Endocrine NBME Review

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What do endocrinologists love best?

A. Sugar
B. Salt
C. Online shopping
D. HORMONES!
<table>
<thead>
<tr>
<th></th>
<th>Cortisol</th>
<th>Thyroid hormone</th>
<th>Parathyroid hormone</th>
<th>Prolactin</th>
<th>Insulin</th>
<th>Aldosterone</th>
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<tbody>
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<td>Production</td>
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<td>Deficiency</td>
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<tr>
<td>Lab testing:</td>
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<tr>
<td>Other:</td>
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</tbody>
</table>
Case 1

- 35 year old man presents complaining of weakness and tingling in his extremities and polyuria.
- Exam notable for blood pressure of 160/100 mm Hg.
- Lab studies reveal sodium 147 mEq/L, K 2.8 mEq/L and low renin.
What is the most likely diagnosis?

A. Diabetes mellitus
B. Pheochromocytoma
C. Hyperaldosteronism
D. Cushings’ syndrome
What is the most likely diagnosis?

A. Diabetes mellitus
B. Pheochromocytoma
C. **Hyperaldosteronism**
D. Cushings’ syndrome
Which one of the following is a direct potent stimulator of aldosterone?

A. Angiotensin I
B. Angiotensin II
C. Angiotensinogen
D. Renin
Which one of the following is a direct potent stimulator of aldosterone?

A. Angiotensin I  
B. **Angiotensin II**  
C. Angiotensinogen  
D. Renin
How is aldosterone normally regulated?

Legend:
Feedback mechanism regulating aldosterone secretion. The dashed arrow indicates inhibition.
Aldosterone is secreted from which one of the following?

A. Zona glomerulosa
B. Zona fasciculata
C. Zona reticularis
Aldosterone is secreted from which one of the following?

A. Zona glomerulosa
B. Zona fasciculata
C. Zona reticularis
Inside the capsule of each adrenal gland is an adrenal cortex, formed from embryonic mesodermal cells, which completely surrounds an innermost adrenal medulla derived embryologically from neural crest cells. Cortical cells are arranged as three layers: the zona glomerulosa near the capsule, the zona fasciculata (the thickest layer), and the zona reticularis.

**Glomerulosa** – aldosterone  
**Fasciculata** – cortisol  
**Reticularis** – dehydroepiandrosterone (DHEA)
Given the patient’s low potassium, what is the most likely EKG finding?

A. ST-segment elevation
B. U waves
C. Poor R wave progression
D. Q wave
Given the patient’s low potassium, what is the most likely EKG finding?

A. ST-segment elevation
B. **U waves**
C. Poor R wave progression
D. Q wave
Prominent U waves

U wave

Normal rhythm strip

II
CT scan of abdomen was done and was unrevealing. What is the next appropriate step for evaluation of this patient?

A. Dexamethasone suppression test  
B. Adrenal vein sampling  
C. Cosyntropin stimulation test  
D. Petrosal sinus sampling
CT scan of abdomen was done and was unrevealing. What is the next appropriate step for evaluation of this patient?

A. Dexamethasone suppression test
B. **Adrenal vein sampling**
C. Cosyntropin stimulation test
D. Petrosal sinus sampling
Adrenal vein sampling: Aldosterone and cortisol measured from: R adrenal vein, L adrenal vein, and IVC. Unilateral source will have aldosterone/cortisol ratio >3:1 compared to the non-affected side.

(Dividing by cortisol is done to correct for dilutional effect of inferior phrenic vein flow into L adrenal vein.)
He undergoes AVS which shows bilateral hyper-secretion of aldosterone. How should this patient be managed?

A. Spironolactone
B. Hydrochlorothiazide
C. Unilateral adrenalectomy
D. Bilateral adrenalectomy
He undergoes AVS which shows bilateral hyper-secretion of aldosterone. How should this patient be managed?

A. **Spironolactone**
B. Hydrochlorothiazide
C. Unilateral adrenalectomy
D. Bilateral adrenalectomy
Which of the following are the most common side effects of spironolactone?

A. Abdominal pain, diarrhea
B. Cough, diarrhea
C. Hypokalemia, cough
D. Hyperkalemia, gynecomastia
Which of the following are the most common side effects of spironolactone?

