CHAPTER
19 Endocrine Tumors

This chapter covers all tumors that may produce hormonally active products. This includes the traditional endocrine glands (thyroid, parathyroid, adrenal cortex and anterior pituitary), as well as, tumors of the dispersed neuroendocrine cells (medullary thyroid carcinoma, paragongliomas, neuroblastoma, pulmonary carcinoids and neuroendocrine tumors of gastrointestinal tract and pancreas)

Few reports are available on the relative frequency of endocrine tumors (Table 19-1), all show a marked predominance of thyroid carcinoma (63 to 91%). Probably, there is under registration of other endocrine tumors in hospital series, partly due to difficulty in diagnosis or lack of specialized services. Moreover, international registries (SEER and WHO) are only interested in thyroid carcinoma and ignoring other endocrine tumors. Endocrine tumors are characterized by the following four common features:

1. Predominance of benign tumors over malignant tumors. This predominance is most marked in pituitary, parathyroid and thyroid tumors. Exceptions to this rule are gastrinoma of pancreas and virilizing adrenal cortical tumors which are commonly malignant as well as, medullary carcinoma of thyroid which is always malignant.

Table 19-1 Relative Frequency (%) of Endocrine Tumors

Site	Mokhtar et al, 2007	DeVita et al, 1997	Bukhari et al, 2008
Thyroid	63	91	77
Adrenal and Paraganglia	32	3	9
Neuroendocrine*	5	4	4
Pituitary	-	0.4	7
Parathyroid	-	0.2	2

*Includes neuroendocrine tumors of lung, pancreas and gastrointestinal tract.

2. Predominance of nonfunctioning tumors (almost 90%) and this is most marked in thyroid carcinoma. An exception to this rule is adrenal tumors which are commonly functioning. Functioning tumors present early due to endocrine manifestations, but nonfunctioning tumors present late with large tumor masses.

3. Unpredictable biologic behavior. It is difficult to predict the clinical course of the tumor from its histologic picture. Thus, tumors with pleomorphic cells may behave benign, and tumors lacking mitotic activity may behave malignant. For this reason, most endocrine tumors are classified under uncertain or unpredictable biologic behavior. Risk or prognostic factors are resorted to help predict prognosis.

4. Multiple endocrine neoplasia (MEN). Some endocrine tumors may rarely occur in a combination of two or more as a result of germline mutation of tumor suppressor genes. These syndromes are inherited as autosomal dominant traits, thus, giving first degree relatives a 50% risk of developing the disease. The endocrine glands commonly involved are: medullary thyroid carcinoma, parathyroid carcinoma, adrenal paragongliomas, anterior pituitary and endocrine pancreas.

THYROID CANCER

Incidence

Thyroid cancer constitutes about 1.2% of total cancers. It is the most common endocrine malignancy contributing about 80% of cases. The fatality is low (8%). Females predominate with a sex ratio of 2.5:1. The median age is 40 years in females and 45 years in males

Etiology

1. Radiation: therapeutic or fallout from nuclear bombing or reactor accidents (radioiodine) e.g. Marshall islands and Chernobyl accident.

2. Iodine deficient diet predisposes to follicular and anaplastic carcinomas.

3. Female sex hormone explains female predominance.

4. Genetic predisposition (RET protooncogene activation) in papillary and medullary carcinomas.

5. *Autoimmunity:* Hashimoto disease predisposes to lymphoma of thyroid, papillary and medullary carcinomas.

Pathogenesis

Two different stem cell types contribute in the development of thyroid carcinomas, namely: the *follicular epithelium* (endodermal origin) and the *parafollicular C-cell* (neural crest origin). Follicular epithelium gives rise to follicular, papillary, Hurthle cell, insular and anaplastic carcinoma. The anaplastic carcinoma may develop de novo or on top of well-differentiated carcinoma (usually papillary type). Medullary carcinoma arises from stem cells of the parafollicular C-cell.

Molecular Oncogenesis

The genetic defects are distinctly different in the four major histologic types of thyroid carcinomas (Kondo et al, 2006). But, ultimately, two signal transduction pathways are activated, namely: RAS/MAPK and PI-3K/AKT resulting in cell growth advantage and survival (Chapter 6).

1. *Papillary carcinoma*: The two characteristic mutations are RET mutation (30-70%) and BRAF mutation (50%). RET is a proto-oncogene located on chromosome 10q 11.2 and encodes a receptor tyrosine kinase. Mutation of this gene (most common after radiation exposure) results in a constitutive expression of the receptor and activation of mitogenic signals. BRAF is a negative regulator of RAS/MAPK mitogenic signal pathway; hence, its mutation will activate this signal pathway.

2. *Follicular carcinoma*: Two characteristic mutations are reported, namely: RAS (40%) and PTEN (10%). Both will result in activation of mitogenic signals. In addition, a unique translocation t (2;3) creates a fusion gene PAX-8 (35%) with oncogenic gene product.

3. *Medullary carcinoma.* It is characterized by RET mutation (100% in familial cases and 50% in sporadic cases). However the codons affected in RET gene are different from those of papillary carcinoma.

4. *Anaplastic carcinoma.* Besides RAS mutation, characteristic additional mutations occur, namely: TP53 (65%) and β-catenin (45%).

Macroscopy

Grossly, papillary carcinoma may appear as solitary and encapsulated (P 19-1), invasive (P 19-2), cystic (P 19-3), multiple, (<1 cm) or microcarcinoma (P 19-4A). It rarely invades thyroid capsule. Conversely, follicular carcinoma is either minimally-invasive, (simulating thyroid adenoma but with thick capsule), or widely invasive, infiltrating thyroid capsule and important structures in the neck such as carotid vessels and trachea (P 19-4B and P 19-5).

Histopathology

The classification of thyroid carcinomas is presented in (Table 19-2 and Fig 19-1). The diagnosis of *papillary carcinoma* is mainly based on nuclear features (clear nuclei) and it may show a papillary or follicular pattern (P 19-6 to P 19-9). Four variants of papillary carcinoma (tall cell, columnar cell, clear cell and diffuse sclerosis) are tumors of intermediate malignancy (P 19-10).

The diagnosis of *follicular carcinoma* (P 19-11) is based on capsular or angioinvasion (Fig 19 -2 and Fig 19-3 and P 19-12 to P 19-14). Follicular tumors of intermediate malignancy include: Hurthle cell carcinoma (eosinophilic cells), and insular carcinoma which forms islands of tumor cells in fibrovascular stroma (P 19-15 and P 19-16).A comparison between papillary and follicular carcinomas is shown in (Table 19-3).

Table 19-2 Histologic Classification and Relative Frequency of Thyroid Cancer

Type	Frequency %
Well-differentiated	90
Papillary (80%)	
Follicular (10%)	
Medullary	6
Familial (MEN)*	
Sporadic	
Anaplastic Carcinoma	1
Lymphoma	3

*MEN multiple endocrine neoplasia is subclassified into MEN-1 and MEN2

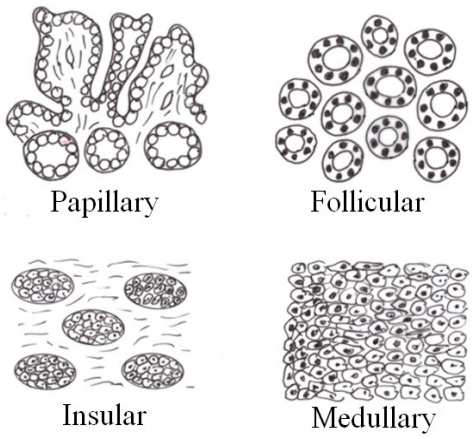

Fig 19-1 *The histologic patterns of thyroid carcinoma. Papillary carcinoma presents with both papillary or follicular pattern, but the nuclei are clear. Follicular carcinoma has dark nuclei. The insular variant of follicular carcinoma, so named, because it resemble islands (Insula means island). Medullary carcinoma is composed of round and elongated cells with solid pattern*

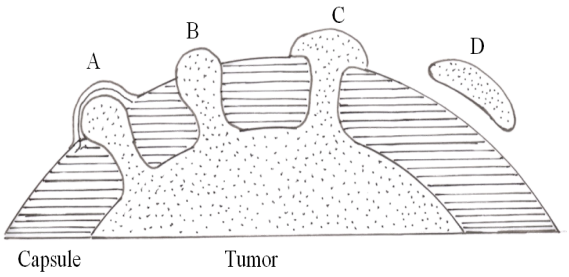

Fig 19-2 *Criteria of capsular invasion in minimally-invasive follicular carcinoma A. Perpendicular invasion but still covered by thin capsule, B. Complete penetration of capsule, C. Mushroom formation by tumor and D. Presence of malignant tissue inside and outside the capsule (P 19-11).*

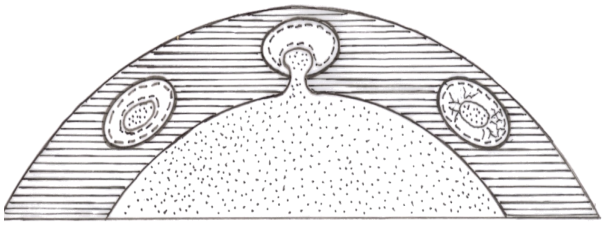

Fig 19-3 *Angioinvasion in thyroid carcinoma. It is best studied at the capsule of tumor, which is characteristically thick and contain thin-walled blood vessels compared to the capsule of benign adenoma. A true malignant invasion must be covered by endothelial cells to distinguish it from dislodged tumors into blood vessels as a result of manipulation (P 19-13 and P 19-14).*

Anaplastic carcinoma is the most lethal and unfavorable tumor (Table 19-6) affecting elderly females. It is composed of spindle cells, giant cells and squamoid cells (P 19-17) with marked anaplasia. It spreads both locally and to the lungs.

