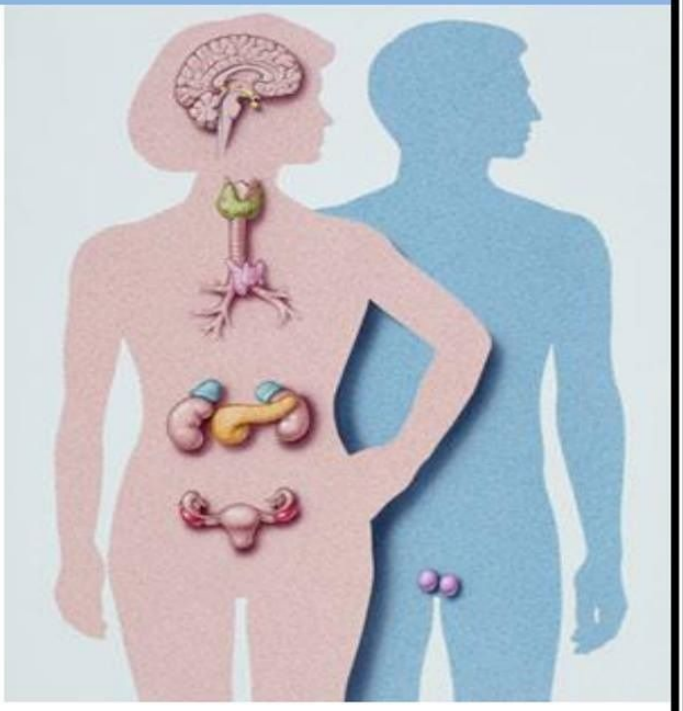
University of Jordan - Faculty of Medicine
(2013-19)

Medical Committee
The University of Jordan

Endocrine System



- [ ] Anatomy/Embryology/Histology
- [ ] Biochemistry
- [ ] Physiology
- [ ] Pharmacology
- [x] Pathology
- [ ] PBL

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Lecture #: **5**

Date:

Dr's Name: **Dr. Heyam**

Price:

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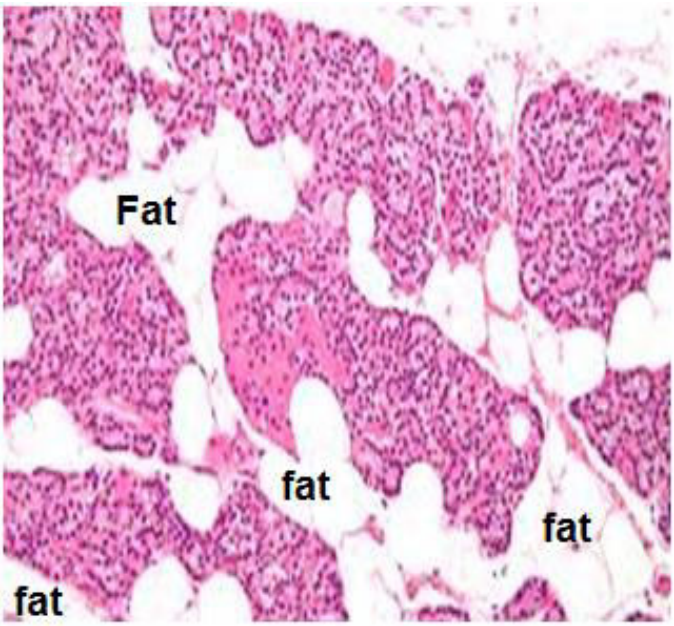
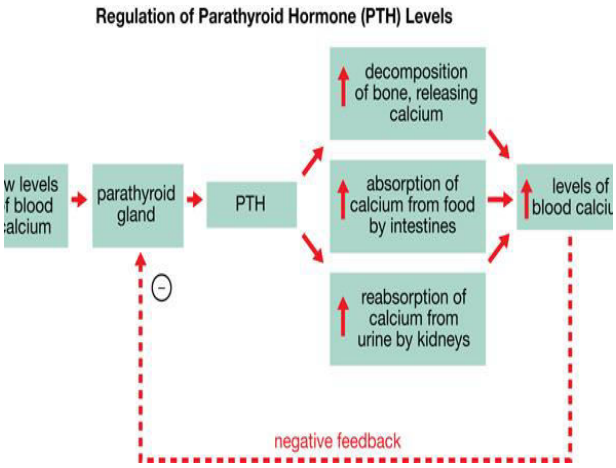
PARATHYROID GLAND

Everything in the slides is mentioned here, and the doctor says you don't need to know any numbers just know the most common cause of each disease without memorizing any percentages. The lecture is only 10 pages—the rest is a summary.