A. Abdominal pain, diarrhea
B. Cough, diarrhea
C. Hypokalemia, cough
D. Hyperkalemia, gynecomastia

Spironolactone = ↑ water, Na\(^+\) secretion; ↓K\(^+\) secretion

Spironolactone inhibits effect of aldosterone by competing for the aldosterone-dependent Na\(^+\)-K\(^+\) exchange site in distal tubule cells. Also inhibits free testosterone from binding to androgen receptors in breast cells.
## Endocrine Hypertension

<table>
<thead>
<tr>
<th>Clinical features</th>
<th>Hyperaldosteronism</th>
<th>Cushing Syndrome</th>
<th>Pheochromocytoma</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HTN, ↓K⁺</td>
<td>HTN, central obesity, wide striae, thin skin, bruising, etc.</td>
<td>Spells of headaches, sweating, tachycardia, HTN</td>
</tr>
<tr>
<td>Lab diagnosis</td>
<td>High aldosterone Low renin</td>
<td>High 24 hr urine or midnight salivary cortisol. Abnormal dexamethasone suppression.</td>
<td>High plasma or 24 hr urine catecholamines, metanephrines/nor-metanephrines</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Unilateral – adrenalectomy Bilateral – medication (spironolactone)</th>
<th>Surgery</th>
<th>Surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Other</td>
<td>Pituitary vs ectopic (high ACTH) vs adrenal source (low ACTH)</td>
<td>Tumor of adrenal medulla. Alpha blockade prior to surgery (and never beta blockade alone).</td>
<td></td>
</tr>
</tbody>
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Another cause of endocrine hypertension is congenital adrenal hyperplasia. Which one of the following are consistent with classic 21-Hydroxylase deficiency?

<table>
<thead>
<tr>
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<th>A</th>
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<th>D</th>
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</thead>
<tbody>
<tr>
<td>Mineralocorticoids</td>
<td>↑</td>
<td>↑</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Cortisol</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
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<tr>
<td>Sex hormones</td>
<td>↑</td>
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<tr>
<td>Sex hormones</td>
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<td>↓</td>
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</table>
Synthetic pathways for adrenal steroid synthesis

The first step in adrenal steroid synthesis is the combination of acetyl CoA and squalene to form cholesterol, which is then converted into pregnenolone. The enclosed area contains the core steroidogenic pathway utilized by the adrenal glands and gonads.

17α: 17-alpha-hydroxylase (CYP17, P450c17); 17,20: 17,20 lyase (also mediated by CYP17); 3β: 3-beta-hydroxysteroid dehydrogenase; 21: 21-hydroxylase (CYP21A2, P450c21); 11β: 11-beta-hydroxylase; (CYP11B1, P450c11); 18 refers to the two-step process of aldosterone synthase (CYP11B2, P450c11as), resulting in the addition of an hydroxyl group that is then oxidized to an aldehyde group at the 18-carbon position; 17βR: 17-beta-reductase; 5αR: 5-alpha-reductase; DHEA: dehydroepiandrosterone; DHEAS: DHEA sulfate; A: aromatase (CYP19); SK: sulfokinase; SL: sulfotransferase.
### Congenital Adrenal Hyperplasia

<table>
<thead>
<tr>
<th></th>
<th>11β hydroxylase</th>
<th>17α hydroxylase</th>
<th>21 hydroxylase</th>
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<tbody>
<tr>
<td>Mineralocorticoids</td>
<td>↑</td>
<td>↑</td>
<td>↓</td>
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<tr>
<td>↑ = HTN, ↓K⁺</td>
<td></td>
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<tr>
<td>↓ = hypotension, ↑K⁺</td>
<td></td>
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<tr>
<td>Cortisol</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Sex hormones</td>
<td>↑ XX virilization</td>
<td>↓ XY ambiguous genitalia XX lack of secondary sex development</td>
<td>↑ XX virilization</td>
</tr>
</tbody>
</table>

**ONE UP!**
First number refers to mineralocorticoids
Second number refers to sex hormones
If the number is a ONE, that indicates elevation
Case 2

• A mother brings in her 7-year-old son to see the pediatrician. He has been less active and wetting his bed at night. His weight has dropped from 75\(^{th}\) percentile to 50\(^{th}\) percentile.