Medullary thyroid carcinoma (MTC) is a rare (6%) neuroendocrine tumor of intermediate malignancy arising from parafollicular C-cells. It secretes calcitonin (especially after calcium provocation), as well as, VIP, CEA and ACTH. The tumor is commonly (75%) sporadic, whereas, 25% occur in one of three well-defined (MEN-2) familial syndromes. The histopathology of medullary thyroid carcinoma is characterized by solid groups of cells with amyloid in the stroma (P19-18 and P 19-19). By immunohistochemistry, the tumor is positive for calcitonin, NSE and chromogranin. In individuals with MEN-2 syndrome, C- cell hyperplasia may be detected in needle biopsies before the development of carcinomas (P 19-20).

Table 19-3 Papillary and Follicular Carcinomas Compared

	Papillary	**Follicular**
Frequency	80%	10%
Etiology	Radiation	Iodine def.
Gene Mutation	RET	RAS, PTEN
Median age	40 years	50 years
Multicentricity	Multifocal (30%)	Unifocal
Capsulation	-	+
Empty nuclei	+	-
Psammoma bodies	+	-
Node metastasis	35%	5%
Blood spread	1%	5%
10-year survival*	85-98%*	70-92%

* High survival figure obtained from recent reports (Kantarjian et al, 2011)

Needle Aspiration Cytology

Fine needle aspiration cytology (FNAC) is indicated as a first step for all palpable thyroid nodules (>1 cm). For smaller lesions, the procedure is guided by ultrasound. Cytology is reliable in the diagnosis of papillary, medullary and anaplastic carcinomas (P 19-21), but indefinitive for follicular lesions (P 19-22). Tissue examination is needed in such cases to distinguish between follicular adenoma and carcinoma and reach a precise diagnosis. The diagnostic accuracy of FNAC is about 95%, with false negative diagnosis of 5% and false positive diagnosis of 1 to 2%.

Recently, it is recommended to use five diagnostic categories which are associated with different risks of malignancy and subsequent management strategies (Table 19-4). The rate of unsatisfactory or inadequate samples (Category 1) varies between 5% to 20% depending on the experience in taking the sample. A satisfactory sample must contain a minimum of 6 clusters of epithelial cells in the smears. Cysts with solid mural component should be reaspirated to avoid false negative results.

Non-neoplastic lesions (Category 2) are easily diagnosed. Thus, nodular goiter shows macro– and micro-follicles with abundant colloid. Lymphocytic thyroiditis, and Hashimoto disease show many mature lymphocytes in the smears.

The indeterminate follicular lesion (Category 3) includes follicular adenoma and well-differentiated follicular carcinoma. Tissue examination for evidence of capsular or angioinvasion is needed to make the distinction and reach a definitive diagnosis. However, a neoplastic follicular lesion must be suspected when the colloid is scanty, high cellularity, and large overlapping nuclei. Ultrasonography may also help. Features such as hypoecoic lesion, irregular borders, microcalcification and abnormal vessels, all favor a malignant nodule.

Differential Diagnosis

The following thyroid lesions may simulate thyroid malignancy:

1. Adenoma and follicular carcinoma. Follicular adenoma differ grossly from carcinoma by its thin capsule, gray color with shining cut surface and soft consistency and may show cystic change and hemorrhage (P 19-23). Thyroid adenomas do not show capsular or angioinvasion. Some unusual variants of adenomas (trabecular and signet ring,

Table 19-4 Needle Aspiration Cytology of Thyroid Nodule, The Bethesda Diagnostic Categories and Subsequent Management

Category and Cytologic Diagnosis	Risk of Malignancy	Management
1. Inadequate sample (nondiagnostic)	-	Repeat, under Ultrasound guidance
2. Non-neoplastic (Nodular hyperplasia and thyroiditis)	< 1%	Follow up every 4 months
3. Undeterminate Significance (Follicular lesion)	5-10%	Review cytology Ultrasonography Lobectomy and FS
4. Suspicious of neoplasia	20-75%*	Lobectomy and FS
5. Positive for malignancy (Papillary, medullary, Anaplastic or lymphoma)	100%	Total Thyroidectomy

Abbreviation: FS Frozen section, *Malignancy risk is 20-30 if the diagnosis is suspicious of neoplasm, but 50-75% if suspicions of malignancy

may be confused with malignancy (P 19-24 and P 19-25) but again they lack invasiveness.

2. Nodular goiter (dominant nodule) and *follicular carcinoma*. The follicles are of large size and non-invasive (P 19-26), and lack a capsule.

3. Hyperplastic pseudopapillae and papillary carcinoma. The nuclei are hyperchromatic and stroma contains follicles rather than fibrous tissue (P 19-27).

4. Dyshormonogenetic goiter and *widely invasive follicular carcinoma*. It is caused by a genetic defect of thyroxin synthesis. Grossly it presents by multiple nodules with fibrosis inbetween (P 19-28). Histologically, the follicles are hyperplastic but lack colloid. It affects mainly adolescents with evident hypothyroidism

5. Hashimoto disease and lymphocytic thyroiditis produce firm ill-defined whitish lesions which grossly may simulate malignancy (P 19-29). However, histologically, the lesions are rich in lymphoid tissue with germinal centers, a feature completely against malignancy.

6. Grauulomatons thyroiditis (de Quervain disease). This possibly viral or autoimmune lesion produces firm thyroid nodules which may be mistaken for malignancy. The diagnostic feature are the large multinucleated giant cells phagocytosing colloid (P 19-30).

7. Thyroid teratoma produces a firm mass lesion, but grossly it is multicystic (P 19-31) and histologically the multiphasic complex structure is evident.

Spread

1. Local spread: Initially, there is invasion of tumor capsule and thyroid tissue, then invasion of thyroid capsule which is a critical step. With extrathyroid spread, important structures in the neck (trachea, esophagus, carotid artery or jugular vein) may be invaded.

2. Lymphatic spread: The first station of metastases is the central group of neck (level VI) and bilateral nodal spread is common (Fig 19-4).

3. Metastatic spread: Hematogenous spread metastases, mainly, in lungs and bones.

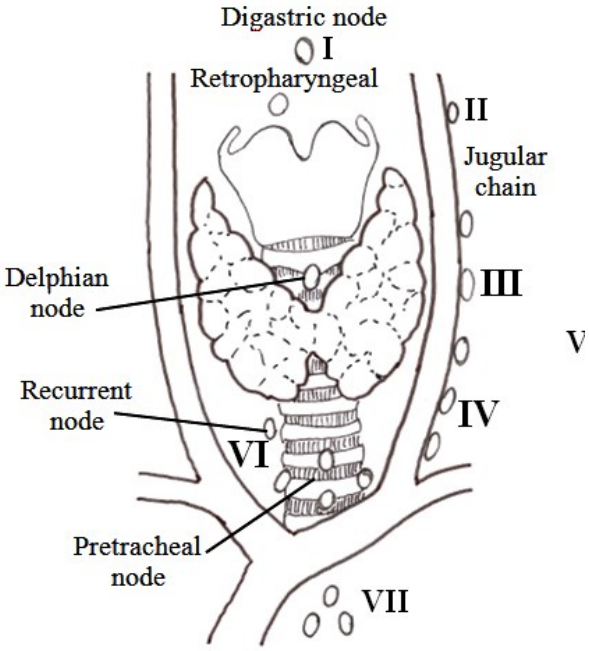

Fig 19-4 *The regional lymph nodes of thyroid gland. The first station is the central or level VI group of cervical nodes. The jugular chain and mediastinal nodes may also be involved by metastases. Affection of digastric and retropharyngeal lymph nodes is rather rare. The frequency of node metastases is 50% in medullary carcinoma, 35% in papillary carcinoma and 5% in follicular carcinoma.*

Staging

The stage of tumor is the most important indicator of survival. The TNM staging system (which integrates histologic type of carcinoma) is presented in (Table 19-5, Fig 19-5 and Fig 19-6). In the SEER staging system, the TNM stages II and III are considered regional. The 5 year survival in SEER data is 99.6% for localized tumors, 93.4% for regional tumors and 49.3% for distant tumors. Survival of different histologic types is presented in (Table 19-6).

Table 19-5 TNM Pathologic Staging of Thyroid Cancer

Stage	Papillary or follicular (Well differentiated)		Medullary	Anaplastic
	Age <45 yr	Age> 45 yr		
I	Any T, any N, MO	T1	T1	-
II	M1	T2-T3	T2-T4	-
III	-	T4 or N1	N1	-
IV	-	M1	M1	Any

(Edge, 2010) N.B. The age of patient, histologic type of tumor and stage are integrated together in this system.

