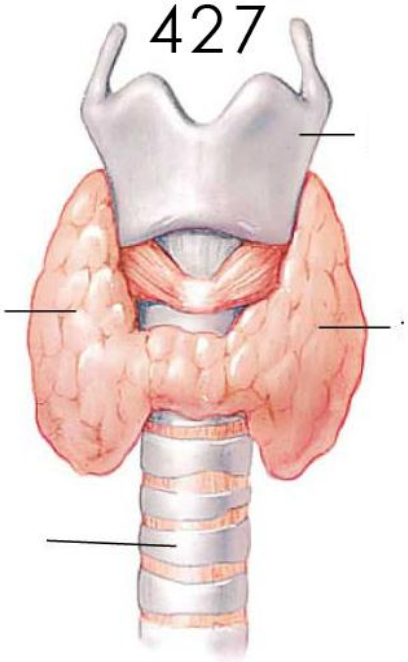
KSU 427 College of Medicine

Pathology

Endocrine System

:: Done By ::

PaThOlOgY TeAm 427



In the name of ALLAH, the Most Gracious, the Most Merciful

brothers and sisters,
the "PATHOLOGY TEAM" is proud to present "ENDOCRINE PATHOLOGY" .

hope that u find it helpful, and hope that u get full marks.
thanks to our fans, our team members and, special thanks to those who worked on this project (see credits ^^).

plz, give us your prayers. :)

credits

	Done By	Revised by
thyroid part	meshal_s	مازن العمرو
adrenal part	سعد العييد	`im lonly & صالح المطلق
diabetes mellitus part	عادل الأحيدب	i`m lonly

Page stylist : Dafoor Mo3aser

Head of Pathology Team ..... AZK

Hyperthyroidism

-Thyrotoxicosis is a hypermetabolic state caused by elevated circulating levels of free T_3 and T_4.

-Because thyrotoxicosis is caused most commonly by HYPERFUNCTION of the thyroid gland, it is often referred to as HYPERTHYROIDISM.

-In certain conditions the oversupply is related either to excessive release of preformed thyroid hormone (e.g., in thyroiditis) or to an extra-thyroidal source, rather than to hyperfunction of the gland.

Table 20-2. Cause of Thyrotoxicosis

Associated with Hyperthyroidism
PRIMARY
Diffuse toxic hyperplasia (Graves disease)
Hyperfunctioning ("toxic") multinodular goiter
Hyperfunctioning ("toxic") adenoma
SECONDARY
TSH-secreting pituitary adenoma (rare)*
Not Associated with Hyperthyroidism
Subacute granulomatous thyroiditis (*painful*)
Subacute lymphocytic thyroiditis (*painless*)
Struma ovarii (ovarian teratoma with thyroid)
Factitious thyrotoxicosis (exogenous thyroxine intake)

*Associated with increased TSH; *all other causes of thyrotoxicosis associated with decreased TSH.*
TSH, Thyroid-stimulating hormone.

The clinical manifestations:

Include changes referable to the *hypermetabolic state* induced by excessive amounts of thyroid hormone as well as those related to *overactivity of the sympathetic nervous system*.

A- Constitutional symptoms:

-The skin: soft, warm, and flushed

- *Heat intolerance* and excessive sweating are common.

- *Weight loss despite increased appetite* due to increased sympathetic activity and hypermetabolism.

B- Gastrointestinal:

- hypermotility, malabsorption, and diarrhea due to Stimulation of the gut.

C- Cardiac:

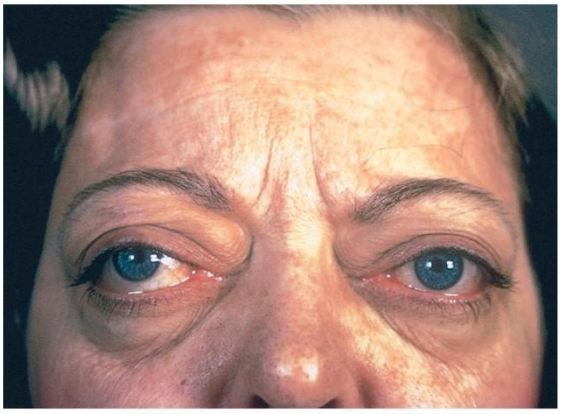
- Palpitations and tachycardia are common.
- Congestive heart failure may in elderly patients due to aggravation of preexisting heart disease.

D- Neuromuscular:

- Nervousness, tremor, and irritability are frequent.
- Nearly 50% develop proximal muscle weakness *(thyroid myopathy).*

E- Ocular manifestations:

- A wide, staring gaze and lid lag are present because of sympathetic overstimulation of the levator palpebrae superioris.



- However, true *thyroid ophthalmopathy* associated with proptosis is a feature seen only in Graves disease.

F- Thyroid storm:

- It is a medical emergency caused by severe hyperthyroidism.
- This condition occurs most commonly in individuals with underlying Graves disease, probably resulting from an acute elevation in catecholamine levels, as might be encountered during stress.
- Untreated patients die of cardiac arrhythmias.

G- Apathetic hyperthyroidism:

- Thyrotoxicosis occurring in the elderly.
-With various co-morbidities may blunt the typical features of thyroid hormone excess seen in younger patients.

The diagnosis of hyperthyroidism is based on:

1- Clinical features:

- Unexplained weight loss or worsening cardiovascular disease etc...

2- Laboratory data:

-The diagnosis of thyrotoxicosis has been confirmed by a combination of TSH, free thyroid hormone assays and measurement of radioactive iodine uptake by the thyroid gland

.

A - TSH (Thyroid Stimulating Hormon):

- the most useful single screening test for hyperthyroidism.
- TSH levels are decreased even at the earliest stages, when the disease may still be subclinical,
- TSH levels may normal or raised in rare cases of pituitary- or hypothalamus-associated (secondary) hyperthyroidism.
- A low TSH value is usually associated with increased levels of free T_4.

B - T_3:

- In an occasional person, hyperthyroidism results predominantly from increased circulating levels of T_3 (T_3toxicosis). In these cases free T_4 levels may be decreased so, direct measurement of serum T_3 may be useful.

C - Radioactive iodine:

- Valuable in determining the etiology:

I- Graves disease: increased uptake diffusely in the whole gland.
II- Toxic adenoma: increased uptake in solitary (isolated) nodule.
III- Thyroiditis: decreased uptake.

Chronic Lymphocytic (Hashimoto) Thyroiditis

- *The most common cause of hypothyroidism if iodine levels are sufficient.*
- So, NO iodine deficiency.
- It is characterized by gradual thyroid failure because of autoimmune destruction of the thyroid gland.
- This disorder is most prevalent between 45 and 65 years of age and is more common in women than in men, with a female predominance of 10 : 1 to 20 : 1.
- Although it is primarily a disease of older women, it can occur in children and is a major cause of nonendemic goiter in children.

-Pathogenesis

- Progressive depletion of thyroid epithelial cells (thyrocytes).
- Gradually replaced by mononuclear cell infiltration and fibrosis.
- Multiple immunologic mechanisms may contribute to the death of thyrocytes.
- Sensitization of autoreactive CD4+ T-helper cells to thyroid antigens is *The initiating event.*

- The effector mechanisms include:

A-Thyrocyte Injury:

The possible reaction of CD4+ T cells to thyroid antigens, thus producing cytokines-notably interferon γ (IFN-γ)-which promote inflammation and activate macrophages, as in delayed-type hypersensitivity reactions. Injury to the thyroid results from the toxic products of inflammatory cells

.

