IV. GRAVES DISEASE

- *Is the most common cause of endogenous hyperthyroidism with a peak incidence in women* between the ages of 20 and 40
- It is characterized by a triad of manifestations:

A. Thyrotoxicosis,

- Caused by a diffusely enlarged, hyper-functional thyroid, is present in all cases.

B. Infiltrative *ophthalmopathy*

- with resultant exophthalmos is present in 40% of

patients as a result of increased volume of the retro-orbital tissues by

1. Marked infiltration by T cells with inflammatory edema
2. Accumulation of glycosaminoglycans
3. Increased numbers of adipocytes (fatty infiltration).

- These changes displace the eyeball forward, potentially interfering with the function of the extraocular muscles

Note

- Exophthalmos may persist after successful treatment of the thyrotoxicosis, and may result in corneal injury.

C. A localized, infiltrative *dermopathy* (*pretibial myxedema*)

- Is seen in a minority of cases and involves the skin overlying the shins, and manifests as scaly thickening

PATHOGENESIS :-

- Genetic factors are important in the causation of Graves disease,

a. The incidence is increased in relatives of affected patients, and the concordance rate in monozygotic twins is 60%.

b.- A genetic susceptibility is associated with the presence of HLA-DR3,and the disease is characterized by a breakdown in self-tolerance to thyroid autoantigens, and production of multiple autoantibodies, including:

1. Thyroid-stimulating immunoglobulin:

- An IgG antibody binds to the TSH receptor and mimics the action of TSH, with resultant increased release of hormones
- All persons have detectable amounts of this autoantibody
- It is specific for Graves disease

2. Thyroid growth-stimulating immunoglobulins:

- Directed against the TSH receptor,
- have been implicated in the proliferation of follicular epithelium

3. TSH-binding inhibitor immunoglobulins:

- Prevent TSH from binding to its receptor on thyroid cells
- Therefore; it inhibit thyroid cell function, a finding explains why some patients with Graves spontaneously develop episodes of hypothyroidism.

Note: - The coexistence of stimulating *and* inhibiting immunoglobulins in the serum of the same patient may explain why some patients with Graves disease spontaneously develop episodes of hypothyroidism

.Gross: Symmetrical enlargement of the thyroid gland with intact capsule,

On microscopic examination,

a. The follicular cells in untreated cases are tall, and more crowded and may result in formation of small papillae
b. Lymphoid infiltrates, consisting predominantly of T cells, with few B cells and plasma cells are present throughout the interstitium; with formation of germinal centers

Laboratory findings and radiologic findings

- Elevated serum free T_4 and T_3 and depressed serum TSH
- Because of ongoing stimulation of the thyroid follicles by TSIs, radioactive iodine uptake is increased, and radioiodine scans show a *diffuse uptake* of iodine.