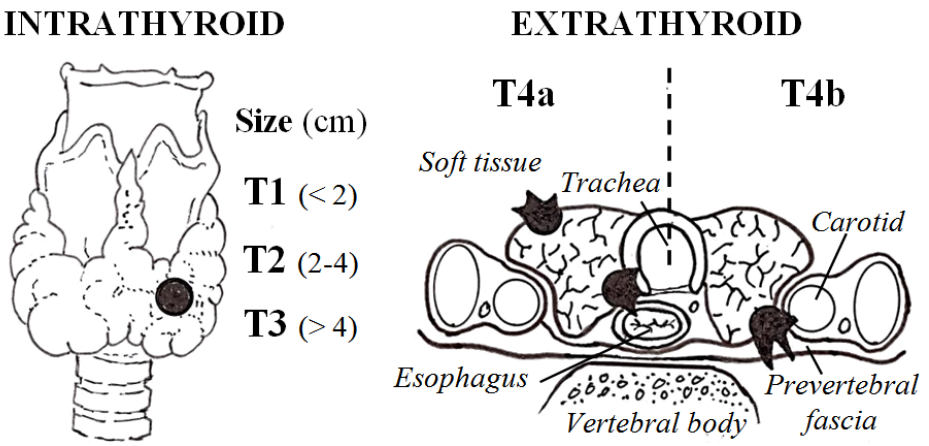

Fig. 19-5 Pathologic T categories of thyroid carcinoma. Tumor size and extrathyroid spread are key points in this classification.

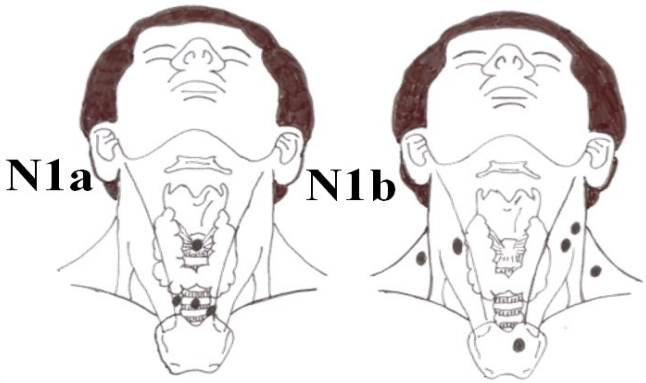

Fig 19-6 *The N categories of thyroid carcinoma is subclassified according to site of metastases (a) are confined to the central group VI and (b) other groups are involved.*

Prognostic factors

The AMES system (Cady and Rossy 1988) considered Age, Metastases, Extrathyroid extension and Size of tumor as important indicators of survival in well-differentiated thyroid carcinoma (Table 19-7). An advantage of this system is its dependence on clinical parameters; hence, it is applicable preoperatively and could serve as a guide for therapy. The 40-year survival rate was about 95% for low-risk patients, compared with about 45% for high-risk patients.

Table 19-6 Survival of Thyroid Carcinoma as Related to Histologic Type

Prognostic group	5-Year Survival %
Favorable	> 90%
Papillary	
Follicular	
Intermediate	40-80%
Tall cell papillary	
Columnar cell papillary	
Diffuse sclerosis	
Hurthle cell carcinoma	
Insular carcinoma	
Medullary	
Unfavorable	< 10%
Anaplastic Carcinoma	

Table 19-7 The AMES Prognostic System for Differentiated Thyroid Cancer

Low-Risk	High-Risk
1. No metastases, Low-risk age and tumor	1. Metastases, or
2. No Metastases, High-risk age but low-Risk tumor	2. High-risk age* With high-risk tumor**
DF Survival: 95%	DF Survival: 45%

*Male >40 years or female >50 years **Size >5 cm or extrathyroid spread

PARATHYROID TUMORS

Embryology and Anatomy

The superior parathyroid glands develop from the fourth branchial pouch, and the inferior parathyroid glands develop from the third pharyngeal pouch along with the thymus (Chapter 4). Both neural crest and endoderm participate in parathyroid histogenesiss. The four glands descend to their normal position in relation to upper and lower poles of thyroid. Ectopic locations are more common in inferior parathyroid glands (mediastinum or intra-thymic). The superior glands may rarely be located retroesophageal or intrathyroid. Five percent of individuals have more than four glands.

Histologically, the parathyroid gland contains 4 cell types, namely: (1) *chief cell*, with basic secretory function of parathormone which stimulates osteo-clasts resulting in liberation of calcium in blood from its bony store, (2) *oxyphil cell*, with granular eosino-philic cytoplasm (mitochondria rich), only seen in adults with focal distribution, (3) *water clear cell* (a rare type) and (4) *fat cells* or adipocytes, which increase with age up to 50%.

Pathology

Tumors of the parathyroid gland include: hyperplasia, adenoma and carcinoma. Hyperplasia and adenomas may be sporadic or familial (as a component of MEN-I or IIA syndromes). Hyper-plasia affects the gland diffusely (P 19-32), but an adenoma is a localized lesion often compressing remnants of normal parathyroid tissue (P 19-33). The histologic structure may be a chief, oxyphil or clear cell type.

Parathyroid carcinoma is a rare tumor which presents over a wide age range, from 28-72 years (mean 45). It has an equal sex incidence, compared with adenoma which is more common in females. About one-third of patients present with a palpable neck mass due to the relatively large tumor size. It is difficult to distinguish carcinoma from adenoma of parathyroid gland. However, helpful histopathologic diagnostic criteria include: fat invasion, angioinvasion. desmoplastic stroma, necrosis, spindle-shaped tumor cells, elevated mitotic count and abnormal mitosis (P 19 -34). The prognosis is poor, with approximate 50% 10-year survival. More patients die from severe hypercalcemia rather than metastatic disease.

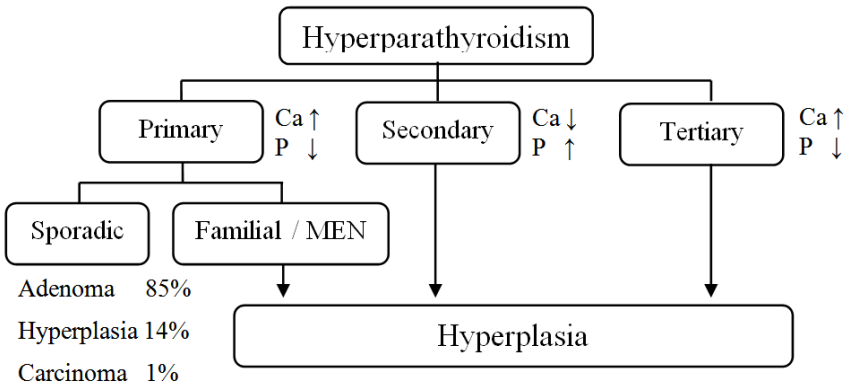

Fig 19-7 *Primary hyperparathyroidism is the result of a parathyroid pathology or syndromic. Secondary hyperparathyroidism is a reversible hyperplasia associated with chronic renal failure. Prolonged secondary hyperplasia may develop autonomous function referred to as tertiary hyperplasia (irreversible state). The profile of calcium and phosphorous in blood is distinctively different in the 3 types of hyperparathyroidism, but, parathormone is high in all types.*

Primary hyperparathyroidism is commonly (85%) caused by a benign parathyroid tumor (adenoma or hyperplasia), rarely (1%) a carcinoma (Fig 19-7). There is hypercalcemia, osteolytic bony changes (osteitis fibrosa cystica), renal calculi, and metastatic calcification in kidneys, stomach and lungs.

ADRENAL CORTICAL TUMORS

Adrenal cortical tumors (hyperplasia, adenoma and carcinoma) are epithelial in origin, whereas, tumors of the adrenal medulla are neuroendocrine neoplasms (Table 19-8). Autopsy series suggest that asymptomatic *adrenal adenomas* are present in 2% of adult patients, and in 20% of hypertensive patients, and up to 30% of elderly obese diabetic patients. The frequency of incidental adrenocortical nodules detected by CT scan is about 1% (P 19-35, P 19-36 and P 19-37).

Adenocarcinoma of the adrenal cortex is rare, accounting for 0.02% of all cancers. It has a bimodal age distribution at 5 years and 50 years, and the sex incidence is equal. Distinction from adrenal cortical adenoma is difficult (P 19-38 and P 19-39), however, the following parameters are helpful indicators of malignancy: (1) clinical: old age and adrenogenital syndrome, (2) gross: size >5 cm, weight >50 g, necrosis and capsular invasion, (3) histologic: mitosis >1 per 10 HPF, abnormal mitosis, angioinvasion, cytoplasmic eosinophilia, spindle cells and strong vimentin positivity and (4) DNA aneuploidy. The 10 year survival rate is about 20%. The differential diagnosis of adrenal cortical carcinoma is renal cell carcinoma (Table 19-9).

