Pathology of the Endocrine System II:

Case Studies to Illustrate Principles of Endocrine Pathology and the Role of the Clinical Laboratory in the Delivery of Care

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DUHS Clinical Pathology Laboratories
Learning Objectives

By the conclusion of this session/lecture students will be able to:

- broadly characterize endocrinopathies as disorders of hypo- or hyperfunction and for each type list several general abnormalities that can contribute to the pathogenesis of endocrine disease;
- realize how clinical test “numbers” must be interpreted in their proper physiological/clinical context to provide meaningful information to the caregiver; and
- appreciate the importance of the clinical laboratory in the routine differential diagnosis of endocrine disorders.
Endocrine problems when there is an absolute or functional deficit of a hormone.

Functional deficits may occur when hormone is present but the end organ receptors may not recognize the hormone (for example)
Case Studies to Illustrate Principles of Endocrine Pathology and Use of the Endocrine Laboratory
Case A: Truncal obesity, striae, hypertension and glucose intolerance in a 39-year old man

- Patient’s visit to the local ER was prompted by a nasty coffee burn. He was driving his delivery van through a complicated intersection, shifting gears and balancing a cup of very hot coffee, when the spill occurred. The burn extended over his anterior thighs and upper abdomen and quickly blistered.

- The ER physician was more impressed by patient’s appearance than by the burns. At age 39 patient’s past medical history was largely unremarkable, but he had noticed some changes over the past several years. His weight had increased about 30 pounds, most of it distributed in his trunk and face. He also noted some purple stretch marks on his abdomen, mild but persistent facial acne, and a slightly scaly patchy discoloration of his chest and back. He always looked red-faced, as if he had been out in the sun or wind. His muscle strength had decreased. Loading and unloading his van was more difficult and he even had difficulty getting out of his easy chair, needing to use his hands to pick himself up.
Case A: Truncal obesity, striae, hypertension and glucose intolerance in a 39-year old man

• Physical Examination

  • Vital Signs: Blood Pressure 160/80; pulse 98
  • Skin: Tinea versicolor of the upper chest and second degree burns of the upper abdomen and mid-thighs bilaterally
    Violaceous pigmented striae of the abdomen
  • HEENT: Normal
  • Chest: Normal
  • Abdomen: Protuberant without palpable organomegaly
  • Extremities: Thin compared to body size, no edema
**Case A: Truncal obesity, striae, hypertension and glucose intolerance in a 39-year old man**

**Laboratory Studies (Initial)**

<table>
<thead>
<tr>
<th>Test</th>
<th>Patient</th>
<th>Normal</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABC</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td><strong>No hematological abnormalities</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum Sodium</td>
<td>140 mEq/L</td>
<td>135-145</td>
</tr>
<tr>
<td>Serum Potassium</td>
<td>3.1 mEq/L</td>
<td>3.5-5.0</td>
</tr>
<tr>
<td>Glucose (random)</td>
<td>162 mg/dL</td>
<td>70-99 mg/dL, fasting</td>
</tr>
<tr>
<td>Creatinine</td>
<td>0.9 mg/dL</td>
<td>0.3-1.5 mg/dL</td>
</tr>
<tr>
<td>BUN</td>
<td>10 mg/dL</td>
<td>8-22 mg/dL</td>
</tr>
</tbody>
</table>
Case A: Truncal obesity, striae, hypertension and glucose intolerance in a 39-year old man

Laboratory Studies (Initial)

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</thead>
<tbody>
<tr>
<td>Glucose (random)</td>
<td>162 mg/dL</td>
<td>70-99 mg/dL, fasting</td>
</tr>
<tr>
<td></td>
<td></td>
<td>70-140 mg/dL, non-fasting</td>
</tr>
</tbody>
</table>

162 mg/dL is elevated even in the non-fasting reference range. (It should be noted that the blood glucose in the ER is NOT a fasting glucose since the patient came in unexpectedly and did not fast)
Which of the following hormones can exert well-documented effects on blood pressure, serum potassium concentration, and carbohydrate, fat and protein metabolism?