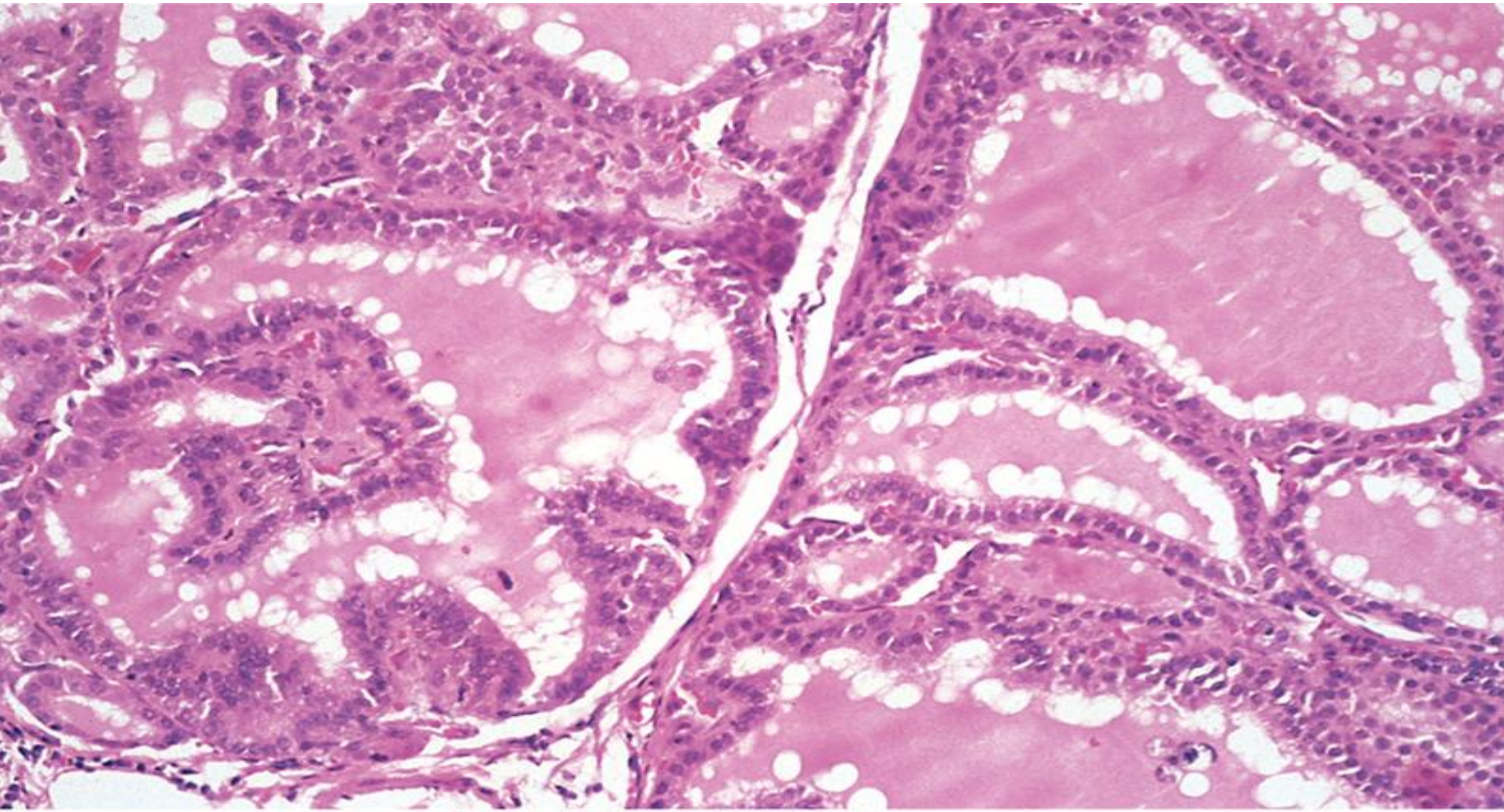
V. DIFFUSE AND MULTINODULAR GOITER

- Enlargement of the thyroid, or *goiter,* is the most common manifestation of thyroid disease

Mechanism :

- *The goiters reflect impaired synthesis of thyroid hormone* often caused by dietary iodine deficiency and this leads to a compensatory rise in the serum TSH, which in turn causes hyperplasia of the follicular cells and, ultimately, gross enlargement of the thyroid gland .,

Graves Disease



- The compensatory increase in functional mass of the gland is enough to overcome the hormone deficiency, ensuring a *euthyroid* state in the vast majority of persons
- If the underlying disorder is sufficiently severe (congenital biosynthetic defect), the compensatory responses may be inadequate to overcome the impairment in hormone synthesis, resulting in *goitrous hypothyroidism* .

- The degree of thyroid enlargement is proportional to the level and duration of thyroid hormone deficiency

I. Endemic goiter :

- Occurs in geographic areas where the soil, water, and food supply contain little iodine.
- The term *endemic* is used when goiters are present in more than 10% of the population in a given region.
- Is common in mountainous areas of the world, including the Himalayas and the Andes but with iodine supplementation, the frequency and severity of endemic goiter have declined

II. Sporadic goiter :

- Less common than endemic goiter.
- with a peak incidence in puberty or young adulthood, when there is an increased physiologic demand for T_4.
- It may be caused by several conditions, including the:

a. Ingestion of substances that interfere with thyroid hormone synthesis , such as excessive calcium and vegetables such as cabbage, cauliflower, sprouts, .

b. Hereditary enzymatic defects that interfere with thyroid hormone synthesis *(dyshormonogenetic goiter).*

- In most cases, the cause of sporadic goiter is not apparent.