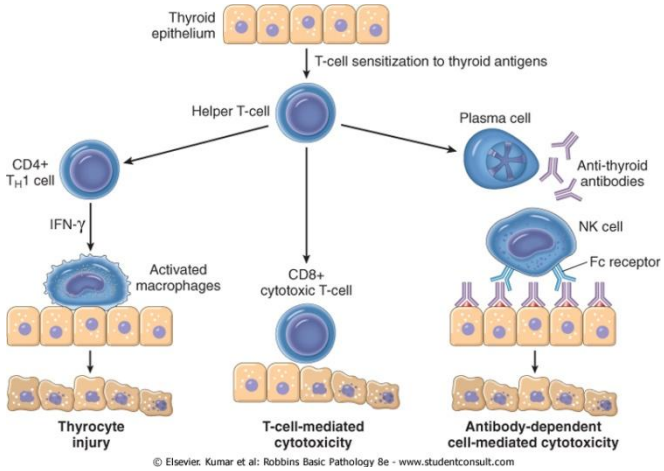
B-T cell mediated cytotoxicity:

CD8+ cytotoxic T cells may recognize antigens on thyroid cells and kill these cells.

C- antibody-dependent cell-mediated cytotoxicity:

mediated by natural killer (NK), the importance of this mechanism is not proved.

-NOTE FOR THE FIGURE:
Pathogenesis of Hashimoto thyroiditis. Sensitization of autoreactive CD4+ helper T cells to thyroid antigens seems to be the initiating event for all proposed mechanisms of thyroid cell death. Sensitized CD4+ helper T cells then either differentiate into T_H1 cells with resulting delayed-type hypersensitivity reaction, or stimulate cytotoxic T-cell responses and help B cells (not shown) to develop into antibody-secreting plasma cells.



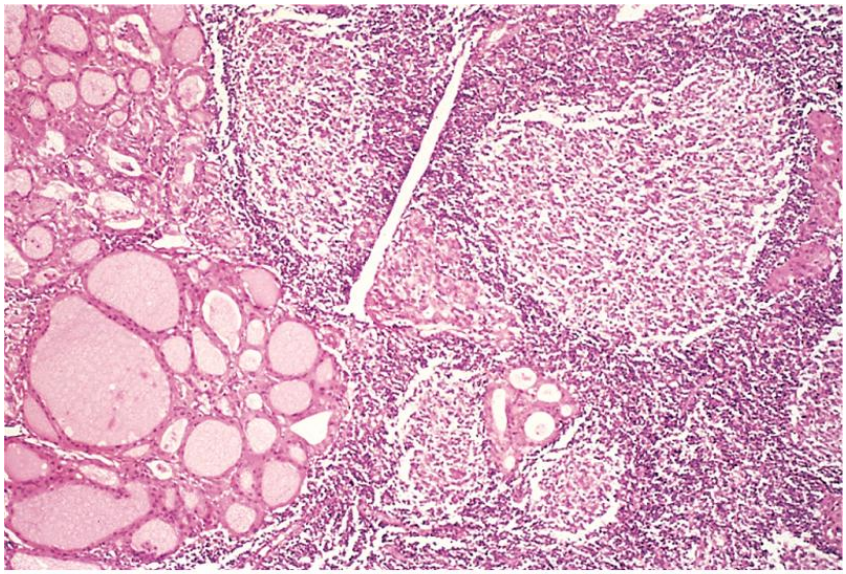
-Morphology:

A- Grossly:

- The thyroid is usually diffusely and symmetrically enlarged, although more localized enlargement may be seen in some cases.
- The capsule is intact, and the gland is well demarcated from adjacent structures.
- The cut surface is pale, gray-tan, firm, and somewhat friable.
- Less commonly, the thyroid is small and atrophic as a result of more extensive fibrosis (fibrosing variant)
- The fibrosis does NOT extend beyond the capsule of the gland.

B- Microscopically:

- Widespread infiltration of the parenchyma by a mononuclear inflammatory infiltrate.
- Containing small lymphocytes, plasma cells, and well-developed germinal centers.
- The thyroid follicles are atrophic,
- and are lined in many areas by epithelial cells distinguished by the presence of abundant eosinophilic, granular cytoplasm, termed Hürthle, or oxyphil, cells.



-NOTE FOR THE FIGURE:
Photomicrograph of Hashimoto thyroiditis. The thyroid parenchyma contains a dense lymphocytic infiltrate with germinal centers. Residual thyroid follicles lined by deeply eosinophilic Hürthle cells are also seen.

Clinical Features:

- *Painless enlargement of the thyroid.*
- *Usually associated with some degree of hypothyroidism.*
- The enlargement of the gland is usually symmetric and diffuse.

- But in some cases it may be sufficiently localized to raise a suspicion of neoplasm.
- the usual clinical course, hypothyroidism develops Gradually.
- But in some cases, however, it *may be preceded by transient thyrotoxicosis* caused by disruption of thyroid follicles, with secondary release of thyroid hormones ("hashitoxicosis").
- hashitoxicosis (a transient hyperthyroidism) is followed by decreasing levels of T3 & T4 accompanied by a compensatory increase in TSH (these effects are produced as hypothyroidism supervenes)
- Patients with Hashimoto thyroiditis often have *other autoimmune diseases* and are at *increased risk for the development of B-cell non-Hodgkin lymphomas*
- There is no established risk for developing thyroid epithelial neoplasms.

Carcinomas

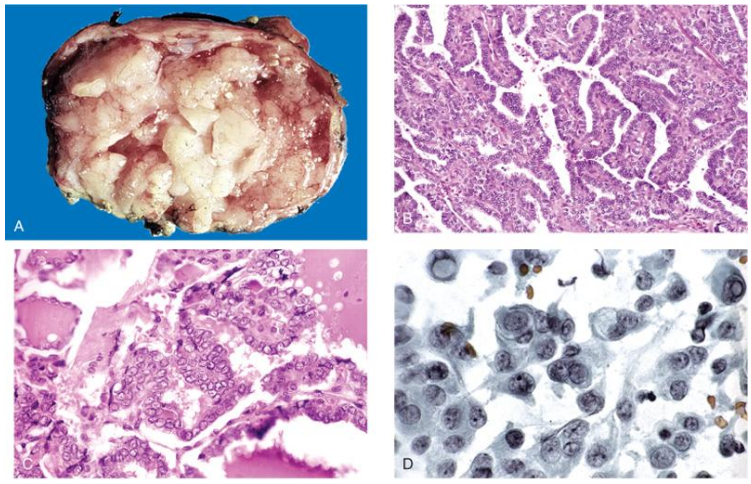
- It is not unusual to detect a microscopic (*clinically silent*) tumor as an incidental finding at autopsy.
-occur more in adults (female more than male).
-But some forms, particularly papillary carcinomas, may present in childhood (equally♀&♂).
-And in late adult life (equally♀&♂).
-All are derived from the follicular epithelium, except for medullary carcinomas which is from the parafollicular, or C, cells.
-The major subtypes of papillary carcinomas are:

1- Papillary Carcinoma:

~ The most common form of thyroid cancer.
~ Occurs at any age.
~ Associated with previous exposure to ionizing radiation.