Table 19-8 Classification of Primary Adrenal Tumors

	Benign	Malignant
Epithelial (cortical)	Adenoma	Carcinoma
Neuro-endocrine (medullary)	Pheochromocytoma Ganglioneuroma Composite tumor	Pheochromocytoma Neuroblastoma Malignant melanoma
Others	Myelolipoma Adenomatoid tumor	

N.B. Common origin of metastases are the lung and breast.

Table 19-9 Differential Diagnosis of Adrenal and Renal Carcinoma by Immunophenotyping

Marker	Adrenal cortical Ca.	Pheochromocytoma	Renal Ca.
Pancytokeratin	+	-	+
EMA	-	-	+
Leu-M1 (CD-15)	-	+	+
Chromogranin A	-	+	-
Vimentin	+	-	+
Inhibin	+	-	-

(Livolsi and Asa, 2002)

Adrenal cortical tumors produce a variety of clinical endocrine syndromes according to the hormones secreted (Table 19-10). Hypercorticalism *(Cushing syndrome)* may result from several causes (Table 19-11 and Fig. 19-8), but the most common cause is iatrogenic administration of steroids to treat other diseases. There are four basic causes of non-iatrogenic Cushing syndrome: (1) Hypercorticalism caused by pituitary-dependent ACTH overproduction (Cushing disease), which accounts for 65% of cases in adults, (2) Autonomously (cortisone) secreting adrenocortical tumors (20%), more commonly an adenoma rather than carcinoma, (3) Ectopic production of ACTH and/or corticotropin releasing factor (CRF) by non-endocrine tumors (e.g. small cell lung cancer, carcinoid tumors, pheochromocytoma, medullary carcinoma of thyroid and thymoma) contributing about 15% of cases; and (4) Rare cases of adrenocortical hyperplasia. Ectopic ACTH syndrome is distinguished from classic Cushing's disease by the male predominance marked wasting rather than obesity and rise of NSE in the serum.

In order to determine the cause of hypercorticalism, multiple tests are performed. High-dose dexamethasone (8 mg/dL) will suppress urinary levels of 17-hydroxysteroids or free cortisol to less than 50% of baseline levels in patients with pituitary dependent hypercorticalism (Cushing's disease), but it will not suppress patients with primary adrenal causes of hypercorticalism or ectopic ACTH syndrome. Serum levels of ACTH is reduced in functioning adrenal cortical tumors but not in other causes of hypercorticalism. A very high level of serum ACTH is characteristic of ectopic ACTH syndrome.

The most common cause of *primary aldosteronism (Conn syndrome)* is an aldosterone-producing adenoma (70%), next is hyperplasia and third is carcinoma. The essential diagnostic features of primary aldosteronism are: hypertension, hypokalemia, hyperaldosteronism and decreased plasma renin levels. Secondary aldosteronism which occurs with renal artery stenosis, cirrhosis and conditions of decreased kidney perfusion is diagnosed by an increase in plasma renin activity.

The adrenogenital syndrome is more commonly associated with malignant rather than benign adrenal cortical tumor. The clinical manifesttations depend on the type of hormone secreted and the sex of the patient.

Table 19-10 Functioning Adrenal Cortical Tumors and Their Corresponding Frequency of Malignancy

Hormonal Syndrome	Malignant (%)
Virilizing	45
Cushing	30
Pheochromocytoma (Hypertension)	10
Feminizing	6
Non-Functioning	< 5
Aldosteronism	< 1

Table 19-11 Causes of Cushing's Syndrome

ACTH-Dependent
Pituitary/hypothalamic disorder
Ectopic ACTH syndrome
Iatrogenic ACTH
ACTH-Independent
Adrenal tumor
Adrenal hyperplasia
Iatrogenic corticosteroids

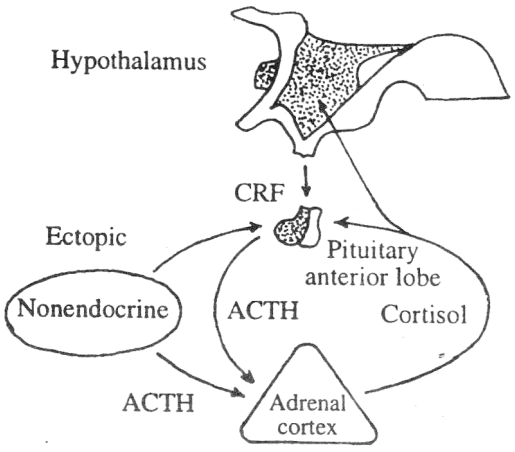

Fig 19-8 *Endocrine basis of Cushing syndrome. (CRF corticotrophin releasing factor, ACTH adrenocorticotropic hormone). Cushing syndrome is commonly the result of pituitary or adrenal hyperfunction, but, rarely it may represent a paraneoplastic syndrome due to ectopic production of ACTH from a nonendocrine malignant tumor.*

ANTERIOR PITUITARY TUMORS

Classification

The current classification of anterior pituitary tumors is based on cell type as determined by immunohistochemistry against the specific hormones and by electron microscopy. The frequency of tumor types and their associated hormonal syndromes are presented in (Table 19-12) and histologic features shown in (P 19-40 to P 19-42) The tumors are also classified according to their size into: microadenoma (<1 cm) and macroadenoma (>1 cm) usually with suprasellar extension, as well as, biologically classified into: benign, invasive and malignant.

Clinical effects

Functioning tumors will present by hormonal syndromes (Table 19-12). Nonfunctioning tumors may present by hypopituitarism or mass effect which may be acute (pituitary apoplexy) due to hemorrhage in the adenoma. The tumor may locally invade the sphenoid or cavernous sinus (cranial nerve palsy) or optic chiasma (visual defects).

Prognosis

The majority of adenomas are benign, but few are of borderline malignancy (locally invasive) or rarely malignant (1%) capable of producing metastases or implants. Evaluation of cell proliferation by MIB-1 or immunoreactivity for p53 and cyclin D1 may help to predict the biologic behavior.

In patients with Cushing syndrome due to ACTH-secreting adenoma, an aggressive tumor develops in the pituitary if adrenalectomy is done (Nelson syndrome). It is caused by loss of the negative corticosteroid feedback mechanism.

TUMORS OF POSTERIOR PITUITARY

Tumors of the neurohypophysis belong to the nervous system and include: (1) gangliocytoma, (2) mixed gangliocytoma-adenoma, (3) astrocytoma (Pituicytoma). Various types of hypopituitarism may occur including Frohlich syndrome (dystrophia adiposogenitalis), dwarfism and diabetes insipidus.

NEUROENDOCRINE TUMORS (NETS)

Neuroendocrine tumors have the enzyme system that can convert some amino acids into bioactive amines with hormone-like effect. The term neuroendocrine indicates expression of neural marker and/or hormonal secretion. Neuroendocrine tumors have a double embryologic origin (neuroectoderm and endoderm), and are classified on this basis into two classes:

Class I. Neuroendocrine tumors of neuroectodermal origin. They arise from the migratory cells of neural

Table 19-12 Classification and Frequency of Anterior Pituitary Tumors

Cell type (Hormone)	Endocrine syndrome	Frequency (%)
Lactotrope (PRL)	Galactorrhea-Amenorrhia*	26
Null (None)		17
Corticotrope (ACTH)	Cushing	15
Somatotrope (GH)	Gigantism, Acromegaly	14
Plurihormonal (PRL+GH)	Multiple	13
Gonadotrope (FSH,LH)	Hypopituitarism	8
Oncocytoma (None)	Hypopituitarism	6
Thyrotrope (TSH)	Thyrotoxicosis	1

Abbreviations: PRL prolactin, ACTH adrenocorticotropic hormone, GH growth hormone, FSH follicle stimulating hormone, LH leutenizing hormone and TSH thyroid stimulating hormone. * Forbes-Albright syndrome

crest (Chapter 4).This group includes: medullary carcinoma of thyroid (C-cell origin), paragangliomas (adrenal and extra-adrenal) and neuroblastoma. The histology is neural with common rosette formation. The precursor amino acid is tyrosine.

Class II. Neuroendocrine tumors of endodermal origin. They are derived from gut epithelium (endoderm). This group includes: neuroendocrine tumors of lung, gastrointestinal tract and pancreas. This group is characterized by an epithelioid histology (simulating carcinoma, hence, the name carcinoid). Their precursor amino acids are tryptophan and histidine.

Despite the different embryologic origin, neuroendocrine tumors have four basic similarities, namely:(1) secretion of bioactive amines detectable in blood and urine, (2) common immunoreactivity to chromogramin A, synaptophysin, CD56 and neuron-specific enolase (NSE) and (3) similar eltectron microscapic features (membrane-bound neurosecretory granules) and (4) an indolent clinical course (compared to carcinomas)

Both classes of NETs show elevated level of chromogranin A in serum. However, analysis of metabolic products in 24 urine sample may be done, namely: catecholamines (VLA and VMA) in class I NETs and 5-H/AA in class II NETs.

