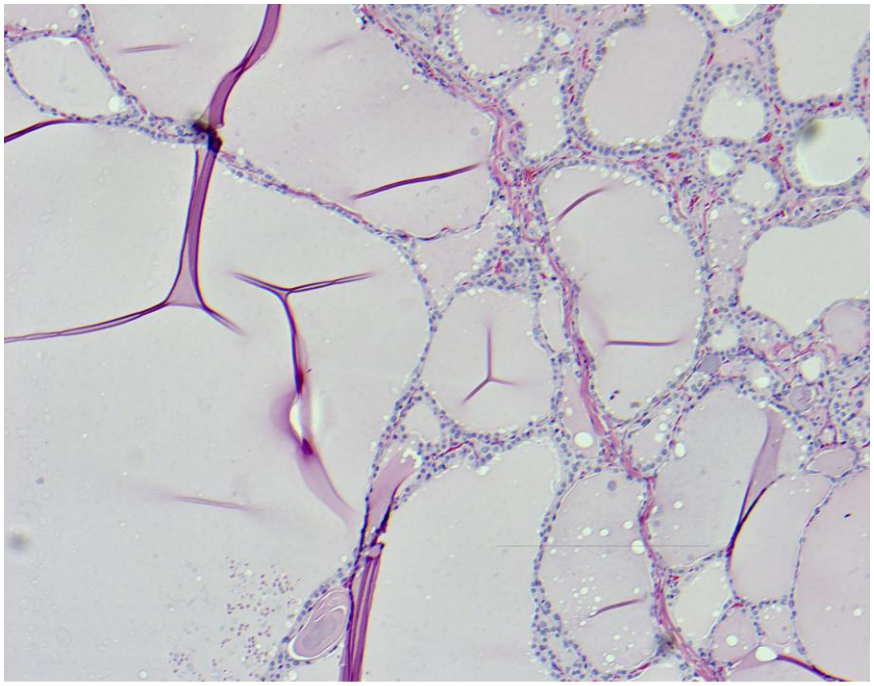
Is the most common manifestation of thyroid disease, reflecting impaired synthesis of thyroid hormones, often caused by dietary deficiency of iodine. Endemic goiter occurs in geographic locations where soil, food and water supplies contain little iodine, and occurs in more than 10% of the population, common in mountainous areas

of the world. Sporadic goiter occur much less commonly, with a peak incidence in puberty and late adult life.

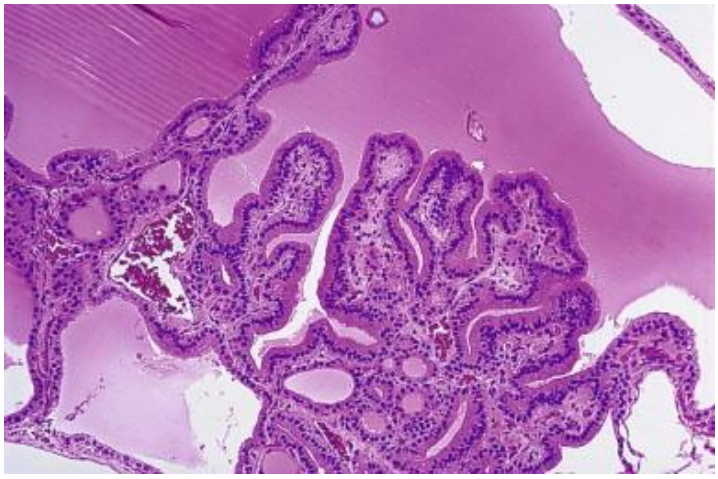
In early cases there is diffuse enlargement of the thyroid, induced by increased TSH levels. If the dietary supplies increase with iodine, the hyperplasia will decrease forming enlarged colloid rich glands (colloid goiter). With time, recurrent episodes of hyperplasia combine to produce a more irregular enlargement called multinodular goiter.