• Labs reveal:

\[
\begin{align*}
\text{WBC: } & 11,400/\text{mm}^3, \text{ normal differential} & \text{Creatinine: } & 1.2 \text{ mg/dL} \\
\text{Chloride: } & 100 \text{ mEq/L} & \text{Potassium: } & 5.0 \text{ mEq/L} \\
\text{Blood urea nitrogen: } & 14 \text{ mg/dL} & \text{Glucose: } & 350 \text{ mg/dL} \\
\text{Sodium: } & 132 \text{ mEq/L}
\end{align*}
\]
What is the most likely diagnosis?

A. Diabetes insipidus
B. Diabetes mellitus type 1
C. Diabetes mellitus type 2
D. Mature onset diabetes of the young (MODY)
What is the most likely diagnosis?

A. Diabetes insipidus
B. Diabetes mellitus type 1
C. Diabetes mellitus type 2
D. Mature onset diabetes of the young (MODY)
Which of the following set of lab values are consistent with DKA?

A. Glucose 400, pH 7.2, bicarbonate 12, anion gap 22
B. Glucose 400, pH 7.4, bicarbonate 18, anion gap 10
C. Glucose 400, pH 7.2, bicarbonate 12, anion gap 8
D. Glucose 400, pH 7.6, bicarbonate 28, anion gap 10
Which of the following set of lab values are consistent with DKA?

A. **Glucose 400, pH 7.2, bicarbonate 12, anion gap 22**
B. Glucose 400, pH 7.4, bicarbonate 18, anion gap 10
C. Glucose 400, pH 7.2, bicarbonate 12, anion gap 8
D. Glucose 400, pH 7.6, bicarbonate 28, anion gap 10

**Diabetic ketoacidosis = hyperglycemia + anion gap metabolic acidosis**

Serum anion gap = Na - (Cl + HCO3). Normal ~ 3-10 meq/L

Gap increases from any strong acid other than HCl (bicarb falls, Cl unchanged)
Diabetic Ketoacidosis

- Hyperglycemia
  - Glucose usually over 300 mg/dL
- Ketonemia
- Acidosis (arterial pH < 7.3)
Sulfonylureas are commonly used in the treatment of type 2 diabetes and work by increasing endogenous insulin production via SUR-1 receptors by what direct mechanism?

A. ↑ ATP generation  
B. Closure of K⁺ channels  
C. Opening of Ca²⁺ channels  
D. Stimulation of insulin exocytosis
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A. ↑ ATP generation

B. **Closure of K^+ channels**

C. Opening of Ca^{2+} channels

D. Stimulation of insulin exocytosis
Glucose Sensing & Insulin Secretion

- Glucose metabolism results in increased ATP
- ATP binds and closes the ATP-sensitive K⁺ channel
- ATP-sensitive K⁺ channel consists of subunits, SUR1 subunit regulates the opening
- SUR1 contains unique binding sites for ATP, sulfonylureas and other drugs
- Cell depolarization opens voltage-sensitive calcium channel
Insulin Secretion from Beta Cells

- Elevations in intracellular calcium
- Entry of calcium drives the fusion of insulin granules with the cell surface membrane via SNARE proteins, causing exocytosis of insulin.

SNARE = soluble N-ethylmaleimide sensitive factor attachment protein receptor
Endogenous insulin production can best be differentiated from exogenous insulin using which one of the following assays?

A. Insulin  
B. Beta-hydroxybutyrate  
C. GLUT-4  
D. C-peptide
Endogenous insulin production can best be differentiated from exogenous insulin using which one of the following assays?

A. Insulin  
B. Beta-hydroxybutyrate  
C. GLUT-4  
D. **C-peptide**
Insulin Synthesis

Insulin gene located on chromosome 11

Translated into pre-proinsulin in ribosomes of rough ER

Cleaved into proinsulin

Transported to Golgi apparatus where it is packaged into secretory granules

In the granules, proinsulin is cleaved into mature insulin

C-peptide secreted in equimolar ratio with insulin
Case 3

- A 52-year-old woman presents to the clinic with several months history of fatigue, cold intolerance, and weight gain. Exam reveals prolonged relaxation phase of deep tendon reflexes.
- Labs: TSH 31 µU/mL, free T4 0.5, morning cortisol 20
What is the most likely diagnosis?

A. Primary adrenal insufficiency
B. Secondary adrenal insufficiency
C. Primary hypothyroidism
D. Secondary hypothyroidism
What is the most likely diagnosis?