- Morphology:

- *Grossly*
  - May present as solitary or multifocal lesions within the thyroid.
  - May be well circumscribed and even encapsulated OR
  - They can infiltrate adjacent parenchyma with ill-defined margins.
  - The lesions may contain areas of fibrosis and calcification and are often cystic.
  - On the cut surface, they may appear granular and may sometimes contain grossly discernible papillary foci. (Fig. below "A")



- *Microscopically:*
  - µ The definitive diagnosis of papillary carcinoma can be made only after microscopic examination.
  - µ the diagnosis of papillary carcinoma is based on nuclear features even in the absence of a papillary architecture.
  - µ "ground-glass" or "Orphan Annie eye" nuclei (fig. above C,D) due to that it contains very finely dispersed chromatin, which imparts an optically clear appearance.
  - µ pseudo-inclusions , from the invaginations of the cytoplasm which may give the appearance of intranuclear inclusions in cross-sections.
  - µ A papillary architecture is present in many cases (Fig. above B).
  - µ Follicular variants are seen when the tumor contain follicles & behave biologically as papillary carcinoma by forming the nuclear features.
  - µ The papillae of papillary carcinoma differ from hyperplastic ones in:
  - µ Psammoma bodies, a characteristic feature in the neoplastic papillae
  - µ Dense fibrovascular cores, which are found in papillary carcinoma.
  - µ Foci of lymphatic permeation by tumor are often present.
  - µ But invasion of blood vessels is relatively uncommon, particularly in smaller lesions.
  - µ Metastases to adjacent cervical lymph nodes are estimated to occur in about half of cases.

Clinical Features:

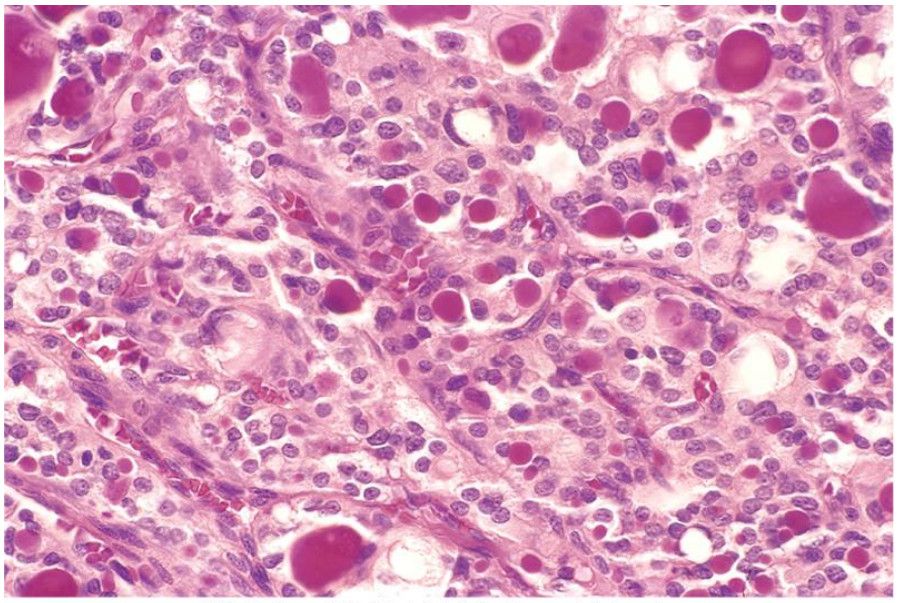
- ° Painless mass in the neck, either within the thyroid or as metastasis in a cervical lymph node.
- ° The presence of isolated cervical nodal metastases does not influence a good prognosis of these lesions.
- ° In minority of patients, Hematogenous metastases are present at the time of diagnosis, most commonly to the lung.
- ° Papillary carcinomas are indolent lesions, with 10-year survival rates in excess of 95%.

2-Follicular Carcinoma:

§ The second most common form of thyroid cancer.
§ They usually present at an older age than do papillary carcinomas, with a peak incidence in the middle adult years.
§ Increased in areas of dietary iodine deficiency.
§ Nodular goiter may predispose to the development of the neoplasm.
§ The high frequency of *RAS* mutations in follicular adenomas and carcinomas suggests that they may be related tumors.

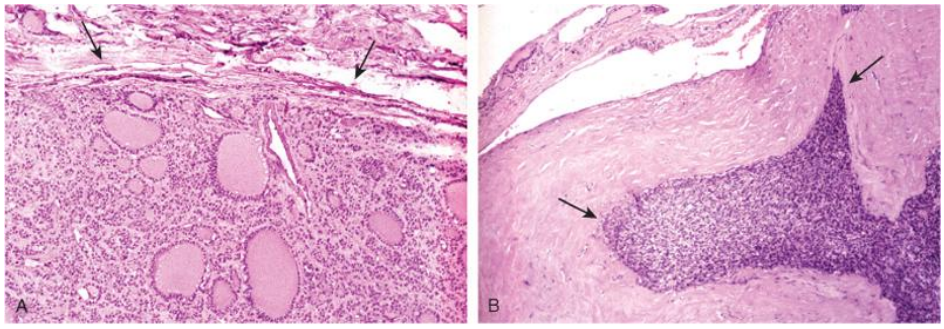
Morphology:

- *Microscopically:*
  - µ Composed of fairly uniform cells forming small follicles.
  - µ Follicular differentiation may be less apparent (in some cases).
  - µ Reminiscent of normal thyroid.
  - µ Hürthle cell variants of follicular carcinomas may be seen.



© Elsevier. Kumar et al: Robbins Basic Pathology 8e - www.studentconsult.com

- *Grossly:*
  - ¤ Infiltrative or minimally invasive.
  - ¤ The latter are sharply demarcated lesions that may be impossible to distinguish from follicular adenomas on gross examination.
  - ¤ This distinction requires extensive histologic sampling of the tumor-capsule-thyroid interface, to exclude capsular and/or vascular invasion.



- Extensive invasion of adjacent thyroid parenchyma makes the diagnosis of carcinoma obvious in some cases (Fig. above B).
-While Fig. (A) It is follicular adenomas "note that there is no capsular invasion".
-Follicular lesions in which the nuclear features are typical of papillary carcinomas should be regarded as papillary cancers.

Clinical Features:

- -Present most frequently as solitary "cold" thyroid nodules.
- -Rarely, they may be hyperfunctional.
- -Metastasize through the bloodstream to the lungs, bone, and liver.
- -Regional nodal metastases are uncommon, in contrast to papillary carcinomas.
- -Treated with surgical excision.
- -Well-differentiated metastases may take up radioactive iodine, which can be used to identify, and ablate, such lesions.
- -Because better differentiated lesions may be stimulated by TSH, patients are usually <u>treated with thyroid hormone after surgery to suppress endogenous TSH.</u>

3-Medullary Carcinoma

- Neuroendocrine neoplasms derived from the parafollicular cells, or C cells, of the thyroid.
- Secrete calcitonin (like normal C cells) "this plays an important role in the diagnosis and postoperative follow-up of patients".
- Somatostatin, Serotonin, and Vasoactive intestinal peptide (VIP) are other polypeptide hormones elaborated by the tumor cells.
- In about 80% of cases it arise *sporadically*.
- The remaining 20% are:
  1- *Familial* associated with MEN syndromes 2A or 2B.
  2-Familial medullary thyroid carcinoma (FMTC) without an associated MEN syndrome.
- Both familial and sporadic medullary forms demonstrate activating *RET* mutations.
- Sporadic medullary carcinomas, as well as FMTC, occur in adults, with a peak incidence in the fifth to sixth decades.
- Cases associated with MEN-2A or MEN-2B(multiple endocrine neoplasia), in contrast, occur in younger patients and may even arise in children.

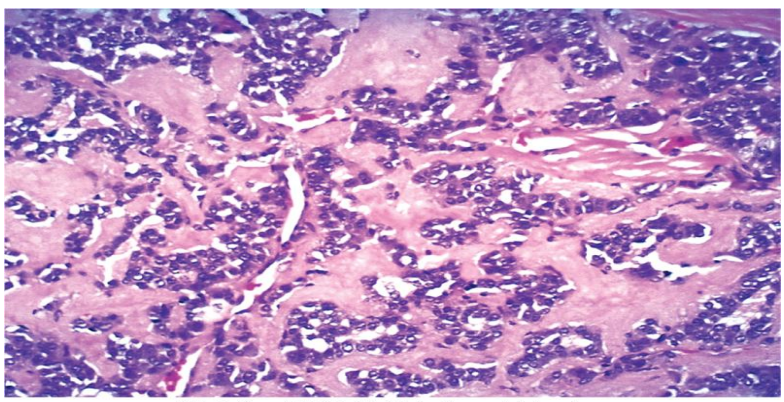
Morphology*:*

-Medullary carcinomas may arise as a solitary nodule or may present as multiple lesions involving both lobes of the thyroid.
-Multicentricity is particularly common in familial cases.
-Larger lesions often contain areas of necrosis and hemorrhage and may extend through the capsule of the thyroid.