There are four parathyroid glands located behind the thyroid gland: Upper right, Upper left, lower right and lower left. Under the microscope, cells of the parathyroid gland appear epithelial, and found between these cells is white adipose tissue. This adipose tissue is important *for differentiating normal parathyroid tissue from a parathyroid adenoma or hyperplasia*; where fat tissue abundance indicates normal parathyroid tissue, and lack of fat reflects hyperplastic or adenomatous parathyroid tissue.



Unlike hormones of other endocrine glands, parathyroid hormone secretion is *not regulated by the pituitary or the hypothalamus*. Instead, it is regulated by the levels of free serum Calcium. The role of the parathyroid gland is to increase Calcium levels in the blood; so when plasma Calcium concentration decreases, the gland is stimulated to



produce PTH.

PTH has physiologic actions on bone, kidney and intestine that are coordinated to increase the plasma Calcium concentration. PTH causes an increase in bone resorption, prevents urinary excretion of Calcium by the kidney and indirectly stimulates intestinal Calcium absorption.

Calcium homeostasis involves the coordinated interaction of PTH and Calcitonin. In contrast to PTH, the major action of Calcitonin is to *decrease the plasma Calcium concentration*.

Diseases of the parathyroid

Diseases of the parathyroid include hypoparathyroidism, hyperparathyroidism and mass lesions (hyperplasia/adenoma/carcinoma). Notice that the parathyroid glands *produce no mass effect* as they are very small.

Hyperparathyroidism

Hyperparathyroidism could be primary, secondary or *tertiary*.

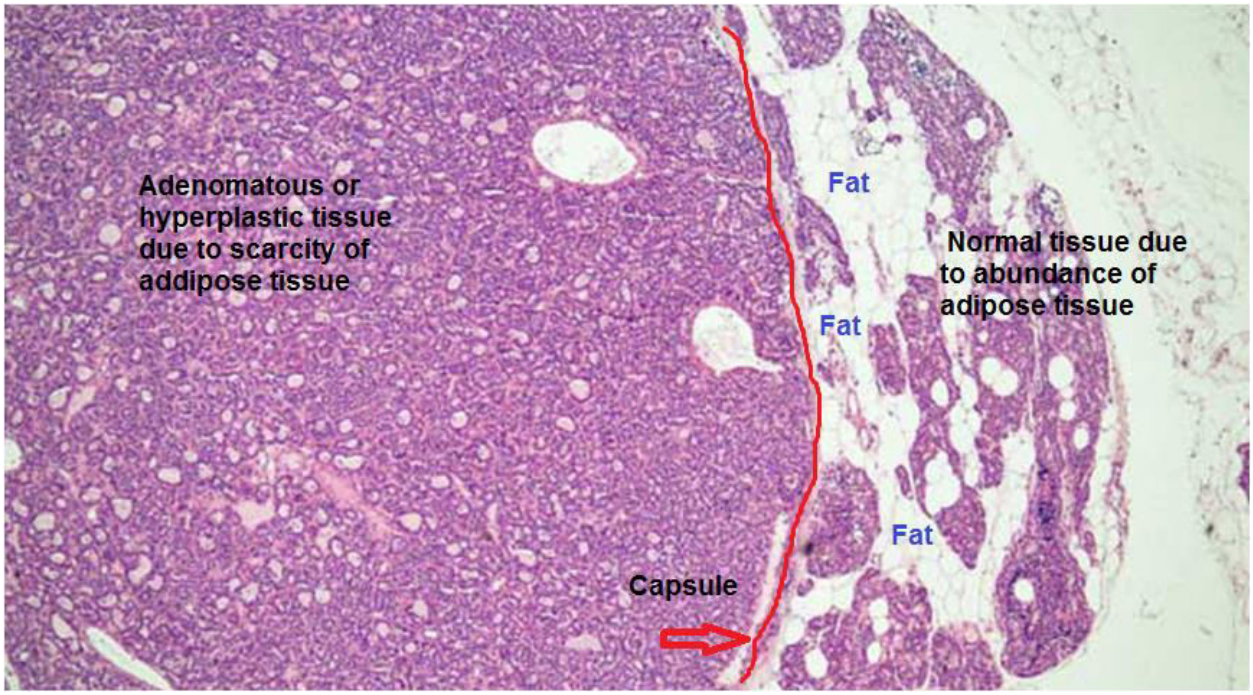
- **Primary hyperparathyroidism:** The initial problem is *in* the parathyroid gland, which is secreting excessive PTH. Primary hyperparathyroidism could be caused by **parathyroid adenoma** (85% to 95%), primary parathyroid hyperplasia (5% to 10%) or parathyroid carcinoma (1%; rarely cause hyperparathyroidism as most parathyroid carcinomas are non-functional). The majority of cases are sporadic, but there are some familial cases associated with MEN syndromes (mentioned later.) The consequences of primary hyperparathyroidism are predictable from the known physiologic actions of PTH on bone, kidney and intestine: Hypercalcaemia (which is often clinically silent), changes in the