Adenomatous goiter:
solid, cystic, and hemorrhagic nodules (gross)



Variable sized dilated follicles with flattened hyperplastic epithelium

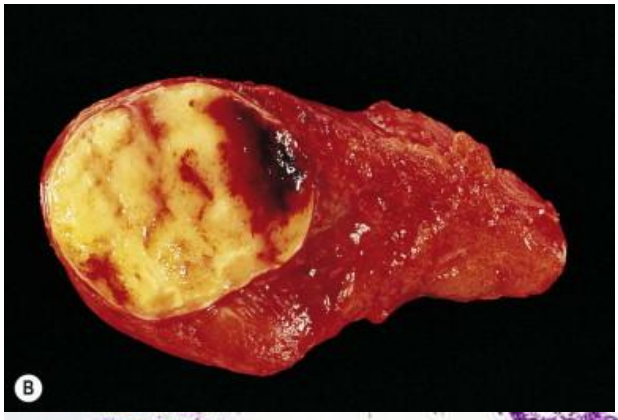


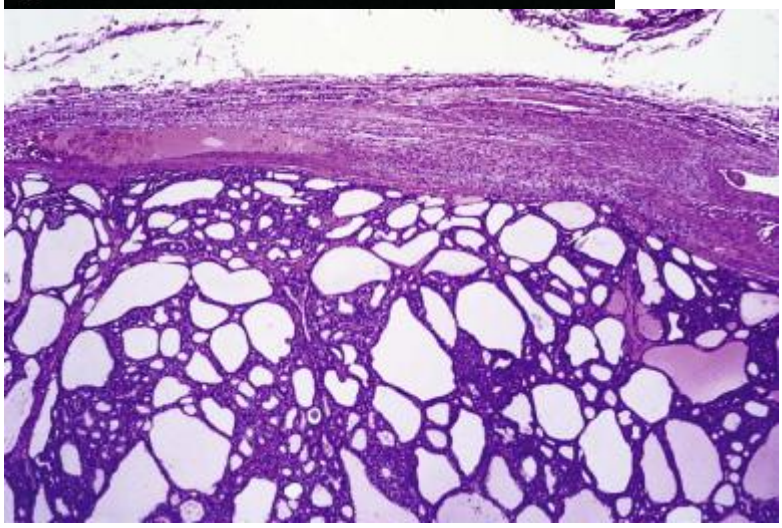
Neoplasms of The Thyroid:

Carcinomas of the thyroid are less common than benign enlargement accounting for <1% of goiters.

Adenomas:

Are benign neoplasms derived from follicular epithelium, usually solitary, spherical, compressing adjacent non-neoplastic thyroid, completely surrounded by a well defined intact capsule.



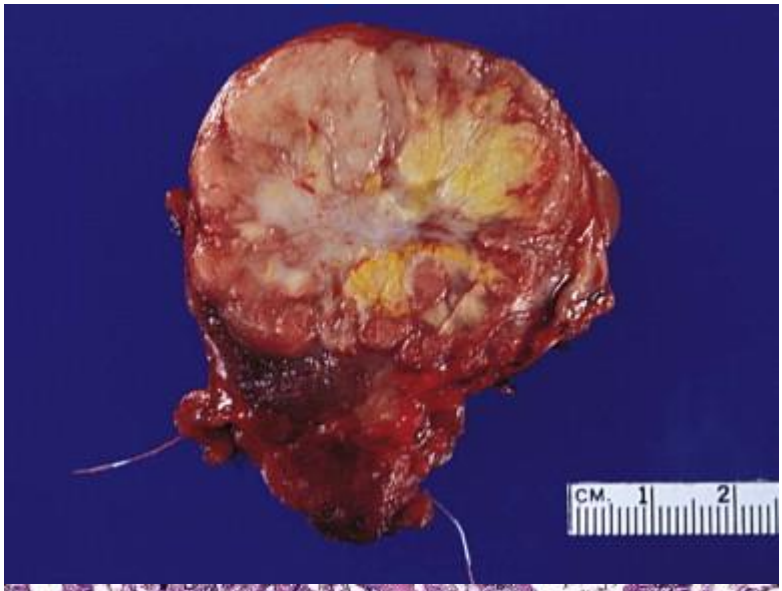


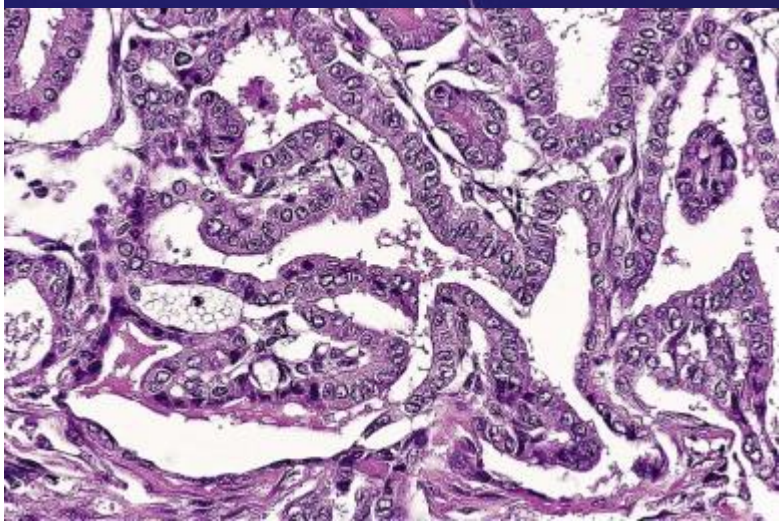
Carcinomas:

- Papillary carcinoma: 75-85%.
- Follicular carcinoma: 10-20%.
- Medullary carcinoma: 5%.
- Anaplastic carcinoma: <5%. But 40% of thyroid cancer death.
- Poorly differentiated thyroid carcinoma less than 5%

Most carcinomas are derived from follicular epithelium except for medullary carcinoma which is derived from C-cells.

Papillary Carcinoma: May occur at any age, associated with a history of previous exposure to ionizing radiation. It may be solitary or multifocal. In some cases, the tumour is well circumscribed and encapsulated, most are infiltrative. Cut section is granular white with papillary structures. Microscopically appears having papillary structures lined by follicular cells with irregular cleaved nuclei with groundglass appearance.





Papillary thyroid carcinoma with Orphan Annie eye nuclei:
optically clear (empty, ground-glass) nuclei with thick nuclear membrane (H&E, ×40)

Adrenal Gland Diseases:

Adrenal Cortex:

Cushing's Syndrome:

Most cases of Cushing's syndrome are caused by the administration of corticosteroids. The remaining cases are caused by:

1. Primary hypothalamic-pituitary diseases causing hypersecretion of ACTH (Cushing's disease): Is the most common cause of endogenous Cushing's syndrome

(>50%). M:F ratio is 1:5, most frequently caused by a small pituitary adenoma, or corticotroph cell hyperplasia of the anterior pituitary gland. Both situations cause nodular cortical hyperplasia of the adrenal gland.

2. Primary adrenocortical hyperplasia or neoplasia: 15-30% of cases (adrenal Cushing's syndrome), most commonly caused by adrenocortical tumours (adenomas or carcinomas) and less commonly by adrenocortical hyperplasia.

3. Ectopic ACTH secretion by non-endocrine neoplasms: Mostly by small cell carcinoma of the lung, others include carcinoid tumour, medullary carcinoma of the thyroid and islet cell tumours of the pancreas.

The laboratory diagnosis of Cushing's syndrome is made by: 1. Increased 24 hours urinary free cortisol level. 2. Loss of the normal diurnal pattern of cortisol secretion.

Hyperaldosteronism:

Causes sodium retention and potassium excretion, with hypertention and hypokalæmia. Secondary hyperaldosteronism is associated with activation of the renin-angiotensin system, encountered in congestive heart failure, decreased renal perfusion, hypoalbuminæmia and pregnancy. Primary hyperaldosteronism is caused adrenocortical neoplasms (80%) or hyperplasia (15%), and is characterized by decreased serum renin.

Adrenogenital Syndromes:

Virilization may be caused by:

1. Primary gonadal disorders.
2. Primary adrenal neoplasms: more likely to be carcinomas.
3. Congenital adrenal hyperplasia: Is a group of autosomal recessive disorders each is characterized by a hereditary defect in an enzyme involved in cortisol biosynthesis, resulting in decreased cortisol and increased ACTH with resultant adrenal hyperplasia, with increased levels of cortisol precursor steroids that have virilizing effects. The most common enzymatic defect is 21-hydroxylase.

Chronic Adrenocortical Insufficiency (Addison's Disease):

Appears after progressive destruction of around 90% of adrenal cortex. Causes:

1. Autoimmune adrenalitis (60-70%): In about half of patients occurs without involvement of other glands, the rest half is associated with other autoimmune diseases such as Hashimoto's thyroiditis, pernicious anæmia, Type I DM and hypoparathyroidism.

2. Infections: By tuberculosis and fungal infection (Histoplasma capsulatum).

3. Metastatic neoplasms: Mostly by carcinomas of the lung and breast.

Acute Adrenocortical Insufficiency:

Causes:

1. Massive adrenal hæmorrhage: a. Birth trauma. b. Anticoagulant therapy. c. DIC. d. Pregnancy. e. Sepsis (Waterhouse-Frederichsen syndrome).