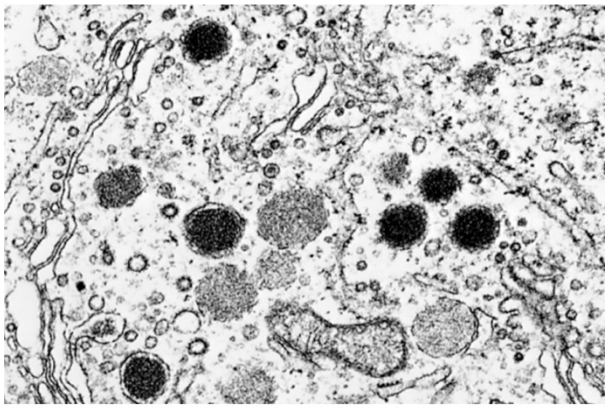
- *Microscopically:*

µ Composed of polygonal to spindle-shaped cells which may form nests, trabeculae, and even follicles.

µ Acellular amyloid deposits, derived from altered calcitonin molecules, are present in the adjacent stroma in many cases and are a distinctive feature of these tumors.



- Calcitonin is readily demonstrable both within the cytoplasm of the tumor cells and in the stromal amyloid by immunohistochemical methods.
- Electron microscopy reveals variable numbers of intracytoplasmic membrane-bound electron-dense granules.



- One of the peculiar features of familial medullary carcinomas is the presence of multicentric C-cell hyperplasia in the surrounding thyroid parenchyma.
- A feature usually absent in sporadic lesions.
- While the precise criteria for defining what constitutes hyperplasia are variable, the presence of multiple prominent clusters of C cells scattered throughout the parenchyma should raise the specter of a familial tumor, even if that history is not available. Foci of C-cell hyperplasia are believed to represent the precursor lesions from which medullary carcinomas arise.

Clinical Features:

- -Sporadic:
  - Present most often as a mass in the neck.
  - sometimes associated with compression effects such as dysphagia or hoarseness.
- In some instances the initial manifestations are caused by the secretion of a peptide hormone (e.g., diarrhea caused by the secretion of VIP).
- Hypocalcemia is <u>not</u> a feature, despite the presence of raised calcitonin levels.
- Screening of relatives for elevated calcitonin levels or *RET* mutations permits <u>early detection</u> of tumors in <u>familial cases.</u>
- All MEN-2 kindred carrying *RET* mutations are offered prophylactic thyroidectomies to preempt the development of medullary carcinomas.
- Often, the only histologic finding in the resected thyroid of these asymptomatic carriers is the presence of C-cell hyperplasia or small (<1 cm) "micromedullary" carcinomas.
- Recent studies have shown that specific *RET* mutations correlate with an aggressive behavior in medullary carcinomas.

4-Anaplastic Carcinoma:

- The most aggressive human neoplasms, with a near-uniform mortality rate.
- Individuals with anaplastic carcinoma are older than those with other types of thyroid cancer, with a mean age of 65 years.
- About half of the patients have a history of multinodular goiter.
- whereas 20% of the patients with these tumors have a history of differentiated carcinoma.
- another 20% to 30% have a concurrent differentiated thyroid tumor, frequently a papillary carcinoma.
- These findings have led to speculation that anaplastic carcinoma develops by "dedifferentiation" from more differentiated tumors as a result of one or more genetic changes, including loss of function of the *p53* tumor suppressor gene.

Morphology:

-Present as bulky masses that typically grow rapidly beyond the thyroid capsule into adjacent neck structures.

- *Microscopically:*

µ Composed of highly anaplastic cells.

µ Which may take on several histologic patterns, including:

1. Large, pleomorphic giant cells.
2. Spindle cells with a sarcomatous appearance.
3. Mixed spindle and giant-cell lesions.
4. Small cells, resembling those seen in small-cell carcinomas at other sites.

µ It is unlikely that a true small-cell carcinoma exists in the thyroid, and most of the "anaplastic small-cell" tumors ultimately proved to be medullary carcinomas or malignant lymphomas.

µ Foci of papillary or follicular differentiation may be present in some tumors, suggesting origin from a better differentiated carcinoma.

Clinical Features:

° -Anaplastic carcinomas grow with wild abandon despite therapy

° -Metastases to distant sites are common, but in most cases death occurs in less than 1 year as a result of aggressive local growth and compromise of vital structures in the neck.

Hyperaldosteronism
(Conn Syndrome)

- Excessive levels of aldosterone cause:
  1- *sodium retention.*
  2- *potassium excretion.*

- *The result is :*
  1- hypertension.
  2- hypokalemia.

- Hyperaldosteronism may be primary, or it may be secondary to an extra-adrenal cause.

v *secondary hyperaldosteronism:*

- ø aldosterone release occurs in response to activation of the renin-angiotensin system.
- ø characterized by ***increased levels of plasma rennin.***

- encountered in conditions associated with:
  1) ↓ renal perfusion (arteriolar nephrosclerosis, renal artery stenosis).
  2) Arterial hypovolemia and edema (congestive heart failure, cirrhosis, nephrotic syndrome)
  3) Pregnancy (caused by estrogen-induced increases in plasma renin substrate)

v *Primary hyperaldosteronism*:

- primary autonomous overproduction of aldosterone

Results in:

- suppression of the renin-angiotensin system .
- *decreased plasma renin activity.*
  (remember secondary hyperaldosteronism has increased levels of plasma rennin)

Caused by:

1- aldosterone-producing adrenocortical neoplasm (usually an adenoma)
2- primary adrenocortical hyperplasia.

(Some cases are idiopathic; these may be caused by overactivity of the aldosterone synthase gene, *CYP11B2*.)

Morphology:

Primary hyperaldosteronism (80% of cases)is caused by an aldosterone-secreting adenoma in one adrenal gland ,a condition referred to as Conn syndrome.

- *Features of adenoma:*
  - solitary.
  - small (<2 cm in diameter).
  - encapsulated lesions.
  - multiple adenomas may be present in an occasional patient; (carcinomas resulting in hyperaldosteronism are rare).
  - bright yellow on cut section.
  - composed of lipid-laden cortical cells more closely resembling fasciculata cells than glomerulosa cells (zona glomerulosa is the normal source of aldosterone).
  - cells tend to be uniform in size and shape.
  - occasionally there is some nuclear and cellular pleomorphism.

- characteristic feature of aldesterone-producing adenomas is the presence of

1. eosinophilic.
2. laminated cytoplasmic inclusions.

- known as spironolactone bodies

(typically found after treatment with the anti-hypertensive drug spironolactone, which is the drug of choice in primary hyperaldosteronism)

Remember: cortical adenomas associated with hyperaldosteronism do not usually suppress ACTH secretion (adenomas associated with Cushing syndrome suppress ACTH).

* adjacent adrenal cortex and that of the contralateral gland are not atrophic.

- primary hyperaldosteronism (15% of cases) is caused by bilateral primary adrenocortical hyperplasia,

characterized by:

- bilateral nodular hyperplasia of the adrenal glands.

* highly reminiscent of those found in the nodular hyperplasia of Cushing syndrome.