skeletal system, changes in the kidney and metastatic calcification.

Hyperparathyroidism is the most common cause of silent hypercalcaemia (increase in Calcium serum levels isn't sufficient to produce signs and symptoms.) Detection of asymptomatic hypercalcaemia cases has increased as a result of routine inclusion of serum calcium assays in testing for a variety of clinical conditions.

On the other hand, the *most common cause of clinically apparent hypercalcaemia is malignancy*. Malignancies could cause hypercalcaemia by either *metastasizing to bone*, destroying it and increasing serum Calcium levels, or by *paraneoplastic syndromes* (the secretion of ectopic Calcium by malignant neoplasms.)

- **Parathyroid adenoma**
  Like all endocrine adenomas, Parathyroid adenomas could be functional or non-functional. They are usually encapsulated, soft, **solitary** and could exhibit endocrine atypia (Features of malignancy –like pleomorphic nuclei and, rarely, mitotic figures– seen in benign lesions *only in the endocrine system*.) Parathyroid adenomas weigh barely 6 grams and that's why they produce no mass effect (you do have a mass but it isn't big enough to compress surrounding tissues.) *One way to differentiate between parathyroid hyperplasia and adenoma is the number of enlarged glands*; if one gland is enlarged, it's mostly likely an adenoma (or rarely carcinoma), if all four glands are enlarged we're talking about hyperplasia.

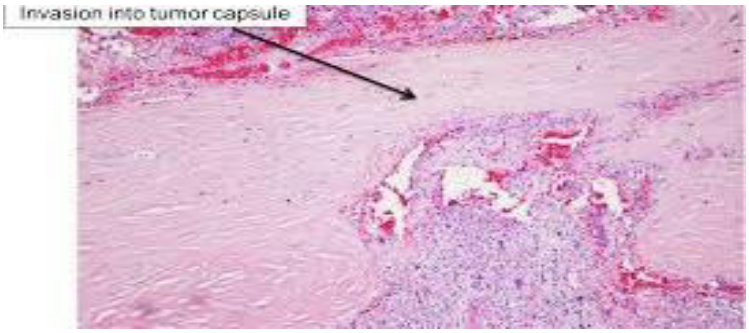


Notice how a rim of compressed, non-neoplastic tissue, separated by a fibrous capsule, is visible at the edge of the adenoma.

- **Parathyroid hyperplasia**
  Usually involves all four glands, and the combined weight of all glands rarely exceeds 1.0 g. Stromal fat is inconspicuous (unnoticeable) within foci of hyperplasia.

- **Parathyroid carcinoma**
  Only one gland is affected, and the diagnosis of carcinoma based on cytologic detail is unreliable, so *invasion of tissues and metastasis* are the only definitive criteria. Rarely exceeds 10 g in weight, but still doesn't produce any mass effect. Local recurrence occurs in one third of cases, and more distant spreading occurs in another third.