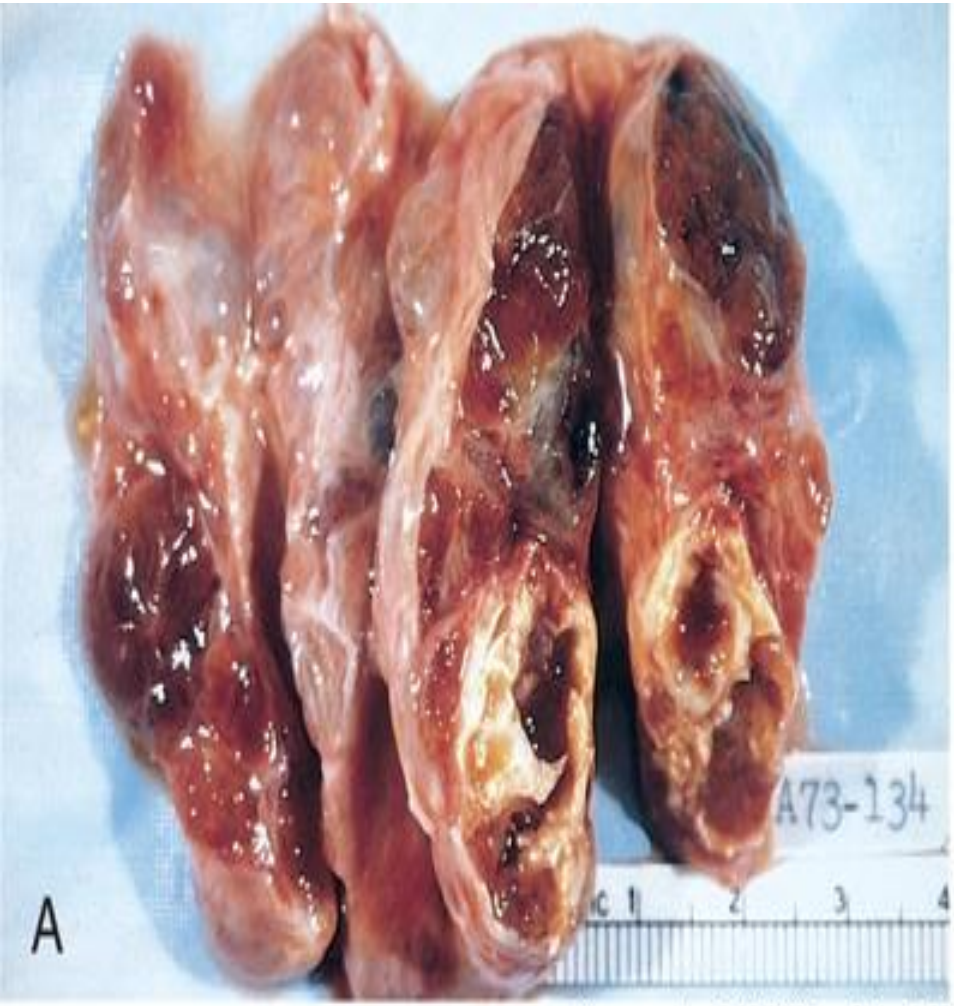
MORPHOLOGY :

