Case index patient 1

- Patient 75 years old treated for arteritis temporalis during 2 years
- Initial high dose medrol during two months, with tapering and followed by low dose medrol (6mg)
- Medrol is further decreased in order to stop glucocorticoids: 4mg every day and 4mg alternate days
- After 48h withdrawal : ACTH 6ng/l
  Cortisol 84µg/l
Case index patient 1

- Is it safe to stop corticosteroids?
- Do you order an additional test?
- Which test? ITT, Synacthen, others?
Case index patient 2

- JDRF 32 years type 1 diabetes admitted for hypoglycaemic attacks
- Fatigue, hypotension
- Biology:
  Na 125 Meq/l
  K 5.2 Meq/L
  Cl 89 Meq/l
  HCO3 21 Meq/l
Case index patient 2

- Is your diagnosis established
  ACTH 255 ng/l
  Cortisol 56 µg/l

- Do you order an additional test?
- 21-hydroxylase antibodies?
- AIRE gene mutation?
- Other antibodies?
- Additional hormonal evaluation?
Case History

- 50 year old freelance journalist
- Nasopharyngeal cancer
- Surgery and Radiotherapy October 1999
- 30 Gy in 15 fractions (2 courses)
January 2002

• GP noted serum Na 122
• Kept under review by Oncologists

November 2002

• Abnormal Thyroid Tests
• Started on T4 (50mcg → 100mcg)

February 2003

Patient felt worse
Still tired, feeling cold, aches/pains, light-headed, loss of balance

May 2003

Referred to Endocrinologist
## Results

<table>
<thead>
<tr>
<th></th>
<th>2002</th>
<th>Jan</th>
<th>Feb</th>
<th>Mar</th>
<th>Nov</th>
<th>Nov</th>
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<tbody>
<tr>
<td>Na</td>
<td>124</td>
<td>124</td>
<td>-</td>
<td>-</td>
<td>127</td>
<td>-</td>
</tr>
<tr>
<td>TSH</td>
<td>-</td>
<td>4.21</td>
<td>3.24</td>
<td>3.6</td>
<td>3.89</td>
<td></td>
</tr>
<tr>
<td>fT4</td>
<td>-</td>
<td>5.9</td>
<td>6.1</td>
<td>8</td>
<td>11</td>
<td></td>
</tr>
</tbody>
</table>

(8.3-18) (8.3-18) (8.3-18) (8.3-18)
What do the Thyroid hormones suggest?

Secondary Hypothyroidism

What is the patient’s ↓ Na due to?
Case index patient 3

- Do you want ACTH, cortisol 8 a.m.
- Do you want ACTH, cortisol 11 p.m.
- Synacthen test
- ITT, glucagon ?
Short synacthen test

mins - Cortisol 27 µg/l

30 mins - Cortisol 57µg/l

ACTH deficiency
Why did T4 exacerbate his symptoms?

T4 introduced before hydrocortisone in cortisol deficient patient can lead to acute cortisol deficiency

• Potentially Fatal •

Clues

• Large dose of radiation
• TSH deficient
• ↓ Na
• Symptoms worsen on T4
Physiology of the adrenal cortex
Physiology of Hypothalomo-Pituitary-Adrenal axis

- Cerebral cortex
- Hypothalamus
- Dermal rhythms
- Physical
- Emotional
- Biochemical

Small-bodied neurons in the hypothalamus synthesize and secrete corticotropin-releasing hormone (CRH).

Long portal vessels carry CRH to the anterior pituitary.

Short feedback (ACTH)

ACTH

Corticotrophs

G protein

G protein

AC

AC

PKA

PKA

Synthesis of several enzymes

Adrenal cortex cell

Melanocortin-2 receptor

G protein

Adrenal medulla

ACTH

G protein

Melanocortin-2 receptor

ACTH

Primary Adrenal Insufficiency Case Index patient 2

Primary A.I. (Addison’s disease)
Etiology of Primary Adrenocortical Insufficiency

Autoimmune
- Isolated
- Autoimmune polyendocrine syndrome type I
- Autoimmune polyendocrine syndrome type II (Schmidt's syndrome)

Infections
- Tuberculosis
- Fungal infections (histoplasmosis, paracoccidiodomycosis)
- Cytomegalovirus
- HIV
- Syphilis

Metastatic tumor (primarily lung, breast, colon or lymphoma)

Infiltrations (Amyloid, hemochromatosis)

Drugs (Ketoconazole, Rifampin, Phenytoin, Barbiturates)

Intra-adrenal haemorrhage (e.g. Waterhouse-Friderichsen syndrome)

Adrenoleukodystrophies / adrenomyeloneuropathy

Congenital adrenal hypoplasia
- *DAX-1* mutations
- *SF-1* mutations

ACTH resistance syndromes (e.g. Mutations in *MC2-R*, Triple A)

Bilateral adrenalectomy
Clinical pearls:

- Mostly in patients with anticoagulation therapy, coagulopathy or thrombocytopenia
- Pain (flank, lower chest, abdominal)
- Occult hemorrhage (rapid Hb drop)
- Progressive hyperkalemia / hyponatremia
- Volume contraction (Shock)
"general languor and debility, feebleness of the heart's action, irritability of the stomach, and a peculiar change of the color of the skin"
Stages in the development of Addison’s Disease

Nat. Rev. Endocrinol. doi:10.1038/nrendo.2010.40
Adrenal Cortex Autoantibodies (ACAs)

**P450scc Abs**
- 17-hydroxylase Abs
  - Strong association premature ovarian failure
    - Very low prevalence in AAD
    - Positive in APS type I (no 21-OH Abs)
    - APS type II
      - 33 % 17-OH Abs
      - 36 % P450scc Abs
      - 96 % 21-OH Abs

**21-hydroxylase Abs**
- 90 % positive in recent onset
- False positive (rare)
  - Adrenal tumors
  - Infections
  - Adrenoleukodystrophy
### Incidence of Other Endocrine and Autoimmune Diseases in Patients with Autoimmune Adrenal Insufficiency (N = 448)

<table>
<thead>
<tr>
<th>Disease</th>
<th>Incidence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thyroid disease</td>
<td></td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>8</td>
</tr>
<tr>
<td>Nontoxic goiter</td>
<td>7</td>
</tr>
<tr>
<td>Thyrotoxicosis</td>
<td>7</td>
</tr>
<tr>
<td>Gonadal failure</td>
<td></td>
</tr>
<tr>
<td>Ovarian</td>
<td>20</td>
</tr>
<tr>
<td>Testicular</td>
<td>2</td>
</tr>
<tr>
<td>Insulin-dependent diabetes mellitus</td>
<td>11</td>
</tr>
<tr>
<td>Hypoparathyroidism</td>
<td>10</td>
</tr>
<tr>
<td>Pernicious anemia</td>
<td>5</td>
</tr>
<tr>
<td>None</td>
<td>53</td>
</tr>
</tbody>
</table>

21-Hydroxylase Autoantibodies

Levels of autoantibodies

- Known Addison's: n=17
- Healthy Controls: n=241
- Negatives: n=942
- Positives: n=15

Follow Up: 0, 1, 2, 3 (years)
# Autoimmune Polyendocrine (Polyglandular) Syndromes

<table>
<thead>
<tr>
<th>Feature</th>
<th>Autoimmune Polyendocrine Syndrome Type I</th>
<th>Autoimmune Polyendocrine Syndrome Type II</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prevalence</td>
<td>Rare</td>
<td>Common</td>
</tr>
<tr>
<td>Time of onset</td>
<td>Infancy</td>
<td>Infancy through adulthood</td>
</tr>
<tr>
<td>Gene and inheritance</td>
<td>AIRE (on chromosome 21, recessive)</td>
<td>Polygenic</td>
</tr>
<tr>
<td>HLA genotype</td>
<td>Diabetes (risk decreased with HLA-DQ6)</td>
<td>HLA-DQ2 and HLA-DQ8; HLA-DRB1*0404</td>
</tr>
<tr>
<td>Immunodeficiency</td>
<td>Asplenism, susceptibility to candidiasis</td>
<td>None</td>
</tr>
<tr>
<td>Association with diabetes</td>
<td>Yes (in 18%)</td>
<td>Yes (in 20%)</td>
</tr>
<tr>
<td>Common phenotype</td>
<td>Candidiasis, hypoparathyroidism, Addison’s disease</td>
<td>Addison’s disease, type 1A diabetes, chronic thyroiditis</td>
</tr>
</tbody>
</table>
**Table 1** Characteristics of autoimmune polyglandular syndromes

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>APS-1</th>
<th>APS-2</th>
<th>IPEX</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prevalence</td>
<td>Rare</td>
<td>Common</td>
<td>Very rare</td>
</tr>
<tr>
<td>Onset</td>
<td>Infancy</td>
<td>Adulthood</td>
<td>Infancy</td>
</tr>
<tr>
<td>Relatives at risk</td>
<td>Siblings</td>
<td>Multiple generations</td>
<td>None</td>
</tr>
<tr>
<td>Genetics</td>
<td>Monogenic with AIRE gene mutations, autosomal recessive</td>
<td>Polygenic associated with HLA-DR3 and HLA-DR4 and non-HLA genes (MICA5.1, PTPN22, CTLA4, VNTR)</td>
<td>Monogenic with FOXP3 gene mutations, X-linked</td>
</tr>
<tr>
<td>Immunodeficiency</td>
<td>Aspleniaism</td>
<td>Muocutaneous candidiasis</td>
<td>None</td>
</tr>
<tr>
<td>Type 1A diabetes mellitus</td>
<td>18%</td>
<td>20%</td>
<td>&gt;50%</td>
</tr>
<tr>
<td>Autoantibodies</td>
<td>100% anti-interferon-ω antibodies</td>
<td>Steroid 21-hydroxylase, TPO, Tg, Insulin, IA-2, GAD, ZnT8, TTG, others</td>
<td>Present depending on disease manifestations</td>
</tr>
<tr>
<td>Common phenotype</td>
<td>Candidiasis, Addison disease, hypoparathyroidism</td>
<td>Addison disease, autoimmune thyroid disease, type 1A diabetes mellitus, celiac disease</td>
<td>Enteropathy, type 1A diabetes mellitus</td>
</tr>
</tbody>
</table>