A. Cortisol
B. Prolactin
C. Parathyroid Hormone
D. Secretin
Clinical effects

- Cortisol excess
  - Diminished protein synthesis
  - Gluconeogenesis
    - Hyperglycaemia and glycosuria
  - Depression of immune reaction
  - Tendency to bacterial infection
  - Suppression of growth hormone
    - Arrest of growth in children

- Fat deposition
- Protein catabolism
- Muscle wasting, weakness

In addition:
1. Osteoporosis → kyphosis
2. Hypertension
3. Degree of virilism common in women.
Clinical Features of Cushing’s Syndrome

- Centripetal obesity
- Hypertension
- Facial fullness
- Hirsuitism
- Menstrual disorders
- Muscle weakness
- Back pain

- Striae
- Acne
- Emotional lability
- Bruising
- Edema
- Diabetes mellitus
- Hypercalciuria
- Hypokalemia
Case A: Truncal obesity, striae, hypertension and glucose intolerance in a 39-year old man

Laboratory Studies (Follow-up)

<table>
<thead>
<tr>
<th>Test</th>
<th>Patient</th>
<th>Normal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose (fasting)</td>
<td>143 mg/dL</td>
<td>70-100 mg/dL, fasting</td>
</tr>
<tr>
<td>Cortisol (10 a.m.)</td>
<td>29 μg/dL</td>
<td>8 a.m.: 5-25 μg/dL, 4 p.m.: 3-12 μg/dL</td>
</tr>
</tbody>
</table>

Follow-up studies for previous case

Why would we have two times listed for Cortisol?

Answer: Cortisol secretion is based on a circadian rhythm. In the morning, cortisol secretion is at its peak.
Pathogenetic Mechanism of Cushing’s Disease

PITUITARY

ACTH

ADRENALS

CORTISOL

RECEPTOR

EFFECTOR

RESPONSE

TARGET CELL(S)

HYPERFUNCTION TUMOR

Pituitary abnormality

also due to hypertrophy of pituitary

Cushing's disease vs Cushing’s syndrome - same presentation but different pathology - more to come.
Pathogenetic Mechanism #1 of Cushing’s Syndrome

Mechanism #1 - With a normal pituitary - abnormal adrenal tumor or hypertrophy can cause hypercortisolism

- PITUITARY
- ↓ ACTH ↓
- ADRENALS
- ↓ CORTISOL ↓
- RECEPTOR
- ↓ EFFECTOR ↓
- RESPONSE
- ↑ ACTH ↑

HYPERFUNCTION TUMOR

CUSHING’S SYNDROME

- Fat pads
- Moon face
- Red cheeks
- Pendulous abdomen
- Bruisability with ecchymoses
- Striae
- Thin skin
- Poor muscle development
- Poor wound healing
Pathogenetic Mechanism #2 of Cushing’s Syndrome

**PITUITARY** ➔ **ACTH** ➔ **ADRENALS** ➔ **CORTISOL** ➔ **RECEPTOR** ➔ **EFFECTOR** ➔ **RESPONSE** ➔ **TARGET CELL(S)**

**HYPERFUNCTION ECTOPIC PRODUCTION**

- **ACTH**
- Mechanism #2 - ectopic production of ACTH contribute to ACTH from pituitary causing hypercortisolism

- **ACTH**
- Lung tumors are one such tumor that commonly secretes ACTH as a paraneoplastic process.

- **ACTH**
- While endogenous ACTH may decrease by negative feedback, ACTH from tumor is unregulated and ACTH levels will be above normal.

**CUSHING’S SYNDROME**
- Fat pads
- Moon face
- Red cheeks
- Pendulous abdomen
- Bruisability with ecchymoses
- Striae
- Thin skin
- Poor muscle development
- Poor wound healing
Mechanism #3 - Cortisol or cortisol mimics (steroids) are taken either illicitly or by prescription - causes same syndrome. We would expect decreased ACTH levels from the pituitary.