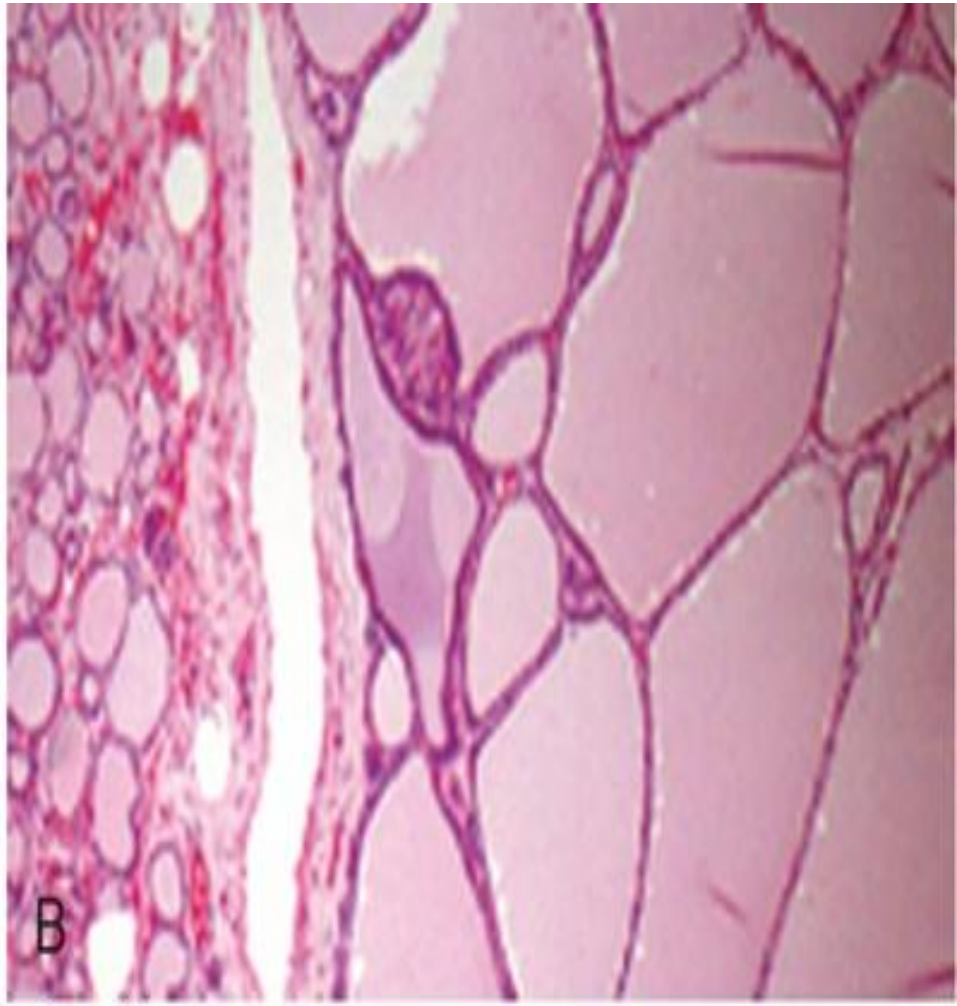
- Initially, the gland is diffusely and symmetrically enlarged (diffuse goiter) but later on it becomes multinodular goiter

On microscopic examination,

a. The follicular epithelium are hyperplastic in the early stages of disease
b. and flattened and cuboidal during periods of involution.
c. With time, recurrent episodes of hyperplasia and involution produce a more irregular enlargement of the thyroid, termed multinodular goiter and virtually all long-standing diffuse goiters convert into multinodular goiters.

Multinodular Goiter





Kumar et al: Robbins Basic Pathology, 9e.

- Multinodular goiters cause multilobulated, asymmetrically enlarged glands which attain massive size and old lesions often show fibrosis, hemorrhage, calcification
- Multinodular goiters are typically hormonally silent,

Note:

- 10% of patients can manifest with thyrotoxicosis due to the development of autonomous nodules producing hormone independent of TSH stimulation and this condition, called toxic multinodular goiter or **Plummer syndrome**

Clinical Features :

a. The dominant features are *mass effects* of the goiter also may cause airway obstruction, dysphagia, and compression of large vessels in the neck and upper thorax (so-called *superior vena cava syndrome.*

b. Cosmetic problem of a large neck mass goiters

c. The incidence of malignancy in long-standing multinodular goiters is low (less than 5%) but not zero and concern for malignancy arises with goiters that demonstrate sudden changes in size or associated symptoms such as hoarseness of voice

VI. Thyroid tumors :

Clinically :

- The possibility of a cancer is of major concern in patients who present with thyroid nodules but fortunately, the majority of solitary nodules of the thyroid prove to be either

a. Follicular adenomas

b. A dominant nodule in multinodular goiter

c. Simple cysts or foci of thyroiditis

- Carcinomas of the thyroid, are uncommon, accounting for much less than 10% of solitary thyroid nodules.
- Several clinical criteria provide a clue to the nature of a given thyroid nodule:

a. *Solitary nodules,* in general, are more likely to be neoplastic than are multiple nodules.
b. *Nodules in younger patients* are more likely to be neoplastic than are those in older patients.
c. *Nodules in males* are more likely to be neoplastic than are those in females.

d. A history of *radiation* therapy to the head and neck associated with an increased incidence of thyroid cancer.

e. Nodules that take up radioactive iodine in imaging studies (*hot nodules*) are more likely to be benign than malignant

- ***Note****:*

- It is the morphologic evaluation of a given thyroid nodule by pathological study of surgically resected thyroid tissue that provides the most definitive diagnosis

Follicular adenomas

- Are benign neoplasms derived from follicular epithelium.

a. Usually are solitary.