CLASS I. NEUROENDOCRINE TUMORS (NEUROECTODERMAL ORIGIN)

PHEOCHROMOCYTOMA

Pheochromocytoma is a neuroendocrine tumor of the chromaffin cells of the sympathoadrenal system. It is by definition, a paraganglioma of the adrenal medulla. It occurs in about 1% of hypertensive individuals. The peak age incidence is 50 years. About 10% of cases affect children, 10% are extra-adrenal (lower para-aortic sympathetic), 10% bilateral, 10% familial (as part of MEN II syndrome), and 10% are malignant (more risk with extra-adrenal location). The tumor is histogenetically related to ret protooncogene expression.

Grossly, the tumors are usually encapsulated, highly vascular with yellowish to reddish brown color (P 19-43). Hemorrhage and necrosis are often present. Histologically, the tumor is composed of clusters of finely granular and basophilic or eosinophilic cells separated by endothelial lined spaces (P 19-44 and Table 19-13). Immunohistochemically, tumor cells are positive for NSE and chromogranin (P19-45). It is difficult to predict biologic behavior from histology. About 10% of tumors considered benign will subsequently develop metastases.

Adrenal pheochromocytoma (a sympathetic related paraganglioma) secretes mainly, epinephrine, whereas, extraadrenal paragangliomas secrete norepinephrine only especially those associated with the parasympathetic system. The clinical diagnosis of pheochromocytoma is confirmed by the demonstration of excessive levels of catecholamines or their metabolites in urine or serum . Measurement of 24-hour urinary catecholamines and their metabolites: vanillyl mandelic acid (VMA) and metanephrines, remain the standard diagnostic tests.

NEUROBLASTOMA

"Neuroblastoma is a tumor of adrenal medulla or sympathetic ganglia of neural crest cell origin (primitive sympathogonia cells of the neuroendrocrine type). Embryogenesis of adrenal medulla continues during the first year of life. Persistence and transformation of these embryonal structures may give rise to neuroblastoma.

Table 19-13 Histologic Criteria of Malignant Pheochromocytoma

Small cell size
Confluent necrosis
Angioinvasion
Invasion of soft tissue
Lymph node metastases
Absence of hyaline globules
Absence of sustentacular cells (S-100 negative)
Ki-index (> 5% /HPF)*
P53 overexpression
Bcl-2 expression

(Thompson, 2009/August et al 2004) * Obtained by counting labeled nuclei among 1000 cells under high power microscopy

Incidence

Neuroblastoma is the third most common malignancy of childhood (7-11%), and the second commonest solid tumor after CNS tumors. It is the first most common solid tumor in infants younger than one year. About 60% of all cases present in children younger than two years and 97% of cases occur in children younger than 10 years. The median age is 2 years.

Pathogenesis

Neuroblastoma arises from neuroendocrine stem cells that migrate from neural crest to adrenal medulla in early embryonic life. Foci of these immature cells are found in the adrenal medulla in one in every 200 autopsies of newly-born infants, and are referred to as neuroblastoma in situ. The majority undergoes spontaneous regression, but some may progress to neuroblastoma. Knudson regards neuroblastoma in situ as representing lesions with germline mutation, but lacking a second hit.

Cytogenetic studies show deletion of the distal short arm of chromosome 1 in 70% of cases. This correlated with poor prognosis. There is also loss of heterozygosity at 14q which is present in up to 50% of cases.

Amplification of N-myc (located on chromosome 2) is seen in about 30% of tumors and this correlates very closely with advanced-stage disease and, within each stage, is valuable to predict unfavorable outcome.

Macroscopy

The most common site of primary disease is the abdomen (68%), of which 65% involve the adrenal gland. Other sites are chest, pelvis, neck and brain. Adrenal tumors range in size from microscopic nodules up to 10 cm masses and they are characteristically present as well-demarcated masses with smooth or nodular surface, appearing soft in consistency with areas of hemorrhage and necrosis.

Histopathology

The tumor is characterized by small, round, blue cells which may show full range of neuronal differentiation from primitive pure neuroblastoma to a highly differentiated tumor with ganglionic cells. Pseudorosette formation is common in classic neuroblastoma (Fig 19-9). Tumor markers include: NSE, synaptophysin, chromogranin and S -100. Electron microscopy demonstrates dense core granules and neuritic processes.

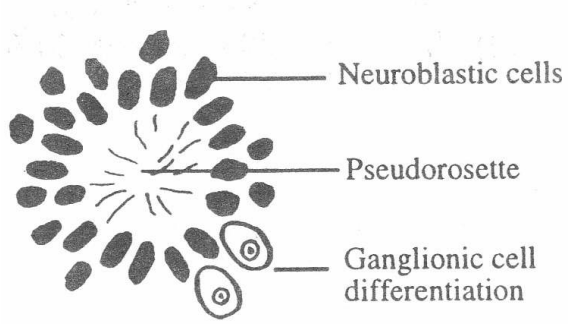

Fig 19-9 *Histopathology of Neuroblastoma. The presence of pseudorosettes with central fibrillary filaments (Homer-Wright type) is diagnostic. However, the presence of nerve ganglion cells is a feature of tumor differentiation (a favorable histology). Ganglion calls immunostain specifically to neurgilament protein.*

Neurogenic tumors are classified into 3 groups (Fig 19-10): neuroblastoma (NB), ganglioneuroma (GN) and ganglioneuroblastoma (GNB). These subgroups recapitulate the stages of normal differentiation of neural crest stem cells.

In neuroblastoma, the tumor is composed predominantly (>50%) or exclusively of neuroblasts and stromal neurophils (P 19-46). Shimada terminology for this tumor is "stroma poor". Tumors with >5% ganglionic cells are known as differentiating neuroblastomas. Ganglionic cells are characterized by abundant cytoplasm, well-defined cell border and eccentric nuclei (P 19-47).

Ganglioneuroma, a benign tumor, is composed exclusively of mature ganglion cells, neurites accompanied by Schwann cells and fibrous tissue (P19-48).

Ganglioneuroblastoma is composed of a predominant benign GN component (>50%) and a small NB component. Three subtypes are recognized (Fig 19-10): Nodular, intermixed and borderline. Shimada terminology for these tumors would be stroma rich neuroblastoma.

The differential diagnosis of neurablastoma is other round cell itumors and metastases (P 19-49).

Spread

Spread is either: (1) local, (2) lymph node metastases (25%) or (3) hematogenous with distant metastases to bones (especially skull), liver and skin. About 60% of patients present initially with metastatic disease (Fig. 19-11).

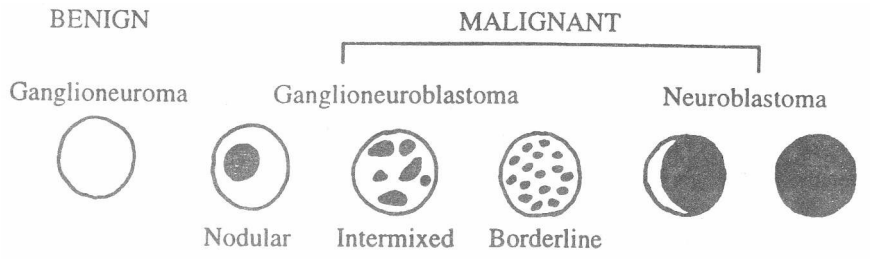

Fig 19-10 *Classification and terminology of neuroblastic tumors, benign component (white) and malignant component (black).*

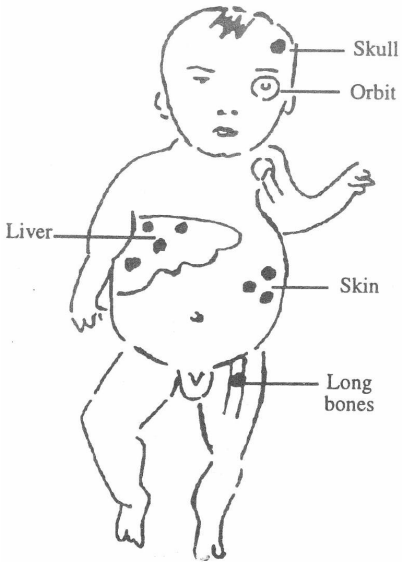

Fig 19-11 *Common sites of metastases from neuroblastoma*

Staging

The international neuroblastoma staging system is presented in **(**Table 19-14). This tumor is unique in the fact that patients less than one year of age with limited dissemination of disease show a good prognosis (stage 4s). This is due to the fact that the tumor has a marked tendency to spontaneous regression and differentiation into more mature forms specially during the first year of life.

Prognosis

Prognostic factors in neuroblastoma include a number of clinical, morphologic and biologic variables (Table 19-15). The most significant in predicting cure are: age, stage, site, grade and biologic markers.

1. *Age:* The outcome of infants less than 2 years is significantly better than in those who are older. However, in other series (Joshi, 1992) the cutoff point for better survival is one year. This is explained by the marked tendency of neuroblastoma to undergo spontaneous regression and differentiation in young infants.

2.. *ISSN stage:* The survival of patients with stages I and IVS neuroblastoma is 80-90%. In contrast, the survival of patients in stage IV is 10-60%, being most unfavorable in patients above the age of 2 years.

Site: Neuroblastomas arising in the adrenal glands carry a worse prognosis than those arising in extra-adrenal sites.