Jerry Lewis - underwent long-term high-dose prednisone for pulmonary fibrosis and ended up looking like this cartoon on the right before his treatment was stopped.
**Case A: Truncal obesity, striae, hypertension and glucose intolerance in a 39-year old man**

**Laboratory Studies (Follow-up)**

<table>
<thead>
<tr>
<th>Test</th>
<th>Patient</th>
<th>Normal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cortisol (8 a.m.)</td>
<td>39 µg/dL</td>
<td>8 a.m.: 5-25 µg/dL</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4 p.m.: 3-12 µg/dL</td>
</tr>
<tr>
<td>ACTH (8 a.m.)</td>
<td>62 pg/mL</td>
<td>8 a.m.: &lt;80 pg/mL</td>
</tr>
<tr>
<td>Cortisol, timed urine</td>
<td>425 µg/d</td>
<td>20-70 µg/d</td>
</tr>
</tbody>
</table>

Why are we interested in urine cortisol vs. serum?

Timed urine cortisol allows 24-period surveillance and avoids seeing anomalies in instantaneous cortisol levels due to pulsatile secretion.

Though this normal level may not immediately indicate Cushing’s disease vs. Cushing’s syndrome - cannot rule out this possibility - there is no black & white in laboratory science.
Which of the following is always true about a diagnostic test’s reference range?

A. Distinguishes between apparently healthy and diseased individuals
B. Follows a normal (bell-shaped) distribution
C. May vary according to the time of sample collection, sex and age of patient and analytical method
D. All of the above

Don't always have an absolute differentiation of diagnostic test as was mentioned about the ACTH panel on the previous slide.

Question about bimodal distribution based on sex - some hormones follow gender differences - some don't PTH, for example, is similar across the sexes Testosterone on the other hand will have very different ranges in males vs. females.

While many tests follow a normal distribution - some do not.
Reference range for ACTH

Notice many Cushing's disease patients fall within normal range

More absolute separation in ectopic ACTH production

Adrenal tumor causes hyosecretion of ACTH as expected
### Case A: Truncal obesity, striae, hypertension and glucose intolerance in a 39-year old man

Study to differentiate Cushing’s disease/syndrome pathologies

Laboratory Studies (Follow-up)

<table>
<thead>
<tr>
<th>Day</th>
<th>Condition</th>
<th>Cortisol 8 a.m. (µg/dL)</th>
<th>Cortisol Timed Urine (µg/d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Baseline</td>
<td>39</td>
<td>425</td>
</tr>
<tr>
<td>2</td>
<td>Baseline</td>
<td>42</td>
<td>389</td>
</tr>
<tr>
<td>3</td>
<td>Low-dose dex</td>
<td>38</td>
<td>392</td>
</tr>
<tr>
<td>4</td>
<td>Low-dose dex</td>
<td>39</td>
<td>402</td>
</tr>
</tbody>
</table>

24h Urinary Free Cortisol
Low-dose dexamethasone suppression

Use steroids to see if cortisol production responds - can indicate which type of cortisol pathology is present

After low-dose dexamethasone treatment, cortisol levels show very little effect if any
**Case A: Truncal obesity, striae, hypertension and glucose intolerance in a 39-year old man**

**Laboratory Studies (Follow-up)**

<table>
<thead>
<tr>
<th>Day</th>
<th>Condition</th>
<th>Cortisol 8 a.m.</th>
<th>Cortisol Timed Urine</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Normal</td>
<td>5-25 μg/dL</td>
<td>20-70 μg/d</td>
</tr>
<tr>
<td>5</td>
<td>High-dose dex</td>
<td>19</td>
<td>227</td>
</tr>
<tr>
<td>6</td>
<td>High-dose dex</td>
<td>9</td>
<td>147</td>
</tr>
</tbody>
</table>

High dose dexamethasone caused reductions in both serum and urine cortisol levels
24h Urinary Free Cortisol
Low-dose dexamethasone suppression

Abnormal

Plasma ACTH

High dose dexamethasone suppression

ACTH low
No Suppression

Adrenal Neoplasm
Adrenal imaging

ACTH > 200 pg/ml
No Suppression

Probable Ectopic ACTH
Pituitary imaging
Inferior petrosal sinus sampling

ACTH nl or sl↑
No Suppression

Probable Pituitary Cushing's
Pituitary imaging

ACTH nl or sl↑
>80% suppression

Pituitary Cushing's

Day | Condition | Cortisol
--- | --- | ---
8 a.m. Timed Urine | Normal 20-70 ug/d
1 | Baseline | 425
2 | Baseline | 389
3 | Low-dose dex | 392
4 | Low-dose dex | 402
5 | High-dose dex | 227
6 | High-dose dex | 147