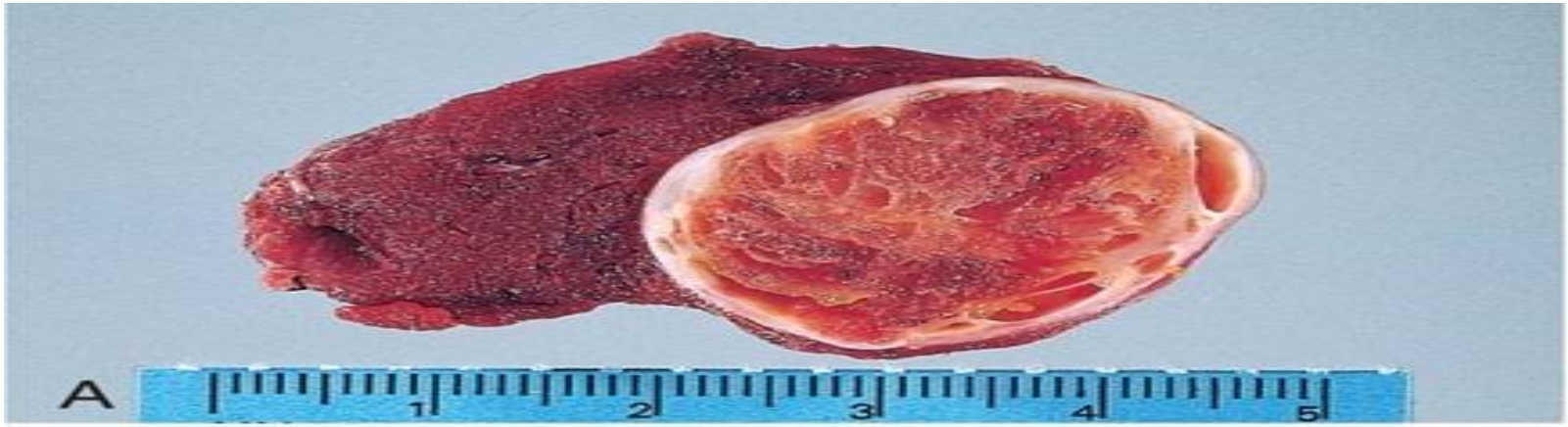
b. The tumor is demarcated from the normal thyroid

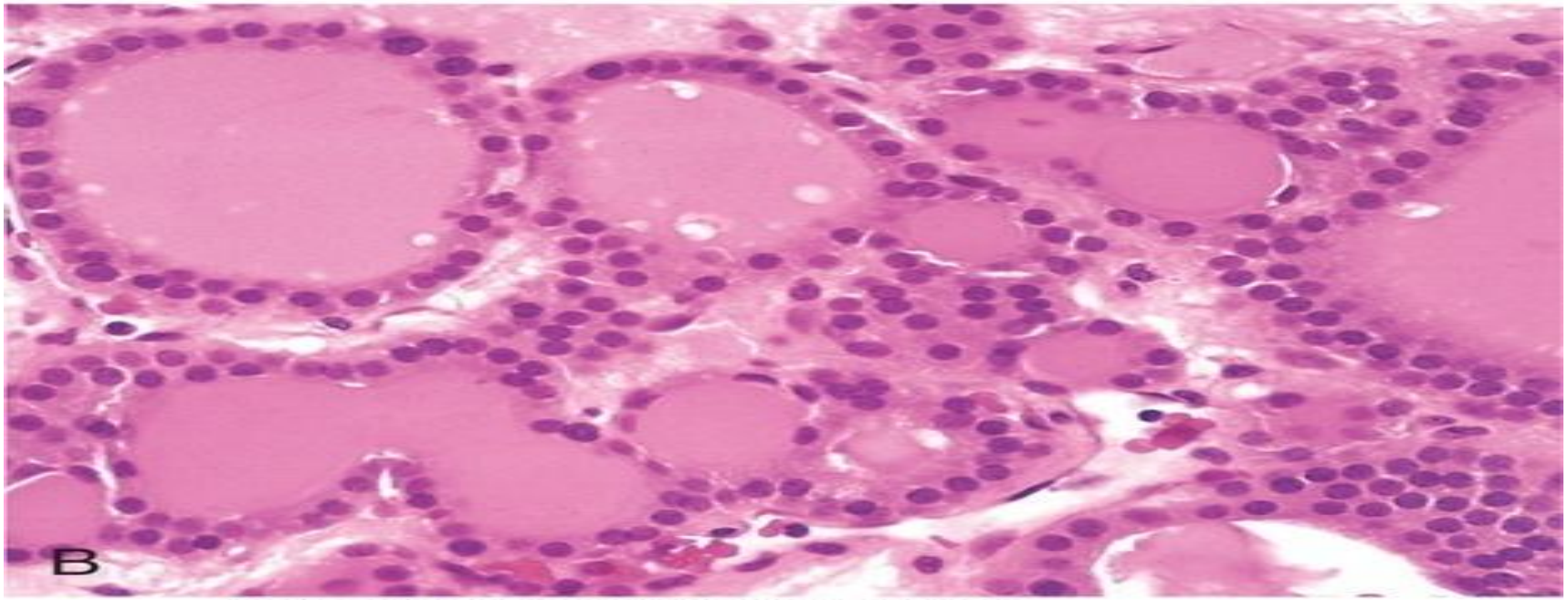
c. The tumor compressed the adjacent thyroid parenchyma by a well-defined, intact capsule