4.*Shimada grading:* In 1984, Shimada introduced his grading system which is based on the age of patient, amount of stroma, tumor undifferentiation and extent of mitosis-karyorrhexis index counted per 5000 cells. The stroma is defined as Schwannian rather than other supportive elements and tumors are divided into two broad groups: stroma-rich and stroma-poor. Shimada grading system is applicable to both neuroblastoma and ganglioneuroblastoma. Patients are divided into those with favorable histology and unfavorable histology, with survival of 87% and 7% respectively (Table 19-15).

5. *Joshi grading:* In this system the three variables found to be associated with favorable prognosis are: low mitotic rate MR (<10 per 10 HPF), tumor calcification and age <1 year. Tumor grades are defined as follows: Grade 1, low (MR) and calcification, Grade 2, low mitotic rate or calcification, and Grade 3, high MR and absence of calcification. The 5 year survival is 90% for Grade 1, 78% for Grade 2 and 34% for Grade 3.

The age and tumor grade are independent prognostic variables and when combined it is

Table 19-14 International Staging System for Neuroblastoma (ISSN)

Stage	Description	Survival
I	Localized tumor with complete gross excision and no lymph node metastases	90%
IIA	Unilateral tumor with incomplete gross excision and negative nodes	75
IIB	Unilateral tumor with positive ipsilateral nodes	40-70%
III	Tumor infiltrating across midline Unilateral tumor with contralateral positive nodes Midine tumor with bilateral node involvement or extension by infiltration	40-70%
IV*	Dissemination to distant lymph nodes, bone, bone marrow, liver or other organs (except as defined in stage 4S)	10-60%
IVS	Localized primary tumor (as stage 1 or 2) with dissemination limited to liver, skin and/or bone marrow (<10% tumor) in infants younger than 1 year	80%

(Philip, 1992) *Most common stage (60%)

Table 19-15 Prognostic Factors in Neuroblastoma

Prognostic Factor	Favorable	Unfavorable
Age	<1 year	>1
Stage	I, II, IVS	III, IV
Histology	Stroma rich	Stroma
MYC-N	Normal	Amplified (>10 copies)
DNA index	Hyperdiploid	Diploid
Chromosome 1p	Normal	Deletion
Ferritin	< 143 ng/ml	>143 ng/ml
LDH	Low	High
NSE	<100	>100
Chromogranin		>190 ng/ml
Urine VMA/HVA	>1	<1

(Thompson, 2006)

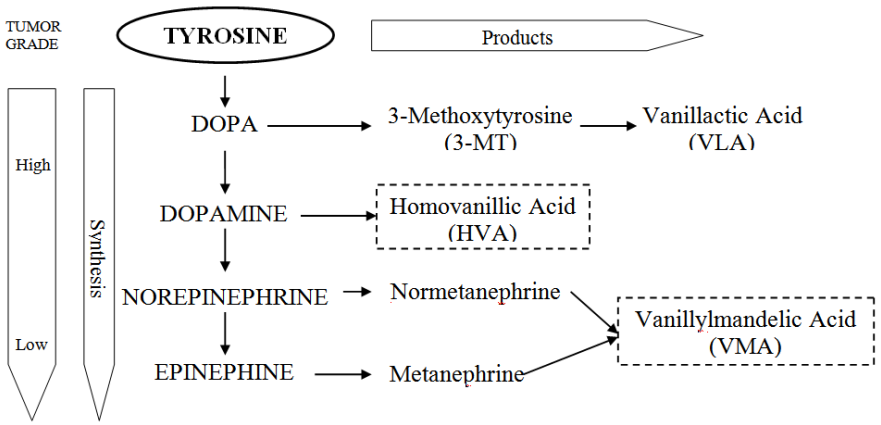

Fig 19-12 *Pathophysiology of catecholamines in neuroectodermal neuroendocrine tumors (neuoblastoma and pheochromocytoma). Tyrosine is a precursor amino acid, but, VLA and VMA are metabolic products excreted in urine and correlate with tumor grode. A high VMA/HVA ratio (>1) is a favorable finding denoting a well differentiated tumor.*

Table 19-16 Risk groups of Neuroblastoma Based on Age, Grade and 5-Y Survival

Low Risk	High Risk
All ages, grade 1	All ages, grade 3
≤ 1 year, grade 2	>1 year, grade 2
Survival 92%	Survival 57%

(Jushi, 1992)

possible to define two risk groups: low-risk and high-risk with 5-year survival of 92% and 57% respectively (Table 19-16). This new grading system has the following advantages: 1) use of familiar terminology and histologic features in grading, and 2) relative ease of assessment because the degree of tumor cell differentiation does not need to be determined. However, Joshi grading system is not applicable for ganglioneuroblastoma, hence; Shimada grading system is used instead for this subtype.

6. *Biologic markers:* Neuroblastoma cells secrete catecholamines in 90% of patients, which could be detected in urine. Dopamine, vanillyl mandelic acid (VMA) and homovanilic acid (HVA) are the most frequent catecholamine precursors and metabolites produced. There is some correlation between the degree of tumor differentiation and the type of catecholamine metabolite. Thus, well-differentiated tumors secrete greater amounts of VMA, whereas, undifferentiated tumors secrete more of HVA. Hence, a low VMA/HVA ratio (<1) is associated with unfavorable prognosis (Fig 19-12).

Other biologic markers associated with unfavorable prognosis include: high serum neuron-specific enolase (>100 ng/ml), high serum ferritin (>143 ng/ml), high serum lactic dehydro -genase LDH (>1500 u/ml). The molecular biological marker most related to prognosis in neuroblastoma is N-myc amplification.

7. *DNA ploidy:* Contrary to other cancers, diploid neuroblastomas (DNA index DI=1) are more unfavorable tumors than hyperdiploid ones (DI >1). Diploid tumors are more likely to have advanced stages of the disease and do not respond well to combination chemotherapy.

CLASS II. NEUROENDOCRINE TUMORS (NETS)

(ENDODERMAL ORIGIN)

The gastrointestinal tract is the most common primary site for NETs, accounating for about 67% of all cases (constituting 20% of all gastrointestinal cancer). Other less common sites of NETs are: the lung (25%), pancreas (6%) and other miscellaneous sites (2%)

About 10% of NETs occur in the context of multiple endocrine syndrome (MEN type I). Only 10% of localized NETs are functioning and

present by carcinoid syndrome (up to 50% in advanced cases). The risk of malignancy is extremely variable and generally related to the site and hormone produced, very low (<10%) in insuli -nomas and pheochromocytoma, intermediate (20 -50%) in extra-adrenal paragngliomas and gastro-intestinal NETs, and high (>80%) in gastrinoma and glucagonoma.

Recently, the WHO introduced a revised classification and terminology of NETs (Bosman et al, 2010). The term neuroendocrine replaces carcinoid, and tumors are classified into three grades according to mitotic activity (Ki-67 labeling index). This classification covers NETs of gastrointestinal tract, as well as, the endocrine pancreas, which are grouped together under the complex term gastro-entero-pancreatic neuro-endocrine tumors or in short GEP-NET (Table 19-17).

Pathophysiology

NETs are capable of amide precursor uptake and decarboxylation, hence, the previous name APUD cell system. They can synthesize numerous bioactive amines and peptides. Thus, serotonin (5HT) is synthesized by the tumor from trypto-phan and subsequently metabolized in the liver to the inactive 5-hydroxy-indole acetic acid (5-HIAA) which appears in urine. In bronchial NETs, however, histamine is synthesized by the tumor from histidine and is secreted in urine together with 5-HTP (Fig 19-13). NETs also release the enzyme kallikrein, which acts on alpha-2-globulin to produce bradykinin. Other secretory products of NEts include: neuron specific enolase (NSE), chromogranin A and C, prostaglandins, growth hormone, ACTH, VIP and calcitonin. Vaso-dilatation which causes the flushing of carcinoid syndrome is caused by bradykinin, tachykinins, prostaglandins and histamine. However, serotonin may be responsible for diarrhea. The classic triad of dermatitis, dementia and diarrhea (seen with pellagra) may be seen with carcinoids. This syndrome is secondary to niacin deficiency as a result of shunting of dietary tryptophan from niacin synthesis to indole synthesis.

Macroscopy

NETs are characterized by their yellow color, submucosal deep spread (iceberg pattern) and marked fibrosis leading to serosal puckering and stricture formation. NETs of appendix and rectum are commonly smaller than 1 cm in diameter, and hence, are usually incidental findings. Conversely, carcinoids of small intestine are larger in size (2-4 cm) and multiple in 35% of cases. They commonly arise at the terminal ileum.

Table 19-17 WHO Updated Classification and Terminology of Gastro-entero-pancreatic Neuroendocrine Tumors (GEP-NET)

Grade	Ki-index (%)	New terminology	Previous terminology
1	<2	Well-differentiated Neuroendocrine tumor (WDNET)	Carcinoid
2	2-20	Well-differentiated Neuroendocrine Carcinoma (WDNEC)	Atypical carcinoid
3	>20	Poorly-differentiated Neuroendocrine carcinoma (PDNEC)	Small or large cell undifferentiated carcinoma

N.B. (1) Benign neuroendocrine tumors are restricted to islet-cell tumor of pancreas <1 cm (2) The classification also recognizes mixed tumors (adenoneuroendocrine tumor and adenoneuroendocrine carcinoma) when associated with epithelial component.