Most likely cause based on results of test on previous slide
The patient’s 6-day dexamethasone suppression results are most consistent with which of the following diagnoses:

A. Normal health
B. Cushing’s Disease (Pituitary)
C. Cushing’s Syndrome (Adrenal)
D. Cushing’s Syndrome (Ectopic)
E. Cushing’s Syndrome (Iatrogenic)
Magnetic Resonance Imaging (MRI) of Pituitary

Pituitary tumor on MRI
Therapeutic Options for Cushing’s Disease

- Surgery with removal of the pituitary adenoma
- Radiation therapy
- Bilateral adrenalectomy

After completing the tests, the patient underwent successful transphenoidal hypophysectomy with removal of the adenoma seen on MRI. Pathology studies revealed a benign tumor with histologic and staining characteristics consistent with an ACTH-secreting adenoma.
Case A: Truncal obesity, striae, hypertension and glucose intolerance in a 39-year old man

- Perioperatively the patient was “covered” with “stress steroids” and postoperatively his dose was tapered down to a physiologic dose. After a few weeks of physiologic replacement, he was tapered gradually to no exogenous cortisol. Over the next several months his body weight decreased by about 20 pounds, his facial redness decreased, his blood pressure improved, and glucose intolerance was no longer present. The stretch marks are still there, but they are less colorful and, in general, the patient feels better. His muscle strength has improved significantly. By 6 months postoperatively his morning cortisol level was normal, at 23 µg/dL.

- At some point it would be useful to test the patient’s hypothalamic-pituitary-adrenal axis for stress responsiveness, to be sure that full, stress-responsive function of the system has returned.
Case B: Coma and hypercalcemia in an older man

- Although he usually loved to walk on the beach in the sun, this summer the patient found himself with less and less energy. On a hot August afternoon he was found by his grandson in a comatose state in his urine-soaked bed.

- In the ER, he was barely responsive and clearly volume depleted. Physical examination revealed a supine blood pressure of 110/70 that fell to 90/60 when he was propped up. His pulse went from 90 to 120 with that maneuver. His mucous membranes were dry. His general physical exam was otherwise unremarkable, except for the neurologic exam, which revealed an obtunded man who could barely respond to simple questions. He was able to move all extremities on command.
### Case B: Coma and hypercalcemia in an older man

**Laboratory Studies (Initial)**

<table>
<thead>
<tr>
<th>Test</th>
<th>Patient</th>
<th>Normal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose (random)</td>
<td>88 mg/dL</td>
<td>70-110 mg/dL, fasting</td>
</tr>
<tr>
<td>Toxic screen</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>Calcium</td>
<td>13.6 mg/dL</td>
<td>8.5-10.5 mg/dL</td>
</tr>
<tr>
<td>Phosphate</td>
<td>5.9 mg/dL</td>
<td>3.0-4.5 mg/dL</td>
</tr>
<tr>
<td>Albumin</td>
<td>5.0 g/dL</td>
<td>3.5-5.5 g/dL</td>
</tr>
<tr>
<td>BUN</td>
<td>55 mg/dL</td>
<td>8-22 mg/dL</td>
</tr>
<tr>
<td>Creatinine</td>
<td>2.0 mg/dL</td>
<td>0.3-1.5 mg/dL</td>
</tr>
<tr>
<td>Alkaline Phosphatase</td>
<td>65 U/L</td>
<td>30-120 U/L</td>
</tr>
</tbody>
</table>

Apparently there was some concern about an overdose because a toxic screen was ordered in addition to normal blood chemistry.
Blood Ca and P Homeostasis

Output

175 mg
Excretion

PTH
(-) Calcium
(+) Phosphate

input

300 mg
Absorption

1,25 D (+)

125 mg

825 mg

300 in, 125
back into
intestine - net is
about 175 mg

Excretion

500 mg
Resorption

PTH (+)
1,25 D (+)