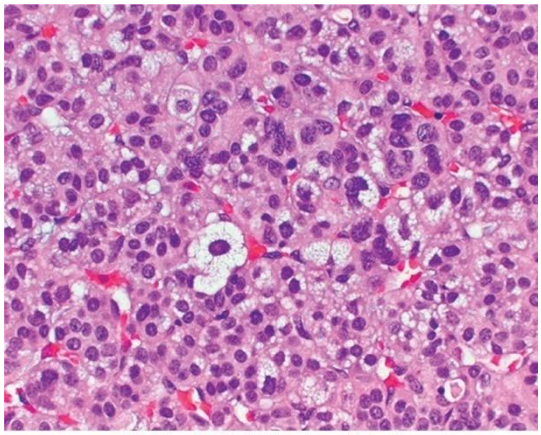


Figure 20-38 Histologic features of an adrenal cortical adenoma

Clinical Features:

In primary hyperaldosteronism there is :

- Hypertension.
- Hypokalemia.
- Serum renin levels are low.

Conn syndrome:

- Occurs most frequently in middle adult life.
- More common in females than in males (2 : 1).

(Although aldosterone-producing adenomas account for less than 1% of cases of hypertension, it is important to recognize them, because they cause a surgically correctable form of hypertension).

Primary adrenal hyperplasia associated with hyperaldosteronism:

- Occurs more often in children and young adults than in older adults.
- Surgical intervention is not very beneficial in these patients.
- Best managed with medical therapy with an aldosterone antagonist such as spironolactone.

(treatment of secondary hyperaldosteronism rests on correcting the underlying cause of the stimulation of the renin-angiotensin system.)

Chronic Adrenocortical Insufficiency

**Primary adrenocortical insufficiency can be:

1. Acute (Waterhouse-Friderichsen syndrome).
2. Chronic (Addison disease).

Chronic Adrenocortical Insufficiency (Addison Disease)

- It is an uncommon disorder resulting from progressive destruction of the adrenal cortex
- More than 90% of all cases are attributable to one of four disorders:
    1. *Autoimmune Adrenalitis*.
    2. *Tuberculosis*.
    3. *Acquired Immune Deficiency Syndrome (AIDS)*.
    4. *Metastatic Cancers*.

Causes of Adrenal Insufficiency

Acute
Waterhouse-Friderichsen syndrome
Sudden withdrawal of long-term corticosteroid therapy
Stress in patients with underlying chronic adrenal insufficiency
Chronic
MAJOR CONTRIBUTORS
Autoimmune adrenalitis
Tuberculosis
Acquired immunodeficiency syndrome
Metastatic disease
MINOR CONTRIBUTORS
Systemic amyloidosis
Fungal infections
Hemochromatosis
Sarcoidosis

♦ Autoimmune adrenalitis:

- accounts for 60% to 70% of cases.
- By far the most common cause of primary adrenal insufficiency in developed countries.
- There is autoimmune destruction of steroid-producing cells
- Autoantibodies to several key steroidogenic enzymes have been detected in these patients.
- In about half of the patients the autoimmune disease is apparently restricted to the adrenal glands *(isolated autoimmune Addison disease)*

- In the remaining patients, other autoimmune diseases coexist *(autoimmune polyendocrinopathy syndrome)* , such as:

    1. Hashimoto disease.
    2. pernicious anemia.
    3. type I diabetes mellitus.
    4. idiopathic hypoparathyroidism.

- A subset of autoimmune polyendocrinopathy syndrome is associated with mutations in the autoimmune regulator 1 *(AIRE1)* gene on chromosome 21q22.

♦ Infections:

- particularly tuberculosis and those produced by fungi, may also cause primary chronic adrenocortical insufficiency

• *Tuberculous adrenalitis:*

- once accounted for as many as 90% of cases of Addison disease, has become less common with the advent of antituberculous therapy.

- However, with the resurgence of tuberculosis in many urban centers, this cause of adrenal deficiency must be borne in mind.

- When present, tuberculous adrenalitis is usually associated with active infection in other sites, particularly the lungs and genitourinary tract.

• *Fungi:*

- disseminated infections caused by
    1. *Histoplasma capsulatum*
    2. *Coccidioides immitis*
- Both may result in chronic adrenocortical insufficiency.

• *AIDS:*

- Patients with AIDS are at risk for developing adrenal insufficiency from several infectious :

    1. *cytomegalovirus (CMV)*
    2. *Mycobacterium avium-intracellulare (MAC)*
    3. *noninfectious (Kaposi sarcoma) complications of their disease*

♦ Tumors:

- *Metastatic neoplasms* involving the adrenals are another potential cause of adrenal insufficiency.
- The adrenals are a fairly common site for metastases in persons with disseminated carcinomas.

- Adrenal function is preserved in most such patients.
- But the metastatic growths sometimes destroy sufficient adrenal cortex to produce a degree of adrenal insufficiency.

- The source of a majority of metastases in the adrenals:
  - Carcinomas of the lung.
  - Carcinomas of the breast.

- Many other neoplasms may also metastasize to the organ , including :
  - gastrointestinal carcinomas.
  - malignant melanomas.
  - hematopoietic neoplasms.

Chronic Adrenocortical Insufficiency:

- Clinical Features

- Generally, clinical manifestations of adrenocortical insufficiency do not appear until at least 90% of the adrenal cortex has been compromised.
- Initial manifestations often include:

1. Progressive weakness
2. Easy fatigability, which may be dismissed as nonspecific complaints.
3. *Gastrointestinal disturbances* are common which includes (anorexia, nausea, vomiting, weight loss, and diarrhea.)
4. Hyperpigmentation of the skin and mucosal surfaces. (due to increased levels of ACTH precursor hormone which stimulate melanocytes)

   " Hyperpigmentation happens ONLY in primary adrenocortical insufficiency "

   Common sites: face, axillae, nipples, areolae, and perineum
5. Hyperkalemia.(potassium retention)
6. Hyponatremia. (sodium loss)
7. Volume depletion.
8. Hypotension.

   (5 , 6, 7, 8 Are linked and are due to Decreased mineralocorticoid (aldosterone) activity in patients with primary adrenal insufficiency)

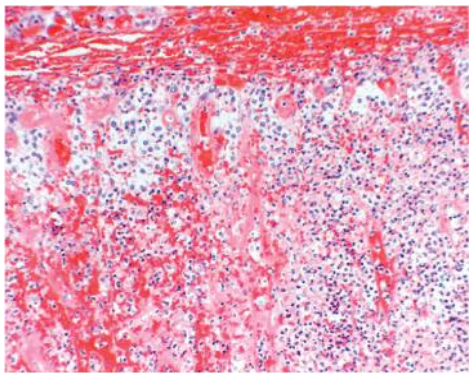
   - In Secondary hypoadrenalism :
     1. Deficient cortisol and androgen output.
     2. Normal or near-normal aldosterone synthesis.

9. Hypoglycemia (occur as a result of glucocorticoid deficiency and impaired gluconeogenesis.

    - Stresses such as infections, trauma, or surgical procedures in such patients may precipitate an acute adrenal crisis, manifested by intractable vomiting, abdominal pain, hypotension, coma, and vascular collapse. Death follows rapidly unless corticosteroids are replaced immediately.

<u>So In conclusion we have 9 manifestations:</u>

Progressive weakness
Easy fatigability
GIT disturbances
Hyperpigmentation
Hyperkalemia
Hyponatremia
Volume depletion
Hypotension
Hypoglycemia.



© Elsevier 2005

Figure 20-39 Acute adrenal insufficiency caused by severe bilateral adrenal hemorrhage in an infant with overwhelming sepsis (Waterhouse-Friderichsen syndrome).