A. Primary adrenal insufficiency
B. Secondary adrenal insufficiency
C. **Primary hypothyroidism**
D. Secondary hypothyroidism
The hypothalamic-hypophysial-thyroidal axis. TRH produced in the hypothalamus reaches the thyrotrophs in the anterior pituitary by the hypothalamo-hypophysial portal system and stimulates the synthesis and release of TSH. In both the hypothalamus and the pituitary, it is primarily T3 that inhibits TRH and TSH secretion, respectively. T4 undergoes monodeiodination to T3 in neural and pituitary as well as in peripheral tissues.
What is the appropriate treatment for this patient?

A. Liothyronine  
B. Levothyroxine  
C. Lithium  
D. Lisinopril
What is the appropriate treatment for this patient?

A. Liothyronine
B. Levothyroxine
C. Lithium
D. Lisinopril
Iodine is covalently linked to which amino acid residue of thyroglobulin in the formation of thyroid hormone?

A. Leucine
B. Isoleucine
C. Tyrosine
D. Tryptophan
Iodine is covalently linked to which amino acid residue of thyroglobulin in the formation of thyroid hormone?

A. Leucine
B. Isoleucine
C. Tyrosine
D. Tryptophan
Which of the following are secreted from the structure indicated by an X?

A. Oxytocin, ADH
B. Oxytocin, LH, FSH
C. TSH, ACTH, GH
D. TSH, ACTH, ADH
Which of the following are secreted from the structure indicated by an X?

A. Oxytocin, ADH  
B. Oxytocin, LH, FSH  
C. **TSH, ACTH, GH**  
D. TSH, ACTH, ADH
Compression of the structure marked by an X results in what clinical phenomenon?

A. Bitemporal hemianopia
B. Central vision loss
C. Quadrantanopsia
D. Visual agnosia
Compression of the structure marked by an X results in what clinical phenomenon?

A. Bitemporal hemanopia  
B. Central vision loss  
C. Quadrantanopsia  
D. Visual agnosia
Legend:

ACTH, TSH, LH, FSH, GH, Prolactin

Oxytocin, ADH

Case 4

• A 62-year-old man presents for annual visit. Mild fatigue, otherwise well. Physical exam unremarkable.

• Labs: Calcium 11.3 mg/dL, phosphorus 2.2 mg/dL, albumin 4.0 mg/dL.
What is the next step in his evaluation?

A. 25-hydroxy vitamin D
B. 1,25-hydroxy vitamin D
C. PTH
D. 24 hr urine calcium collection
What is the next step in his evaluation?

A. 25-hydroxy vitamin D
B. 1,25-hydroxy vitamin D
C. PTH
D. 24 hr urine calcium collection
Signs and Symptoms of Hyperparathyroidism

Stones
- Renal stones
- Nephrocalcinosis
- Polyuria
- Polydipsia
- Uremia

Bones
- Osteitis fibrosa with
  - Subperiosteal resorption
  - Osteoclastomas
  - Bone cysts
- Radiologic osteoporosis
- Osteomalacia or rickets
- Arthritis

Abdominal groans
- Constipation
- Indigestion, nausea, vomiting
- Peptic ulcer
- Pancreatitis

Psychic moans
- Lethargy, fatigue
- Depression
- Memory loss
- Psychoses-paranoia
- Personality change, neuroses
- Confusion, stupor, coma

Other
- Proximal muscle weakness
- Keratitis, conjunctivitis
- Hypertension
- Itching

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Subperiosteal resorption (thin arrows)

Osteolysis (thick arrows)

Brown tumor (arrowhead) = collections of osteoclasts intermixed with fibrous tissue and poorly mineralized woven bone
Approach to Hypercalcemia

Hypercalcemia documented on repeat tests with albumin or ionized calcium

History and physical exam focusing on the acuity of hypercalcemia, presence kidney disease, medication use, and the presence of a personal or family history of malignancy.

Is malignancy likely?

- Yes
  - PTHrP
  - Evaluate for humoral hypercalcemia of malignancy (consider cancers of lung, pancreas, kidney)

- No
  - Consider milk-alkali syndrome, granulomatous disease, thiazide use, hyperthyroidism, hyperparathyroidism
  - High normal or slightly elevated
  - Likely primary hyperparathyroidism
  - Also consider MEN syndromes, secondary or tertiary hyperparathyroidism (if there is CKD), lithium use

- PTH
  - Evaluate for osteolytic hypercalcemia of malignancy (consider breast cancer and multiple myeloma)

CKD, chronic kidney disease; FHH, familial hypercalciuric hypercalcemia; MEN, multiple endocrine neoplasia; PTH, parathyroid hormone; PTHrP, parathyroid hormone-related protein.
What is the most likely genetic mutation in a 25 year old male with medullary thyroid cancer and hyperparathyroidism?