Calcium is stored
long term in
skeleton

Exchange

500 mg
Accretion

PTH (+)
1,25 D (+)

Blood

900 mg

[Calcium]

[Phosphate]

500 mg

Input

1000 mg

125 mg

Hormonal form of
vitamin D formed in
kidney

Modulators

PTH
Calcium (-)
1,25 D (+)

1,25 D
Calcium (-)
Phosphate (-)
**Case B: Coma and hypercalcemia in an older man**

**Laboratory Studies (Follow-up)**

<table>
<thead>
<tr>
<th>Test</th>
<th>Patient</th>
<th>Normal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium</td>
<td>11.6 mg/dL</td>
<td>8.5-10.5 mg/dL</td>
</tr>
<tr>
<td>Phosphate</td>
<td>5.2 mg/dL</td>
<td>3.0-4.5 mg/dL</td>
</tr>
<tr>
<td>BUN</td>
<td>21 mg/dL</td>
<td>8-22 mg/dL</td>
</tr>
<tr>
<td>Creatinine</td>
<td>1.7 mg/dL</td>
<td>0.3-1.5 mg/dL</td>
</tr>
<tr>
<td>PTH, Intact</td>
<td>&lt;10 pg/mL</td>
<td>10-65 pg/mL</td>
</tr>
<tr>
<td>25-OH-Vitamin D₃</td>
<td>352 ng/mL</td>
<td>30-100 ng/mL</td>
</tr>
</tbody>
</table>

ER physician found the Ca and Phosphate abnormalities to be of the most concern and ordered the following studies. Despite elevated calcium, PTH is coming up subnormal, while 25-D is abnormally high. These are the most important diagnostically.
<table>
<thead>
<tr>
<th>Category</th>
<th>Causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common</td>
<td>Malignancy, Hyperparathyroidism</td>
</tr>
<tr>
<td>Uncommon</td>
<td>Vitamin D Poisoning, Thyrotoxicosis</td>
</tr>
<tr>
<td>Rare</td>
<td>Sarcoidosis, Tuberculosis, Thalizide Diuretics, Pheochromocytoma,</td>
</tr>
<tr>
<td></td>
<td>Immobilization, Milk-Alkali Syndrome, Familial Hypocalciuric Hypercalcemia</td>
</tr>
<tr>
<td></td>
<td>Recovery Phase of Acute Renal Failure</td>
</tr>
</tbody>
</table>

- **Common**: Usually hypercalcemia isn't the first sign that alerts patient to malignancy.
- **Uncommon**: XS thyroid hormone over a long time period.
Hypercalcemia in the presence of subnormal PTH would NOT be anticipated in which disorder:

A. Malignancy-associated hypercalcemia
B. Vitamin D intoxication
C. Pseudohypoparathyroidism
D. Thyrotoxicosis

So called because subnormal PTH causing hypoparathyroid but rather an end-organ receptor defect in which normal or high PTH levels do not effect Calcium levels appropriately
Case B: Coma and hypercalcemia in an older man

- After 6 hours and 3.5 L of i.v. saline, the patient’s blood pressure and mental status dramatically improved. He was able to relate his past medical history, which was remarkable for significant osteoarthritis, principally involving his knees. The patient was somewhat vague about what medications, if any, he was taking.

- Later in the day his grandson came to visit and brought with him a bag full of medications that he found in his grandfather’s bathroom. In addition to aspirin, acetaminophen and ibuprofen, a number of vitamin supplements were found. When the contents of the bag were reviewed with the patient, he admitted, rather sheepishly, that he had, in fact, been taking a large number of items in the bag. The salesman at the health food store had been quite convincing that BONEALL contained everything needed to strengthen bones and might help with the osteoarthritis that had plagued him for years. Although the directions clearly stated that only one should be taken daily, the patient did as he often did with medications—he took them when and as often as he wanted to. He felt that BONEALL was really helping and ended up taking 16 to 20 of the large tablets each day. Both BONEALL and several of the other vitamin preparations contained vitamin D.
We measure this, not 1,25 D which actually maintains calcium - This is because 1,25 production is a matter of substrate (25 D) not hormonally production in the kidney and 25 D levels are representative.