2. Sudden withdrawal of long term steroid therapy.

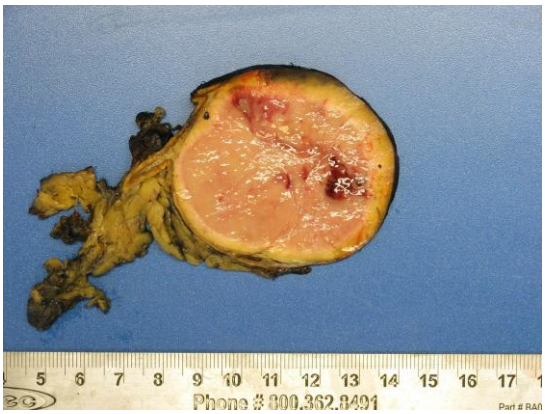
3. Stress in patients with underlying chronic adrenal insufficiency.

Adrenal Tumours:

Adrenocortical adenomas tend to be small and non-functioning, while carcinomas are large, functional tumours, occurs at any age, the median survival is 2 years.

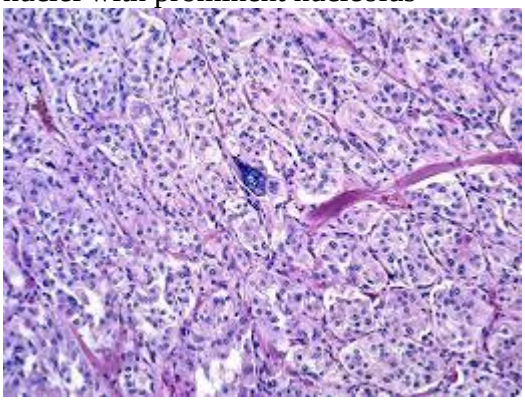
Phæochromocytoma: Is a tumour of the adrenal medulla, only around 10% of tumours are malignant, 10% metastasize, 10% arise elsewhere out of the adrenal, 10% arise associated with MEN.

- Varies from small, circumscribed to large, hemorrhagic and necrotic (1g to 4 kg) .Small tumors have rim of compressed adrenal gland .Lobulated, yellow-red-brown



Microscopically:

- Zellballen (small nests or alveolar pattern), trabecular or solid patterns of polygonal / spindle shaped cells in rich vascular network
- Cells have finely granular basophilic or amphophilic cytoplasm .Round / oval nuclei with prominent nucleolus



Multiple Endocrine Neoplasia Syndromes:

MEN I (Werner's Syndrome): Pituitary adenomas, parathyroid hyperplasia or adenomas, pancreatic tumours, adrenocortical hyperplasia and C-cell hyperplasia of the thyroid.

MEN IIa (Sipple's Syndrome): Parathyroid hyperplasia, phæochromocytoma, medullary carcinoma of the thyroid.

MEN IIb or III: Phæochromocytoma, medullary carcinoma of the thyroid, ganglioneuromas and a Marfanoid habitus.

Pancreas

Neuroendocrine neoplasms

- Can be either well differentiated tumors or poorly differentiated carcinomas
- Functional tumors are associated with elevated serum hormone levels and are associated with a clinical hormonal syndrome
- Nonfunctional tumors are not associated with a clinical hormonal syndrome but may still be associated with elevated serum hormone levels or tissue hormone expression on immunohistochemistry
- tumors which are < 0.5 cm are termed "pancreatic neuroendocrine microadenomas

Clinical features

- Nonfunctional tumors are encountered incidentally and are usually larger at time of diagnosis
- Local obstruction / mass effect, if located in the pancreatic head
- Clinical hormonal syndromes in functioning tumors

- Insulinoma:
  - Most common functioning pancreatic neuroendocrine tumor
  - Insulin secretion
  - Hypoglycemic syndrome
  - Solitary tumor < 2 cm
  - 5 - 10% of insulinomas are associated with MEN1 and are usually multiple
  - Benign in 90%

- Gastrinoma:
  - Second most common functioning pancreatic neuroendocrine tumor
  - Gastrin secretion
  - Zollinger-Ellison syndrome (peptic ulcers, gastroesophageal reflux, diarrhea)
  - "Gastrinoma triangle" (common bile duct, duodenum, pancreatic head)
  - Duodenum affected more than pancreas
  - 20 - 30% of gastrinomas are associated with MEN1
  - Malignant in 80%