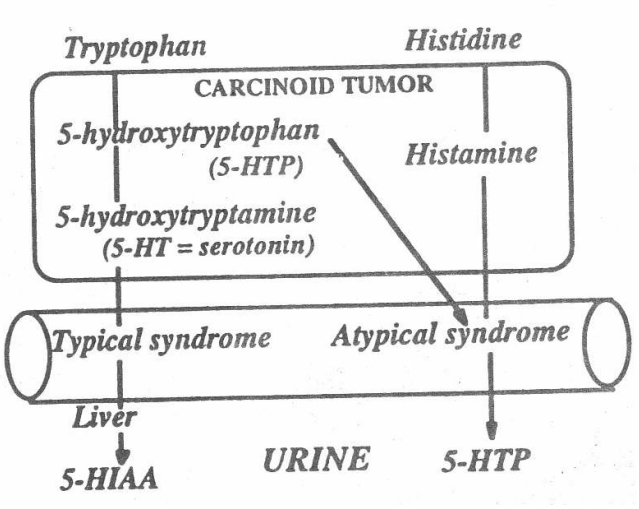

Fig 19-13 *Pathophysiology of carcinoid syndrome associated with gastrointestinal and pulmonary functioning neuroendocrine tumors. Tryptophane and Histidine are the precursor aminoacids, Serotonin is responsible for diarrhea, whereas, kallikrein for flushing symptoms of the syndrome. Metabolic products excreted in urine (S-HIAA and S-HTP) are of diagnostic value. Typical syndromes are common in gastrointestinal neuroendocrine tumors, but, bronchial carcinoids usually present by atypical syndrome.*

Histopathology

Classic neuroendocrine tumors are tumors of borderline malignancy (indeterminate behavior) composed of groups of small cells with uniform nuclei and eosinophilic granular cytoplasm. The cell pattern may be mosaic or trabecular, separated by fibrovascular stroma (P 19-51). But, neuroendocrine carcinomas are truely malignant tumors with size exceeding 2 cm, showing evidence of anaplasia, mitosis and necrosis (P 19-51c). The tumor may show spindle cells, signet-ring cells or glandular differentiation (mixed tumors).

NETs show positive reaction to chromogranin A. Electron microscopy reveals membrane-bound neurosecretory granules (100-200 nm) with dense core, as well as, small clear vesicles that correspond to synaptic vesicles of neurons (P 19-52).

Clinical Presentation

Non-functioning NETS constitute the majority of cases (about 90%), and present by appendicitis, intestinal obstruction or hepatomegaly due to liver metastases.

Functioning carcinoids (Carcinoid syndrome): Manifested in 1 % of appendicular carcinoids, *9%* of small intestinal carcinoids (Table 11-18), and 30% of metastatic carcinoids. The common symptoms are: flushing, diarrhea and abdominal cramps, less common are wheezing, heart valve dysfunction and pellagra.

Flushing: Reddish flushing is attributed to killirein and prostaglandins; but cyanotic flushing and asthmatic attacks are related to histamine. The flushing in classic carcinoids occurs in the face and neck, but flushing in bronchial carcinoids (atypical syndrome) is characterized by diffuse body involvement, itching and face edema suggestive of histamine action.

Diarrhea is often of mild degree and is mainly due to increase of gut motility rather than hypersecretion (serotonin effect).

Carcinoid heart disease is always a late manifestation and is due to endocardial fibrosis. The right side of the heart is involved in classic carcinoid syndrome (pulmonary stenosis and tricuspid regurgitation), but the left side of heart is affected in the atypical syndrome (mitral valve involvement).

Malignant neuroendocrine tumors are most common in small intestine (23%) and least common in appendix (2%) as shown in (Table 19-18).

Diagnosis

In classic carcinoid syndrome, there is increase of 5-HIAA in urine (more than 30 mg/24 hour). This test has a sensitivity of 73% and a specificity of 100%, and is a good marker of tumor burden. In high grade neuroendocrine carcinoma, there is increased excretion of 5HTP and histamine in urine.

Table 19-18 Neuroendocrine Tumors of Gastrointestinal Tract

Site	Frequency (%)	Carcinoid Syndrome(%)	5- Year Survival (%)
Small intestine	29	9	55
Appendix	25	1	85
Rectum	17	-	72
Colon	10	-	41
Stomach	4	-	48

Table 19-19 The Updated WHO Classification and Terminology of Pulmonary Neuroendocrine Tumors and their Survival.

WHO Classification	Previous Terminology	KI-Index %	Necrosis	Survival % 5-Y	10-Y
Well-Differentiated Neuroendocrine Tumor	Carcinoid Tumor	<2	Absent	87	87
Well-Differentiated Neuroendocrine Carcinoma	Atypical Carcinoid	2-10	Focal	56	35
			Marked	9	5
Poorly-Differentiated Neuroendocrine Carcinoma	Small cell lung Cancer (SCLC),	>10			
	Large cell Neuroendocrine carcinoma (LCNEC)			27	9

(Delellis et al, 2004 and Livolsi and Asa, 2002)

N.B. (1) Benign neuroendocrine tumors are only restricted to tumorlets (<0.5 cm), a rare incidental finding in the lung. (2) A combined variant with conventional carcinomas of lung is recognized but rare (3%).

Spread

1. Local spread in the wall of gut, *2. Lymph node* spread (5% in neuroendocrine tumors and 70% in neuroendocrine carcinomas), and *3. Hematogenous* spread, with liver metastases in small intestinal NETs and bone metastases in pulmonary neuroendocrine tumors.

Prognosis

Sex: unfavorable prognosis in males.

Size: unfavorable prognosis for tumors more than 2 cm in diameter (5-year survival only 39%).

Stage: unfavorable prognosis with liver, node or distant metastases.

Site: the prognosis is most unfavorable in NETs of colon and stomach (Table 11-19).

Bronchial carcinoids

Bronchial carcinoids contribute about 5% of primary lung tumors. It is common at young age (below 40 years) and sexes are equally affected.

Grossly, lung carcinoids are classified into central and peripheral. The majority are centrally located in bronchi, show endophytic growth

(iceberg pattern) and lymph node metastases in 5% of cases. The peripheral type tends to be multiple and shows spindle cells. *Atypical carcinoids* are highly aggressive tumors with lymph node metastases in 70% of cases. The recently updated WHO classification of pulmonary NETs is presented in (Table 19-19).

The majority of bronchial carcinoids are non-functioning, but a minority (13%) may show atypical carcinoid syndrome (diffuse flushing, left sided heart valve disease and excretion of 5HTP and histamine in urine). The 10-year survival after surgical resection is about 85%.

ISLET CELL TUMORS

Neuroendocrine tumors of the pancreas are being recognized more frequently because of the development of radioimmunoassays for detection of the secreted polypeptides. The clinical syndromes produced by excessive hormone secretion range from minor biochemical curiosites (PPoma) to life threatening derangements of homeostasis (insulinoma and VIP oma).

Physiology

Normally, the islets of Langerhans contain at least five cell types (Table 19-20):

1. Alpha cells (glucagon) constitute 20% of islet cells and is stimulated by hypoglycemia. Glucagon is catatbolic, causing hyperglycemia by promoting hepatic glycogenolysis, as well as, glucogenesis from proteins. It also inhibits gastric secretion and gastric motility.

Table 19-20 Types of Islet Cells and Their Normal Products

A cell (alpha)	Glucagon
B cell (beta)	Insulin
D Cell (delta)	Somatostatin
PP cell	Pancreatic polypeptide
EC (Enterochromafin)	5 HTP, histamine

N.B. Ectopically functioning tumors may secrete gastrin, VIP, ACTH, PH

2. Beta cells (insulin) comprise 70% of cells of islets; synthesize insulin, which is secreted in response to hyperglycemia and glucagon. It is anabolic, stimulating glycogenesis and glucose metabolism leading to hypoglycemia. Secretion of insulin is inhibited by somatostatin. Insulin is synthesized as an inactive precursor, proinsulin. Normally, proinsulin is cleaved into biologically active insulin and its cleavage fragment C-peptide, which are secreted in equimolar quantities. Normally, less than 20% of proinsulin is released into the bloodstream.

3. *Delta cells* (somatostatin) this is an inhibitory hormone on alpha, beta and acinar cells, hence, it inhibits glucagon, insulin, gastrin secretin, PP and VIP, leading mainly to diabetes. It also inhibits pancreatic exocrine function and gastrointestinal motility.

4. *F cells* (pancreatic polypeptide PP): the secretory product functions as cholinergic and adrenergic modulation resulting in decrease of pancreatic exocrin and biliary functions. It also inhibits smooth muscle contraction of intestine.

5. *Enterochromaffin cells* (serotonin) these cells synthesize serotonin and histamine which cause vasodilatation and increased vascular permeability. They also secrete the peptide motilin, a hormone that stimulates gastric muscle.