As you can see the tumor is invading the capsule, and that it why it's considered malignant.



Morphologic changes in other organs in hyperparathyroidism

1) Skeletal changes

Since PTH results in Calcium mobilization from bone by promoting bone resorption, osteoclastic activity is increased resulting in *erosion and weakening of bone, making it more susceptible to fracture* and causing bone pain.

- Osteitis fibrosa cystica

  Secondary changes in bone related to hyperparathyroidism. Massive bone resorption results in thinning of the cortex, and the marrow will appear to have increased amounts of **fibrous** tissue (non-calcified collagen.) In addition, some areas of bone will eventually be replaced with **cysts**, accompanied by foci of hemorrhage.

- Brown tumors

  Brown tumors are not true neoplasms as the term "tumor" suggests; however, it may mimic a true neoplasm. Brown tumors result from *aggregations and over activity of osteoclasts* (multinucleated cells) due to high levels of PTH. In localized regions where bone loss is particularly rapid, haemorrhage and

proliferating fibrous tissue may replace the normal marrow contents, *forming masses* that may be mistaken for neoplasms. The characteristic brown colouration results from haemorrhage.

Under the microscope, brown tumors appear as bone tumors composed of many giant cells (osteoclasts) surrounded by heamorrhage. Brown tumors are most commonly seen in the mandible.

2) **Kidney changes**

PTH stimulates Calcium reabsorption from the kidney but Calcium levels are so high that it overwhelms the reabsorptive capacity of the nephron, so Calcium levels increase in the kidney making the kidney more susceptible to calcification of the interstitium (***nephrocalcinosis***) and formation of stones in the urinary tract (***nephrolithiasis***).

3) **Metastatic calcification**

The word metastatic here means that Calcium travels to several sites of the body through the blood, depositing and calcifying there. These sites include the stomach, lungs, myocardium, and blood vessels.

Clinical features of primary hyperparathyroidism

Primary hyperparathyroidism is a disease of adults and, like most endocrine diseases, is much more common in women than in men. *The most common manifestation is an increase in serum calcium.*

Clinical Manifestations:

1) **Painful bones**: due to fractures that result from excessive bone resorption and erosion.
2) **Renal stones**: due to increased calcium deposition in the kidney as a result of increased urine calcium concentration.
3) **Abdominal groans**: due to pain resulting from peptic ulcers (Calcium stimulates HCL secretion), pancreatitis, gallstones and renal stones.
4) **Psychic moans**: (Read only: In neurons, Na+ channels are guarded by Calcium, so high levels of Calcium→Na+ channels are always closed→ decreased neural activity→ severe fatigue, lethargy and clinical depression.)

- **Secondary hyperparathyroidism:** The parathyroid glands are normal but are stimulated to secrete excessive PTH *secondary* to **chronic hypocalcemia** which could be caused by vitamin D deficiency or chronic renal failure. *Chronic renal insufficiency is the most common cause*, and it causes decreased phosphate excretion, which in turn results in *hyperphosphatemia*. Because phosphate levels in the blood increase, phosphate starts complexing with calcium resulting in decreased free serum calcium levels and stimulation of parathyroid gland activity. α_1-hydroxylase is found in the kidney, so logically, renal failure results in reduced availability of this enzyme. Because α_1-hydroxylase is the enzyme necessary for the synthesis of the active form of vitamin D, deficiency of this enzyme results in decreased vitamin D, and therefore reduced intestinal absorption of calcium resulting in hypocalcemia and consequent secondary hyperparathyroidism.

Clinical features of secondary hyperparathyroidism

Decreased calcium levels due to renal failure is compensated by an increase in PTH levels, therefore serum calcium remains near normal but NEVER HIGH, which is why bone abnormalities (*renal osteodystrophy*; patients with renal failure develop bone problems) are less severe than those seen in primary type.

- **Tertiary hyperparathyroidism:** where part of the gland of a person with secondary hyperparathyroidism becomes autonomous, resulting in increased secretion of PTH and hypercalcaemia.