PHEOCHROMOCYTOMA

- Pheochromocytomas are neoplasms composed of chromaffin cells, (which like their non-neoplastic counterparts) synthesize and release catecholamines and, in some cases, other peptide hormones.
- It's uncommon, but their importance is in the fact that they (like aldosterone-secreting adenomas) give rise to a surgically correctable form of hypertension.

In Pheochromocytomas remember "rule of 10s":

- *10% of pheochromocytomas arise in association with one of several familial syndromes* which includes:
  1. MEN-2A and MEN-2B syndromes.
  2. Type 1 neurofibromatosis.
  3. Von Hippel-Lindau disease.
  4. Sturge-Weber syndrome.

- *10% of pheochromocytomas are extra-adrenal* (occurring in sites such as the organ of Zuckerkandl and the carotid body) where they are usually called *paragangliomas* rather than *pheochromocytomas*.

- *10% of adrenal pheochromocytomas are bilateral;* mostly in cases associated with familial syndromes. (up to 50% will be bilateral)
  (*note:* the book said 50% ,, but the in the prof's slides it's written 70%)
- *10% of adrenal pheochromocytomas are biologically malignant.*

(the associated hypertension represents a serious and potentially lethal complication of even "benign" tumors.)
Note: Frank malignancy is somewhat more common in tumors arising in extra-adrenal sites.

- 10% of adrenal pheochromocytomas arise in childhood (male preponderance) (adults between 40 and 60 years of age, with a slight female preponderance).

v Morphology:

- Range from small, circumscribed lesions confined to the adrenal to
- large, hemorrhagic masses weighing several kilograms

*On cut surface :

- smaller pheochromocytomas:
  1. Yellow-tan.
  2. well-defined lesions.
  3. compress the adjacent adrenal
- Large pheochromocytomas
  1. hemorrhagic
  2. necrotic
  3. cystic
  4. typically efface(Wipeout , or erase) the adrenal gland.

  - Incubation of the fresh tissue with potassium dichromate solutions turns the tumor a dark brown color.

µ Microscopically:

- composed of polygonal to spindle-shaped chromaffin cells and their supporting cells, compartmentalized into small nests, or "Zellballen," by a rich vascular network.

- cytoplasm of the neoplastic cells:

  1. has a finely granular appearance.
  2. highlighted by a variety of silver stains (because of the presence of granules containing catecholamines)

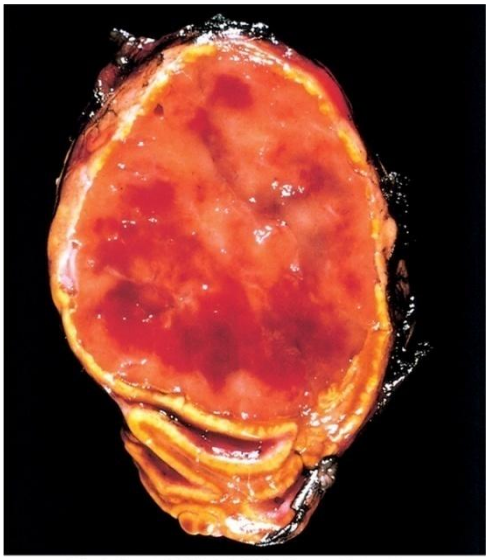
µ Electron microscopy:

- Reveals variable numbers of membrane-bound, electron-dense granules, representing catecholamines and sometimes other peptides.

- Nuclei of the neoplastic cells are often quite pleomorphic.

- Both capsular and vascular invasion may be encountered in benign lesions, and the presence of mitotic figures per se does not imply malignancy.

- The definitive diagnosis of malignancy in pheochromocytomas is based exclusively on the presence of metastases may involve:
  1. Regional lymph.
  2. Liver.
  3. Lung.
  4. Bone.



tumor is enclosed within an attenuated cortex and demonstrates areas of hemorrhage. The comma-shaped residual adrenal is seen below.

v Clinical Feature:

- dominant clinical manifestation of pheochromocytoma is ***hypertension.***
- *Classically, this is described as:*
  1. abrupt.
  2. precipitous elevation in blood pressure.

- *associated with*
  1. tachycardia.
  2. palpitations.
  3. headache.
  4. sweating.
  5. tremor.
  6. sense of apprehension. (Such episodes may also be associated with pain in the abdomen or chest, nausea, and vomiting).

- In practice, *isolated, paroxysmal episodes of hypertension occur in fewer than half of individuals* with pheochromocytoma.
- In about two-thirds of patients the hypertension occurs in the form of a chronic, sustained elevation in blood pressure, although an element of labile hypertension is often present as well.

- Whether sustained or episodic, the hypertension is associated with:

  1. Increased risk of myocardial ischemia.
  2. Heart failure.
  3. Renal injury.
  4. Cerebrovascular accidents.
  5. Sudden cardiac death may occur,(probably secondary to catecholamine-induced myocardial irritability and ventricular arrhythmias).

- In some cases, pheochromocytomas secrete other hormones such as ACTH and somatostatin and may therefore be associated with clinical features related to the secretion of these and other peptide hormone.

v Laboratory diagnosis:

- Lab Dx of pheochromocytoma is based on demonstration of increased urinary excretion of free catecholamines and their metabolites, such as vanillylmandelic acid and metanephrines.

v Treatment:

- Isolated benign pheochromocytomas are treated with surgical excision, after pre- and intraoperative medication of patients with adrenergic-blocking agents.

- Multifocal lesions may require long-term medical treatment for hypertension.

DIABETES MELLITUS

Diabetes mellitus is not a single disease entity but rather a *group of metabolic disorders sharing feature of hyperglycemia.* Hyperglycemia in diabetes results from defects in insulin secretion, insulin action, or, most commonly ,BOTH.

Diagnosis

Blood glucose levels are usually 70 to 120 mg/dL. The diagnosis of diabetes is established by elevation of blood glucose by any one of three criteria:

1. A random blood glucose concentration of 200 mg/dL or higher, with classical signs and symptoms
2. A fasting glucose concentration of 126 mg/dL or higher more than one occasion.
3. An abnormal oral glucose tolerance test (OGTT), in which the glucose concentration is 200 mg/dL or higher 2 hours after a standard carbohydrate load (75 gm of glucose).

- Euglycemic (normal blood glucose concentration).
  1) serum fasting glucose less than 110 mg/dL
  2) OGTT less than 140 mg/dL.

- *impaired glucose tolerance*
  1. serum fasting glucose greater than 110 but less than 126 mg/dL
  2. OGTT values of greater than 140 but less than 200 mg/dL. Note that they have a significant risk of progressing to overt diabetes,Also they are at *risk for cardiovascular disease.*

Classification

Although all forms of diabetes mellitus share hyperglycemia as a common feature, the underlying causes of hyperglycemia vary widely. *The vast majority of cases of diabetes fall into one of two broad classes:*

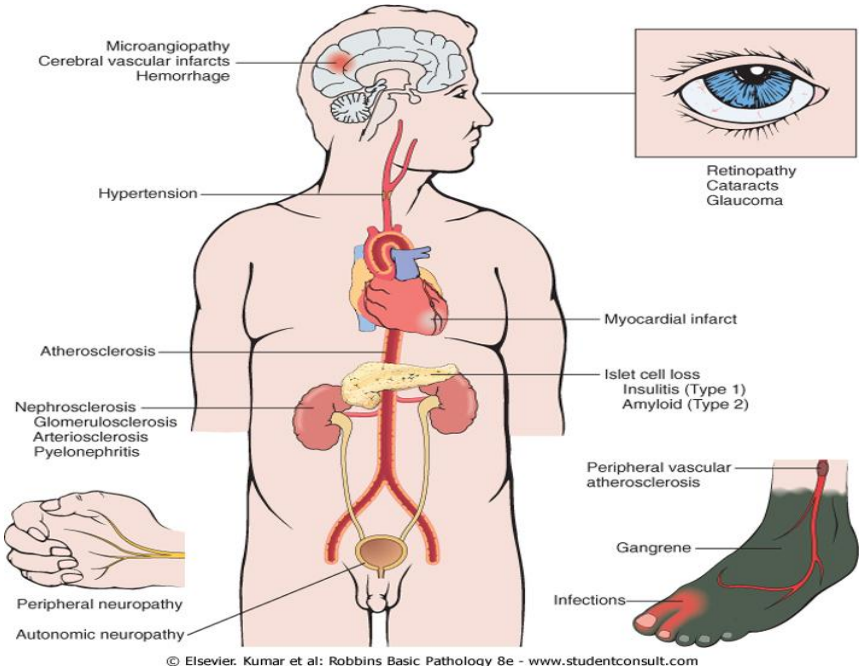
- *Type 1 diabetes* : an absolute deficiency of insulin secretion caused by pancreatic β-cell destruction, approximately 10% of all cases.