Classification

Islet cell tumors are classified into entopic and ectopic neoplasms according to the hormonal product, whether it is native or ectopic to the pancreatic islets (Table 19-21). Apart from insulinoma, pancreatic neuroendocrine tumors are more commonly malignant. However, they are characterized by indolent growth and low malignant potential as compared to carcinoma of the exocrine pancreas. Approximately 10% of islet cell tumors arise in association with multiple endocrine neoplasia MEN type 1. These tumors are commonly non-beta-cell tumors (e.g. PPoma and gastrinoma) and tend to be multifocal. Although many islet-cell tumors are multi-hormonal, one peptide generally predominates and is responsible for producing the clinical syndrome, Non-functioning islet cell tumors present with symptoms caused by mass effect and are invariably malignant.

Entopic Tumors

1. *Glucagonoma* is characterized by diabetes-dermatitis syndrome. While diabetes is mild, the

Table 19-21 Tumors of Endocrine Pancreas

	Syndrome	Malignancy %
ENTOPIC		
Glucagonoma	Diabetes-Dermatitis	90
Insulinoma	Hypoglycemia	10
Somatostatinoma	Inhibitory	80
PP tumor	Hepatomegaly	80
Carcinoid	Atypical carcinoid	20
ECTOPIC		
Gastrinoma	Ulcerogenic (ZE)	90
VIPoma	WDHA	50
Corticotropinoma	Cushing	Common
Parathyrinoma	Hypercalcemia	Common

(Friesen, 1982)

rash is marked and called necrotizing migratory erythema. The rash involves the lower abdomen and thighs. Other prominent features are weight loss, anemia and glossitis due to the catabolic effects of glucagon.

2. *Insulinoma* is the most common pancreatic neuroendocrine tumor. The mean age of patients at presentation is 45 years. About 70% of cases occur in body and tail of pancreas (Fig 19-14), usually solitary and below 2 cm. It is multiple in 10% of cases (with MEN-1 syndrome) and malignant in 10%. The insulin-induced hypoglycemia also causes catecholamine release with consequent autonomic symptoms such as sweating, anxiety and palpitations. Whipple triad is diagnostic: (1) symptoms are precipitated by fasting, (2) blood sugar below 50 mg/100 ml during the attack and (3) relief of symptoms by glucose.

In insulinoma patients, the immunoreactive insulin levels may fluctuate, but they will not fall with fasting. Insulin levels above 6 MU/ml in the presence of blood glucose less than 50 mg/100 ml is diagnostic of insulinoma. Neoplastic tissue releases excess proinsulin (more than 25% of immunoreactive insulin). An ideal method for localization is arteriography, since the majority of these tumors are hypervascular.

3. *Somatostatinoma* is rare and produces the inhibitory syndrome as a result of inhibition of functions of most digestive organs. The symptoms are vague, including: diabetes, gall stones, indigestion, steatorrhea and hypochlorhydria.

4. *PPoma*: pancreatic polypeptide-producing tumors are rare and are not associated with clinical syndromes , but specific hormone (PP) is detected in blood. Some patients present by hepatomegaly due to metastases.

5. *Carcirioid tumor r*secretes histamine and 5-hydroxytryptophan (5HTP), hence, produces atypical carcinoid syndrome,

Ectopic Tumors

1. Gastrinoma is the second most common islet cell tumor and is associated with the ulcerogenic syndrome (Zollinger and Ellisson, 1955). The syndrome includes the following diagnostic triad: (1) multiple peptic ulcers at unusual sites, (2) gastric hypersecretion and hyperacidity resulting in diarrhea, and (3) islet cell tumor. It is most commonly located in an area known as the gastrinoma triangle (Fig 11-9).

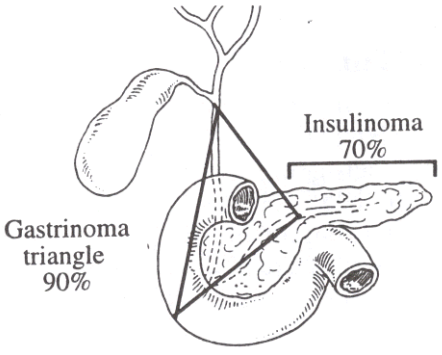

Fig 19-14 *Common sites of tumors of endocrine pancreas. Tumors arising from body or tail of pancreas do not obstruct the biliary duct, hence, present late and may reach a large size.*

bounded by the junction of the cystic and common bile ducts superiorly, the junction of the second and third portion of duodenum inferiorly , and the junction of the neck and body of pancreas medially. Gastrinomas occur in both sporadic (75%) and familial (25%) forms in association with MEN-1 syndrome. The sporadic form is unifocal, but it is commonly malignant. Elevated fasting serum gastrin in a patient with hyperacidity is diagnostic of Zollinger-Ellison syndrome.

2.*Vipoma* (Verner-Morrison syndrome): vasoactive intestinal peptide is both an important neurotransmitter and hormone which is a potent stimulator of cyclic adenosine monophosphate CAMP production in the gut, leading to massive secretion of water and electrolytes (pancreatic cholera). The diagnosis is made on the basis of watery diarrhea, hypokalemia and achlorohydria (WDHA) syndrome, in the presence of an elevated (VIP) in the serum. Flushing is also common due to the vasodilatory effects of the peptide.

MULTIPLE ENDOCRINE NEOPLASIA (MEN)

MENs are familial disorders characterized by the development of tumors or hyperplasia in two or more endocrine glands. They are inherited as autosomal-dominant traits, hence, giving their first-degree relatives a 50% risk of developing the tumors.

MEN syndromes have four distinct features in contrast with their sporadic endocrine tumors, namely: (1) they occur in younger patients, (2) the multiple tumors may develop at the same time (synchronous) or after a time interval (metachronous), (3) frequent multifocality and bilaterality and (4) preceded by a stage of endocrine hyperplasia before neoplastic development.

MEN syndromes are classified into two main groups (MEN-1 and MEN-2) based on differences in molecular oncogenesis and the profile of endocrine glands affected. MEN-1 results from inactivation of MEN-1 tumor suppressor gene and the parathyroid glands are most commonly involved in the syndrome. Conversely, MEN-2 results from activation of RET protooncogene, and all subgroups of the syndrome share in common medullary thyroid carcinoma.

MEN-1 (Wermer Syndrome)

It is caused by germline mutation of MEN-1 tumor suppressor gene located on chromosome 11q13 which expresses *menin* a critical regulator of other genes controlling apoptosis and genomic stability. MEN-1 syndrome is characterized by abnormalities of parathyroid, pancreas and pituitary glands (the 3 Ps) and to a lesser extent other endocrine glands (Table 19-22). Hyperparathyroidism is the main clinical manifestation of MEN-1 syndrome.

MEN-2 Syndromes

These are the result of mutation of RET protooncogene located on chromosome 10 q 11 and expressed as cell surface receptor. MEN-2 is classified into three types according to the profile of endocrine glands affected and prognosis (Table 19-23).

1. *MEN-2A (Sipple syndrome):* This is the most common (60%) and the syndrome includes a triad of endocrinopathy (medullary thyroid carcinoma, pheochromocytoma and hyperparathyroidism).

2. *MEN-2B* syndrome is the most aggressive due to its association with highly malignant medullary thyroid carcinoma. However, instead of hyperparathyroidism, MEN-2b is associated with mucosal neuromas and marfanoid features (tall slender body habitus).

Table 19-22 MEN-1 Syndrome, Frequency of Endocrinopathies

Gland	Frequency (%)	Common Pathology
Parathyroid	90	Hyperplasia Adenoma
Pancreas	50	Gastrinoma, Insulinoma, Glucagonoma
Pituitary	25	Prolactinoma
Other	10	Adrenal hyperplasia C-cell hyperplasia Bronchial NET Gastric NET

Table 19-23 Types of MEN-2 Syndromes

Type	Frequency (%)	Endocrinopathy			Course
		MTC	PCC	PT	
MEN-2A	60	+	+	+	Intermediate
MEN-2B	5	+	+	-	Aggressive
FMTC	35	+	-	-	Indolent

Abbreviations: MTC medullary thyroid carcinoma, PCC pheochromocytoma, PT parathyroid, FMTC Familial medullary thyroid carcinoma.

3. *Familial medullary thyroid carcinoma* (FMTC) is characterized by a familial tendency of medullary carcinoma, not associated with any other endocrinopathy.

In patients with MEN-2 syndrome, the most common cause of death is the medullary thyroid carcinoma (and not pheochromocytoma), hence, it must take priority in treatment. The discovery of RET gene mutation in MEN-2 syndromes have changed the management of these patients and this represents a model of personalized genomic medicine (DeVita et al, 2011). Thus, DNA analysis for RET germline mutation is indicated in all patients with presumably sporadic medullary thyroid carcinoma, as approximately 5% of them will be found to have hereditary disease. It is also imperative to screen family members for RET gene mutation (50% are at risk), as well as, thyroid tissue core biopsy for parafollicular C-cell hyperplasia. Prophylactic surgery may be needed (timely thyroidectormy) before an aggressive medullary carcinoma develops. As a second step, urine analysis for VMA metanephrine and catecholamines must be done for patients with medullary thyroid carcinoma to detect and manage any associated pheochromocytoma.

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