- Glucagonoma:
  - 4Ds: diabetes, dermatitis (necrolytic migratory erythema), deep vein thrombosis, depression
  - Solitary, large
  - Tail > head
  - > 50% have metastasis at presentation

- VIPoma:
  - watery diarrhea, hypokalemia, achlorhydria / hypochlorhydria
  - Solitary, large
  - Tail > head

- Somatostatinoma:
  - Diabetes mellitus, diarrhea or steatorrhea, anemia, malabsorption, cholelithiasis

    - Very rare
    - Solitary, large
    - > 50% have metastasis at presentation

- Ectopic hormone producing neuroendocrine tumor:
    - ACTH (Cushing syndrome), serotonin, growth hormone
    - Usually malignant
    - Solitary, large

Gross description

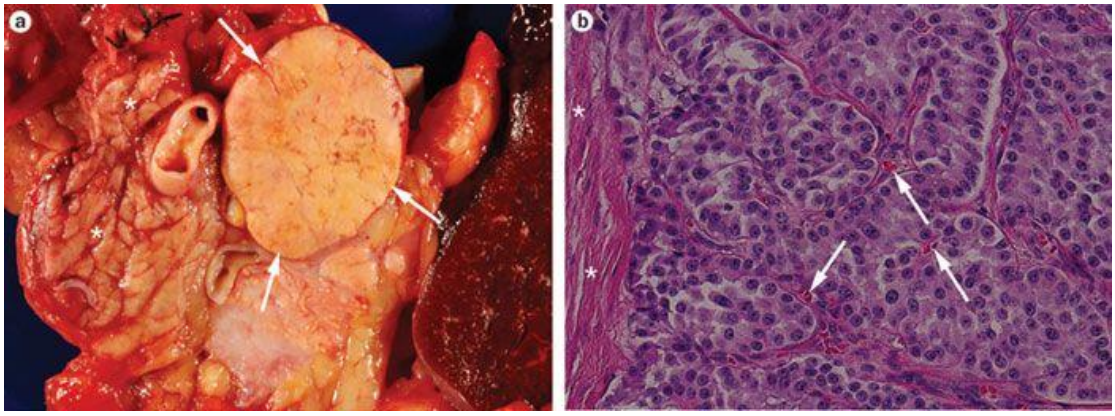
- Firm, commonly well circumscribed, homogeneous
- Tumors may have a cystic component
- Color varies according to the degree of vascularity and amount of stroma and ranges from white to pink to tan to brown; may be yellow if necrosis present
- "Pigmented black pancreatic neuroendocrine tumor" is composed of intracytoplasmic lipfuscin and mimics metastatic melanoma
- "Lipid rich" pancreatic neuroendocrine tumor mimics adrenal cortical neoplasia
- Features of malignancy: invasion of fibroadipose tissue (as satellite nodules), invasion of adjacent organs, invasion of large vessels