- *Type 2 diabetes* is caused by a combination of peripheral resistance to insulin action and relative insulin deficiency. Approximately 80% to 90% of patients have type 2 diabetes.

- A variety of monogenic and secondary causes make up the remaining cases of diabetes.
- Note that *long-term complications in kidneys, eyes, nerves, and blood vessels are the same and are the principal causes of morbidity and death.*

Morphology of Diabetes and Its Late Complications:

In most patients ,morphologic changes are in arteries (macrovascular disease), basement membranes of small vessels (microangiopathy), kidneys (diabetic nephropathy), retina (retinopathy), nerves (neuropathy), and other tissues. These changes are seen in both type 1 and type 2 diabetes.



Pancreas :

Lesions in the pancreas are inconstant and rarely of diagnostic value.

- *Distinctive changes are more commonly associated with type 1 than with type 2 diabetes.
  - Reduction in the number and size of islets:
    This is most often seen in type 1 diabetes, particularly with rapidly advancing disease. Most of the islets are small, inconspicuous, and not easily detected.
  - Leukocytic infiltration of the islets (insulitis) principally composed of T lymphocytes (autoimmune diabetes). This may be seen in type 1 diabetics at the time of clinical presentation. The distribution of insulitis may be strikingly uneven.
  - Eosinophilic infiltrates may also be found, particularly in diabetic infants who fail to survive the immediate postnatal period.

In type 2 diabetes:

1. there may be a subtle reduction in islet cell mass, demonstrated only by special morphometric studies.
2. Amyloid replacement of islets appears as deposition of pink, amorphous material beginning in and around capillaries and between cells. At advanced stages the islets may be obliterated.
3. Fibrosis may also be observed. This change is often seen in long-standing cases of type 2 diabetes. Similar lesions may be found in elderly nondiabetics, apparently as part of normal aging.

NOTE: An increase in the number and size of islets is especially characteristic of nondiabetic newborns of diabetic mothers ?? Because fetal islets undergo hyperplasia in response to the maternal hyperglycemia.

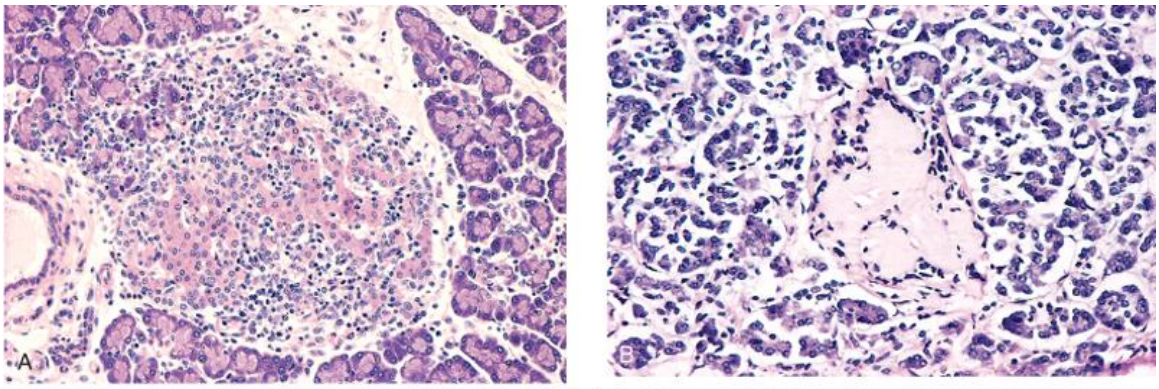


Figure 20-26 A, Insulitis. B, Amyloidosis of a pancreatic islet in type 2 diabetes.

Diabetic Macrovascular Disease :

- The hallmark of diabetic macrovascular disease is accelerated atherosclerosis affecting the aorta and large and medium-sized arteries with greater severity and earlier age of onset and it is indistinguishable from that in nondiabetics.
- Myocardial infarction, caused by atherosclerosis of the coronary arteries, is the most common cause of death in diabetics. Significantly, it is almost as common in diabetic women as in diabetic men. In contrast, myocardial infarction is uncommon in nondiabetic women of reproductive age.
- Gangrene of the lower extremities, is about 100 times more common in diabetics than in the general population. most damaging effect of diabetes on the kidneys is exerted at the level of the glomeruli and the microcirculation.

Hyaline arteriolosclerosis

- is vascular lesion associated with hypertension
- more prevalent and more severe in diabetics than in nondiabetics
- not specific for diabetes and may be seen in elderly nondiabetics without hypertension.
- It takes the form of an amorphous, hyaline thickening of the wall of the arterioles.
- Note: in diabetics it is related not only to the duration of the disease but also to the level of blood pressure.

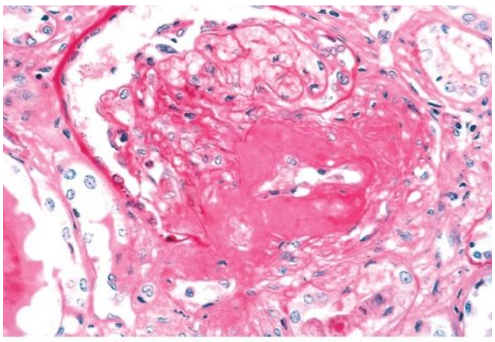


Figure 20-27 Severe renal hyaline arteriolosclerosis

Diabetic Microangiopathy:

- One of the most consistent morphologic features of diabetes is diffuse thickening of basement membranes. The thickening is most evident in the capillaries of the skin, skeletal muscle, retina, renal glomeruli, and renal medulla.
- it may also be seen in such nonvascular structures as renal tubules, the Bowman capsule, peripheral nerves, and placenta.
- By light and electron microscopy, the basal lamina is markedly thickened by layers of hyaline material composed predominantly of type IV collagen. It should be noted that despite increase in the thickness of basement membranes, diabetic capillaries are more leaky than normal to plasma proteins.

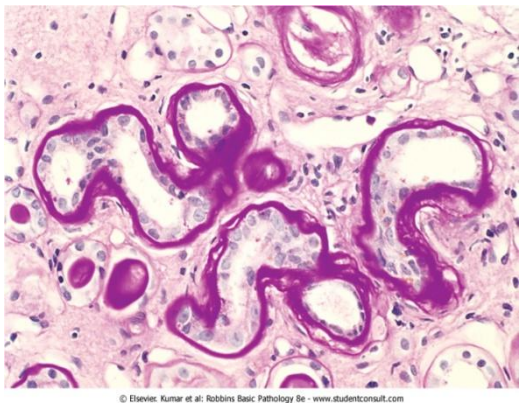


Figure 20-28 Renal cortex showing thickening of tubular basement membranes in a diabetic patient

- The microangiopathy underlies the development of diabetic nephropathy, retinopathy, and some forms of neuropathy.