These features are important in making the distinction from multinodular goiters,

1. Which contain multiple nodules on their cut surface (even if the patient may present with a solitary nodule
2. Do not compress the adjacent thyroid parenchyma,
3. Lack a well-formed capsule

Follicular adenoma





- The hallmark of all follicular adenomas is the presence of an intact well-formed capsule encircling the tumor.
- Evaluation of the integrity of the capsule is critical in distinguishing follicular adenomas from follicular carcinomas, which demonstrate capsular and/or vascular invasion

- Therefore; the *definitive diagnosis of thyroid adenoma can be made after histologic examination of the resected nodule*
- Suspected adenomas of the thyroid are therefore removed surgically to exclude malignancy

Clinical Features

- Manifest as painless nodules.
- Larger masses may produce difficulty in swallowing.
- On radionuclide scanning most adenomas take up iodine less avidly than normal thyroid parenchyma.
- Therefore; adenomas appear as *cold* nodules
- Toxic adenomas can present with thyrotoxicosis and will appear as hotnodules in the scan

Note

- About 10% of *cold* nodules prove to be malignant and by contrast, malignancy is rare in *hot* nodules

Carcinomas of thyroid :

- Accounting for about 1.5% of all cancers
- A female predominance has been noted among patients who develop thyroid carcinoma in the early and middle adult years and cases manifesting in childhood and late adult life are distributed equally between men and women

- The major subtypes of thyroid carcinoma are are

1. Papillary carcinoma (for more than 85% of cases)
2. Follicular carcinoma (5% to 15% of cases)
3. Anaplastic carcinoma (less than 5% of cases)
4. Medullary carcinoma (5% of cases)

PATHOGENESIS

I. Genetic alterations

A. Papillary thyroid carcinomas**:**

1. Rearrangements of *RET* gene

- The *RET* gene is not normally expressed in follicular cells but in papillary cancers, chromosomal rearrangements place the tyrosine kinase domain of *RET* under the transcriptional control of genes that are constitutively expressed in the thyroid epithelium and the novel fusion

proteins so formed are known as RET/PTC are present in 20% to 40% of papillary thyroid cancers.

- The frequency of *RET/PTC* rearrangements is significantly higher in papillary cancers arising in the backdrop of radiation exposure

Note:

- *RET/PTC* rearrangements are not observed in follicular adenomas or carcinomas.

B. Follicular thyroid carcinomas:

a. Gain-of-function point mutations of *RAS*

b. A unique (2;3) translocation presents in one third to one half of follicular carcinomas which creates a fusion gene composed of portions of *PAX8*, a gene that is important in thyroid development, and the peroxisome proliferator-activated receptor gene (*PPARG*), whose product is a nuclear receptor implicated in cell differentiation

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C. Anaplastic carcinomas:

- Inactivation of *TP53*, restricted to anaplastic carcinomas and may also relate to their aggressive behavior

D.Medullary thyroid carcinomas:

- Arise from the C cells,.

a. Familial medullary thyroid carcinomas occur in multiple endocrine neoplasia type 2 (MEN-2) are associated with germline *RET* proto-oncogene mutations

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b. RET mutations are also seen in approximately one half of (sporadic) medullary thyroid cancers.

Note:

- Chromosomal rearrangements involving *RET,* are not seen in medullary carcinomas