Vitamin D supplement caused increase in vitamin D levels which increases Calcium absorption in the gut which caused the hypercalcemia in this case.
Case B: Coma and hypercalcemia in an older man

The patient is no longer taking any of the pills in the bag or anything from the health food store. His calcium level is slightly elevated but controlled by the three or four quarts of fluid he drinks each day and the extra salt he adds to his food. After several months the vitamin D level is still elevated, but closer to normal, and his serum calcium usually is at the upper end of the normal range.
Case C: 67-year old woman in apparent good health given thyroid supplementation for 25 years presenting for a routine physical

- A 67-year old white female in apparent good health scheduled a routine physical with a new physician following a recent out-of-state move.
- Her only medication is levothyroxine 0.2 mg daily for presumed hypothyroidism (after presenting with symptoms of fatigue quarter century earlier).
- The new physician ordered a thyroid panel (i.e. free thyroxine [FT4] and thyroid stimulating hormone [TSH] to assess the patient’s current thyroid function.
- Physical examination demonstrates a normal-appearing woman. Height 65 in, weight 140 lbs, blood pressure 122/80, pulse 70. The exam is entirely normal and the patient denies any tachycardia, nervousness, heat intolerance, palpitations or diarrhea.
Case C: 67-year old woman in apparent good health given thyroid supplementation for 25 years presenting for a routine physical

<table>
<thead>
<tr>
<th>Test</th>
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<th>Normal</th>
</tr>
</thead>
<tbody>
<tr>
<td>FT4</td>
<td>1.05 ng/dL</td>
<td>0.52-1.21 ng/dL</td>
</tr>
<tr>
<td>TSH</td>
<td>0.03 mIU/mL</td>
<td>0.34-5.66 mIU/mL</td>
</tr>
</tbody>
</table>

This normal level is due, in large part, to this patient's thyroid supplement that she is receiving.
Case C: 67-year old woman in apparent good health given thyroid supplementation for 25 years presenting for a routine physical

- The suppressed TSH with “normal” FT4 and an absence of clinical symptoms is consistent with subclinical hyperthyroidism. Like subclinical hypothyroidism the disorder is manifested only as an abnormal TSH result. The most common cause is overadministration of thyroid hormone supplement.
- The physician attempts to decrease the dosage of levothyroxine but is met with resistance from the woman who claims the thyroid medicine “makes me feel good.” Nevertheless, on the next prescription the doctor reduces the dosage to 0.1 mg daily.
- After several weeks the patient reports feeling weak and tired and asks to go back to the higher dosage but agrees to continue the lower level a while longer. After 2 months the TSH remains suppressed at 0.03 mIU/mL.
Why use a pituitary hormone (TSH) to evaluate thyroid function?

- TSH is the trophic hormone which stimulates release of thyroid hormone
Why use a pituitary hormone (TSH) to evaluate thyroid function?

- The best immunoassay methods for TSH are simpler in design, more precise, less sensitive to interference, and more easily automated than the best assays for Free Thyroxine (FT₄).

There is log-linear relationship and since TSH tests are easier and more precise - they are generally used more often.
Case C: 67-year old woman in apparent good health given thyroid supplementation for 25 years presenting for a routine physical

• The dosage is further reduced to 0.05 mg daily, but the patient continues to feel weak and requests referral to an endocrinologist. After 2 months on the 0.05 mg/day supplement TSH is remeasured at 0.21 mIU/mL (Reference Range 0.34-5.66 mIU/mL).

• Despite strenuous objections the woman’s thyroid hormone supplementation was eventually discontinued altogether and TSH concentrations returned to normal. Over time the patient’s symptoms of fatigue subsided and she is doing well off all medication.

• There are thousands of individuals on thyroid hormone supplementation who presented to their physicians as tired and/or overweight with a low basal metabolic rate. Many of these were diagnosed in the 1950’s or 1960’s when accurate thyroid function tests were not available and physicians had little data by which to guide therapy. Most probably never had hypothyroidism.
There was a question about atrophy of the thyroid in a case like the last one presented.

Answer: While noticeable atrophy doesn't usually occur, functional depletion of thyroid production will occur as was seen in this case.