A. AIRE  
B. CASR  
C. MENIN  
D. RET
What is the most likely genetic mutation in a 25 year old male with medullary thyroid cancer and hyperparathyroidism?

A. AIRE – Polyglandular autoimmune syndrome type 1
B. CASR – Familial Hypocalciuric hypercalcemia
C. MENIN – MEN 1
D. RET - MEN 2A/B
# Multiple Endocrine Neoplasia (MEN)

## Incidence of tumor types

<table>
<thead>
<tr>
<th>Genetic Mutation</th>
<th>MEN 1</th>
<th>MEN 2A</th>
<th>MEN 2B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumor Type</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Parathyroid</td>
<td>MENIN</td>
<td>RET*</td>
<td>RET*</td>
</tr>
<tr>
<td>Pancreatic**</td>
<td>Common</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pituitary</td>
<td>Common</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medullary thyroid carcinoma</td>
<td>Very common</td>
<td>Very common</td>
<td>Very common</td>
</tr>
<tr>
<td>Pheochromocytoma</td>
<td>Rare</td>
<td>Sometimes</td>
<td>Common</td>
</tr>
<tr>
<td>Mucosal and gastrointestinal ganglioneuromas</td>
<td>Rare</td>
<td></td>
<td>Very common</td>
</tr>
</tbody>
</table>

*Depends on type of RET mutation

** Such as insulinoma, Zolinger-Ellison syndrome (gastrin-secreting = acid hypersecretion)
<table>
<thead>
<tr>
<th>Hormone</th>
<th>Production stimulated by</th>
<th>Secreted from</th>
<th>Primary effects</th>
<th>Deficiency results in</th>
<th>Excess results in</th>
<th>Lab testing</th>
<th>Other:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cortisol</td>
<td>ACTH</td>
<td>Zona Fasciculata</td>
<td>↑BP, insulin resistance, etc ↓ immune fxn, bone formation</td>
<td>Adrenal insufficiency (N/V, abd pain)</td>
<td>Cushing (central obesity, striae, DM, etc)</td>
<td>Cosyntropin stim test</td>
<td>High ACTH = hyperpigmentation</td>
</tr>
<tr>
<td>Thyroid hormone</td>
<td>TSH</td>
<td>Follicular cells of thyroid</td>
<td>Bone growth, CNS maturation, ↑ BMR</td>
<td>Hypothyroid (fatigue, weight gain, edema)</td>
<td>Hyperthyroid (tremor, palpitations, sweating)</td>
<td>TSH (unless secondary – T4)</td>
<td>Iodine linked to tyrosine. TBG binds most T3/T4 in blood.</td>
</tr>
<tr>
<td>Parathyroid hormone</td>
<td>↓ Calcium via calcium-sensing R</td>
<td>Chief cells of parathyroid</td>
<td>↑ 1,25 vit D production ↑ bone resorption ↓ phos</td>
<td>Hypocalcemia</td>
<td>Hypercalcemia</td>
<td>PTH, calcium, phos</td>
<td>Hyper-parathyroidism very common in MEN 1</td>
</tr>
<tr>
<td>Prolactin</td>
<td>Release from dopamine inhibition</td>
<td>Anterior pituitary</td>
<td>Milk production</td>
<td>Unable to lactate</td>
<td>Galactorrhea/hypogonadism</td>
<td>Prolactin</td>
<td>TRH also stimulates prolactin</td>
</tr>
<tr>
<td>Insulin</td>
<td>Hyper-glycemia</td>
<td>Beta cell</td>
<td>Lower glucose</td>
<td>Diabetes mellitus</td>
<td>Insulinoma-hypoglycemia</td>
<td>A1C/glucose for DM</td>
<td>C-peptide = endogenous insulin production</td>
</tr>
<tr>
<td>Aldosterone</td>
<td>Angiotensin II</td>
<td>Zona glomerulosa</td>
<td>↓K+ ↑Na+ &amp; water retention</td>
<td>Hypotension, hyperkalemia</td>
<td></td>
<td>Aldosterone level</td>
<td>Aldosterone producing tumor causes low renin</td>
</tr>
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