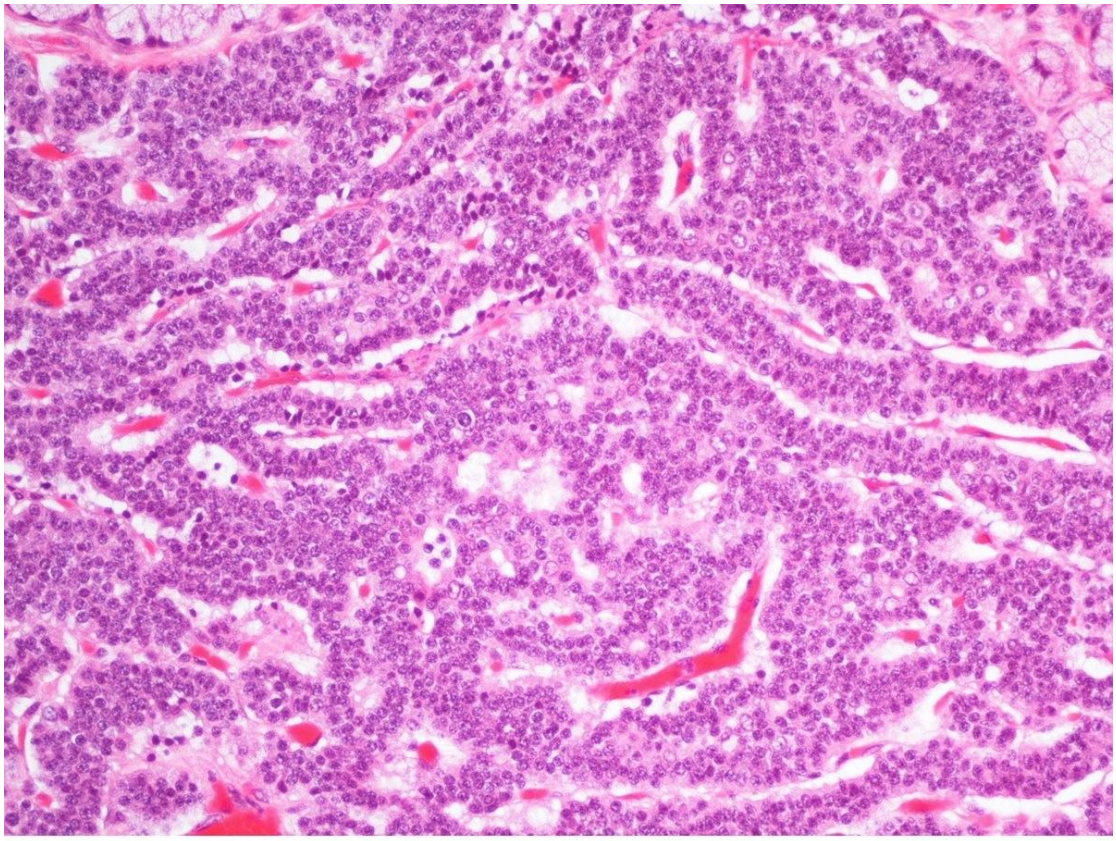
Microscopic (histologic) description

- Well differentiated neuroendocrine tumors:
    - Organoid architecture: solid nests, trabeculae, cords, cribriform
    - Small to medium cells with eosinophilic to amphophilic and finely granular cytoplasm; nuclei are uniform, central, round / oval, with "salt and pepper" (finely stippled) chromatin
    - Rich vascular network
    - Amyloid deposition in insulinomas
    - Psammoma bodies in somatostatinomas

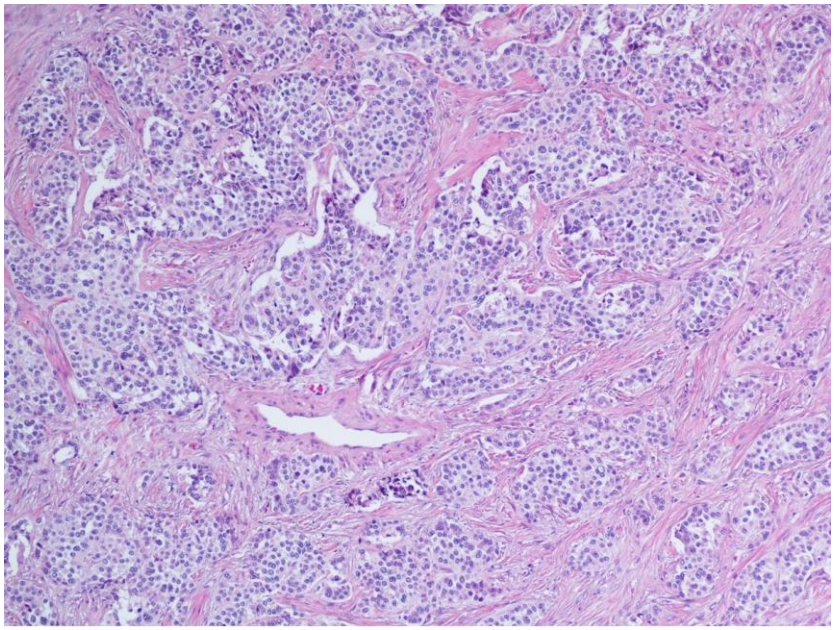
- Poorly differentiated neuroendocrine carcinomas:
    - Sheets or nests of atypical cells with pleomorphic, hyperchromatic nuclei and abundant mitotic figures
    - "Salt and pepper" chromatin is lost
    - Necrosis often present
    - May be small cell (molding nuclei, scant cytoplasm) or large cell (abundant amphophilic cytoplasm; may also have visible nucleoli)

Placing a given tumor into one of these categories depends on well-defined histological features: **size, lymphovascular invasion, mitotic counts, Ki-67 labelling index, invasion of adjacent organs, presence of metastases and whether they produce hormones**


a
b



Neuroendocrine duodenal spread from same pancreatic neuroendocrine tumor



Organoid/nested morphology