Hypoparathyroidism

Hypoparathyroidism is rare and it's a decreased function of the parathyroid glands (mostly due to loss of the gland) with underproduction of parathyroid hormone, leading to low levels of Calcium in the blood. It's less common than hyperparathyroidism and the major causes are:

1) *Accidental removal of all parathyroids upon thyroid surgery* (for treatment of thyroid cancer or Graves disease)
2) *Absent parathyroid from birth.*
   DiGeorge syndrome: a syndrome caused by the deletion of a small piece on chromosome 22 (22q11.2). Characteristic signs include cardiac defects, thymic aplasia (lack of development of Thymus) and congenital absence of parathyroid.
3) *Autoimmune hypoparathyroidism*: this is a hereditary polyglandular deficiency syndrome.

The characteristics of hypoparathyroidism are predictable: low circulating levels of PTH and hypocalcemia leading to tetany, parasthesia (sensitive nerves) and uncontrollable spasm of the limbs. This disorder usually is treated with the combination of Calcium supplement and vitamin D.

MULTIPLE ENDOCRINE NEOPLASIA SYNDROMES (MEN)

Neoplastic conditions (hyperplasia, adenoma, carcinoma) resulting in proliferative lesions of multiple endocrine organs, and *inherited as autosomal dominant disorders.* Endocrine tumors arising in the context of MEN syndromes have distinctive features that are not shared with their sporadic counterparts:

1) Occur at a *younger age* than that for sporadic cases (e.g. medullary carcinoma)
2) As the name indicates, they arise in *multiple endocrine organs*
3) Even in one organ, the tumors often are *multifocal* (e.g. multiple pancreatic adenomas, multiple medullary carcinoma)
4) Are usually *more aggressive* and *recur* in a higher proportion of cases than tumors that occur sporadically.
5) Usually are preceded by an *asymptomatic stage of endocrine hyperplasia* involving the cell of origin of tumor (C-cell hyperplasia in medullary carcinoma)

MEN type 1

Is an *autosomal dominant syndrome*, and the gene (*MEN1*) is located at chromosome 11 and is a tumor suppressor gene (sentence after comma

isn't important). Organs most commonly involved are the *parathyroid, the pancreas, and the pituitary*—the "3 Ps."

- **Parathyroid**: abnormalities include both hyperplasia and adenomas with resultant hyperparathyroidism (*Primary hyperparathyroidism* is the most common manifestation of MEN-1)
- **Pituitary**: the most frequent pituitary tumor in patients with MEN-1 is a prolactin-secreting macroadenoma. In some cases, acromegaly develops in association with somatotropin-secreting tumors.
- **Pancreas**: *endocrine tumors of the pancreas are the leading cause of death in MEN-1* as they are aggressive tumors which manifest with metastatic disease. May find multiple microadenomas scattered throughout the pancreas in conjunction with the dominant lesions (not important). Pancreatic endocrine tumors often are functional, with *patients usually presenting with hypoglycemia as a result of insulinomas*.

MEN type 2A	**MEN type 2B**
Autosomal dominant	Autosomal dominant
Activation of RET proto-oncogene	Activation of RET proto-oncogene
THYROID, PARATHYROID AND ADRENALS	THYROID AND ADRENALS
Thyroid: medullary carcinoma early in life and in all cases	Thyroid: medullary carcinoma early in life and in all cases
10% to 20% of patients develop parathyroid **hyperplasia** → primary hyperparathyroidism	PARATHYROID NOT AFFECTED→ no primary hyperparathyroidism

Adrenal medulla: **Pheochromocytomas** develop in 50% of the patients; and 10% of these tumors are malignant	Adrenal medulla: **Pheochromocytomas** develop in 50% of the patients; and 10% of these tumors are malignant
No extraendocrine manifestations	Extraendocrine manifestations. 1. **Ganglioneuromas** of mucosal sites (gastrointestinal tract, lips, tongue) 2. **Marfanoid habitus**, in which overly long bones of the axial skeleton give an appearance resembling that in Marfan syndrome

Summary of the lecture:

- Adipose tissue abundance → normal parathyroid tissue, while adipose tissue scarcity → hyperplastic or adenomatous parathyroid tissue.
- PTH secretion regulated by the levels of free serum Calcium and NOT by the pituitary or the hypothalamus.
- Low serum Calcium concentration → increased PTH secretion, while High serum Calcium concentration → increased Calcitonin secretion
- PTH causes an increase in bone resorption, prevents urinary excretion of Calcium by the kidney and indirectly stimulates intestinal Calcium absorption.
- **The most common cause of clinically silent hypercalcemia in hyperparathyroidism, while the most common cause of clinically**

apparent hypercalcemia is malignancy: paraneoplastic syndromes or bone metastasis.

Diseases of the parathyroid

	HYPERPARATHYROIDISM	**HYPOPARATHYROIDIM**
TYPES	Primary, secondary, tertiary	–
Causes	See tables below	1) Accidental removal of all parathyroids upon thyroid surgery 2) Absent parathyroid from birth. 3) *Autoimmune hypoparathyroidism*:
PTH	Elevated	Decreased
Serum calcium	Primary: elevated Secondary: normal Tertiary: elevated	Decreased
Bone	Increased resorption	Decreased resorption

Hyperparathyroidism

	PRIMARY	**SECONDARY**	**TERTIARY**
Serum Calcium	Elevated	Near normal	Elevated
Causes	• Parathyroid adenoma (majority) • Primary parathyroid hyperplasia • Parathyroid	Chronic renal insufficiency Vitamin D deficiency	Autonomous parathyroid activity due to continuous stimulation

	carcinoma(rare)		of the parathyroid (Secondary could lead to tertiary)
Effects	1) Bone: **Osteitis fibrosa cystic, Brown tumors** 2) **Kidney: nephrolithiasis, nephrocalcinosis** 3) Metastatic calcification (stomach, lungs, myocardium, and blood vessels)	Renal osteodystrophy	Similar to primary
Clinical manifestations	• painful bones • renal stones • abdominal groans (peptic ulcers, pancreatitis, renal stones, gallstones) • psychic moans	Less severe than those seen in the primary type (due to normal Calcium levels)	Similar to primary

Causes of primary hyperparathyroidism

PARATHYROID ADENOMA	PARATHYROID HYPERPLASIA	PARATHYROID CARCINOMA
Encapsulated, soft, **solitary, endocrine atypia**, devoid of adipose tissue	Devoid of adipose tissue	Invasion of tissues and metastasis
Enlargement of one gland	Multiglandular process	Enlargement of one gland
No mass effect	No mass effect	No mass effect

MEN syndromes

MEN type 1	MEN type 2A	MEN type 2B
Autosomal dominant	Autosomal dominant	Autosomal dominant
Gene (*MEN1*) is located at chr. 11and is a tumor suppressor gene	Activation of RET proto-oncogene	Activation of RET proto-oncogene
PARATHYROID, PANCREAS AND PITUITARY	THYROID, PARATHYROID AND ADRENALS	THYROID AND ADRENALS-
Parathyroid: hyperplasia and adenomas with resultant hyperparathyroidism (most common manifestation of MEN-1)	Thyroid: medullary carcinoma early in life and in all cases	Thyroid: medullary carcinoma early in life and in all cases

Pituitary: prolactin-secreting macroadenoma.	10% to 20% of patients develop parathyroid **hyperplasia** → primary hyperparathyroidism	PARATHYROID NOT AFFECTED→ no primary hyperparathyroidism
Pancreas: endocrine tumors of the pancreas are the leading cause of death in MEN-1. Patients usually present with hypoglycemia as a result of insulinomas.	Adrenal medulla: **Pheochromocytomas** develop in 50% of the patients; and 10% of these tumors are malignant	**Adrenal medulla**: **Pheochromocytomas** develop in 50% of the patients; and 10% of these tumors are malignant
No extraendocrine manifestations	No extraendocrine manifestations	Extraendocrine manifestations. 1. Ganglioneuromas of mucosal sites (gastrointestinal tract, lips, tongue) 2. Marfanoid habitus, in which overly long bones of the axial skeleton give an appearance resembling that in Marfan syndrome