Note: An indistinguishable microangiopathy can be found in nondiabetic patients, but rarely to the extent seen in individuals with long-standing diabetes.

Diabetic Nephropathy:

The kidneys are prime targets of diabetes . Renal failure is second only to myocardial infarction as a cause of death from this disease.

- Three lesions are encountered:
  1. glomerular lesions.
  2. renal vascular lesions, principally arteriolosclerosis.
  3. pyelonephritis, including necrotizing papillitis.

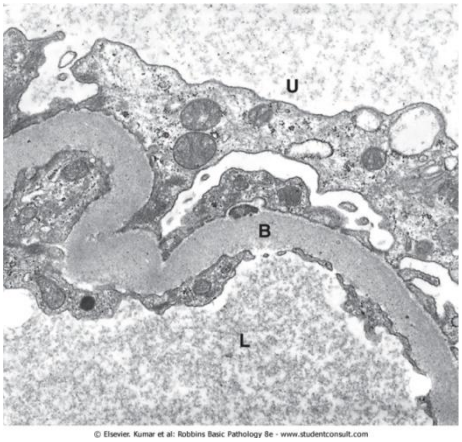


Figure 20-29 Renal glomerulus showing markedly thickened glomerular basement membrane (B) in a diabetic. L, glomerular capillary lumen; U, urinary space.

The most important glomerular lesions are

a. capillary basement membrane thickening,
b. diffuse mesangial sclerosis,
c. and nodular glomerulosclerosis.

The glomerular capillary basement membranes are thickened throughout their entire length. This change can be detected by electron microscopy within a few years of the onset of diabetes, sometimes without any associated change in renal function.

Diffuse mesangial sclerosis

- diffuse increase in mesangial matrix along with mesangial cell proliferation and is always associated with basement membrane thickening.
- It is found in most individuals with disease of more than 10 years' duration.
- When glomerulosclerosis becomes marked, patients manifest the nephrotic syndrome, characterized by proteinuria, hypoalbuminemia, and edema.

Nodular glomerulosclerosis

- ball-like deposits of a laminated matrix situated in the periphery of the glomerulus.
- These nodules are PAS positive and usually contain trapped mesangial cells. This called the Kimmelstiel-Wilson lesion.
- Nodular glomerulosclerosis is encountered in approximately 15% to 30% of long-term diabetics and is a major cause of morbidity and mortality.

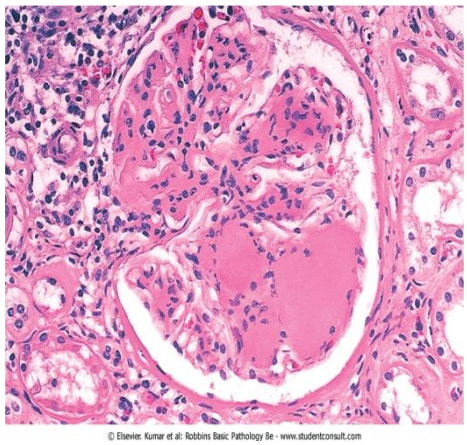


Figure 20-30 Nodular glomerulosclerosis

- Diffuse mesangial sclerosis may also be seen in association with old age and hypertension; on the contrary, the nodular form of glomerulosclerosis, *is essentially pathogonomic of diabetes. Both the diffuse and the nodular forms of glomerulosclerosis induce sufficient ischemia to cause scarring of the kidneys.

Renal atherosclerosis and arteriolosclerosis constitute part of the macrovascular disease in diabetics. The kidney is one of the most frequently and severely affected organs; however, the changes in the arteries and arterioles are similar to those found throughout the body.

Hyaline arteriolosclerosis affects not only the afferent but also the efferent arterioles.*

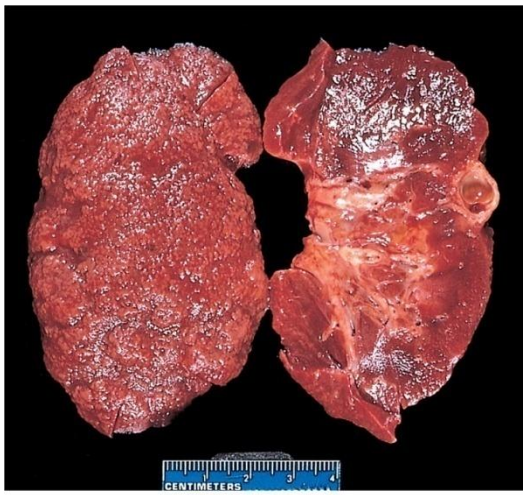


Figure 20-31 Nephrosclerosis

Pyelonephritis is an acute or chronic inflammation of the kidneys that usually begins in the interstitial tissue and then spreads to affect the tubules. One special pattern of acute pyelonephritis, necrotizing papillitis (or papillary necrosis), is much more prevalent in diabetics than in nondiabetics.

Ocular Complications of Diabetes:

Visual impairment and total blindness which is one of the more feared consequences of long-standing diabetes.

The ocular involvement may take the form of retinopathy, cataract formation, or glaucoma. Retinopathy, the most common pattern, consists of a constellation of changes.

The lesion in the retina takes two forms: nonproliferative (background) retinopaty and proliferative retinopathy.

Nonproliferative retinopathy includes intraretinal or preretinal hemorrhages, retinal exudates, microaneurysms, venous dilations, edema, and, most importantly, thickening of the retinal capillaries (micro-angiopathy).

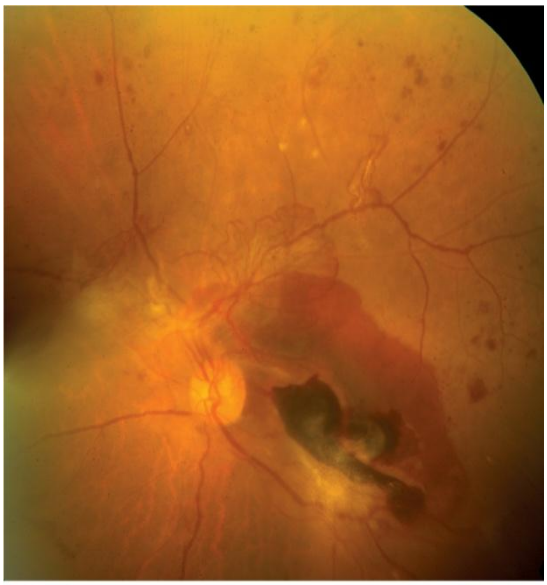


Figure 20-32 Diabetic retinopathy

The retinal exudates can be either "soft" (microinfarcts) or "hard" (deposits of plasma proteins and lipids).

The microaneurysms are discrete saccular dilations as small red dots.
Retinal edema presumably results from excessive capillary permeability.

proliferative retinopathy is a process of neovascularization and fibrosis.

This lesion leads to blindness, especially if it involves the macula. Vitreous hemorrhages can result from rupture of newly formed capillaries and can pull the retina off its substratum (retinal detachment).

Diabetic Neuropathy:

- most frequent pattern of involvement is a peripheral nervous systems,
- symmetric neuropathy of the lower extremities that affects Mainly sensory function.
- Other forms include peripheral neuropathy
- which produces disturbances in bowel and bladder function
- sometimes sexual impotence,
- diabetic mononeuropathy, which may manifest as sudden footdrop, wristdrop, or isolated cranial nerve palsies. It's may be caused by microangiopathy and increased permeability or by direct axonal damage due to alterations in sorbitol metabolism.