**Abbreviations:** APS, autoimmune polyglandular syndrome; CTLA4, cytotoxic T lymphocyte associated antigen 4; FOXP3, forkhead box P3 gene; GAD, glutamate decarboxylase; HLA, human leukocyte antigen; IPEX, immune dysfunction, polyendocrinopathy, enteropathy, X-linked; MICA5.1, MHC class I-related gene A; IA-2, islet antigen 2; PTPN22, protein tyrosine phosphatase, non-receptor 22; TPO, thyroid peroxidase; Tg, thyroglobulin; TTG, tissue transglutaminase; VNTR, variable number tandem repeat in the 5' promoter of the insulin gene; ZnT8, zinc 18 transporter.

Figure 2 Pathogenic model for the autoimmune polyglandular syndromes

Nat. Rev. Endocrinol. doi:10.1038/nrendo.2010.40
Secondary A.I.  Case index patient 3
Etiology of Secondary Adrenocortical Insufficiency

- Panhypopituitarism
  - Pituitary tumors and pituitary surgery, craniopharyngiomas
  - Granulomatous disease (tuberculosis, sarcoid, eosinophilic granuloma)
  - Pituitary apoplexy
  - Lymphocytic hypophysitis
  - Secondary tumor deposits (breast, bronchus)
  - **Pituitary irradiation (effect usually delayed for several years)**
  - Postpartum pituitary infarction (Sheehan's syndrome)

- Isolated ACTH deficiency
  - Lymphocytic hypophysitis
  - POMC mutations
  - Tpit gene mutations
  - CBG deficiency
Tertiary A.I.

Tertiary Adrenal Insufficiency Case index patient 1
Etiology of Tertiary Adrenocortical Insufficiency

- Exogenous glucocorticoid therapy
- Cure of Cushing’s syndrome
- Infiltrative diseases of hypothalamus (tumor, sarcoidosis)
- Post irradiation

<table>
<thead>
<tr>
<th>HPA suppression likely</th>
<th>HPA suppression unknown</th>
<th>HPA suppression unlikely</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 20 mg, &gt; 3 weeks *</td>
<td>10-20 mg, &gt; 3 weeks</td>
<td>Any dose, &lt; 3 weeks</td>
</tr>
<tr>
<td>Cushingoid appearance</td>
<td>&lt; 10 mg, any duration</td>
<td>Alternate day regimes</td>
</tr>
</tbody>
</table>

* Prednisolone equivalent
Frequency of symptoms, signs and lab findings in A.I.

<table>
<thead>
<tr>
<th>Symptoms</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Weakness, tiredness, fatigue</td>
<td>100</td>
</tr>
<tr>
<td>Anorexia</td>
<td>100</td>
</tr>
<tr>
<td>Gastrointestinal symptoms</td>
<td>92</td>
</tr>
<tr>
<td>Nausea</td>
<td>86</td>
</tr>
<tr>
<td>Vomiting</td>
<td>75</td>
</tr>
<tr>
<td>Constipation</td>
<td>33</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>31</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>16</td>
</tr>
<tr>
<td>Salt craving</td>
<td>16</td>
</tr>
<tr>
<td>Postural dizziness</td>
<td>12</td>
</tr>
<tr>
<td>Muscle or joint pains</td>
<td>6-13</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Signs</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight loss</td>
<td>100</td>
</tr>
<tr>
<td>Hyperpigmentation</td>
<td>94</td>
</tr>
<tr>
<td>Hypotension (&lt;110 mm Hg sys)</td>
<td>88-94</td>
</tr>
<tr>
<td>Vitiligo</td>
<td>10-20</td>
</tr>
<tr>
<td>Auricular calcification</td>
<td>5</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Laboratory Findings</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Electrolyte disturbances</td>
<td>92</td>
</tr>
<tr>
<td>Hyponatremia</td>
<td>88</td>
</tr>
<tr>
<td>Hyperkalemia</td>
<td>64</td>
</tr>
<tr>
<td>Hypercalcemia</td>
<td>6</td>
</tr>
<tr>
<td>Azotemia</td>
<td>55</td>
</tr>
<tr>
<td>Anemia</td>
<td>40</td>
</tr>
<tr>
<td>Eosinophilia</td>
<td>17</td>
</tr>
</tbody>
</table>

Clues in laboratory diagnosis of adrenal insufficiency

**Routine blood analysis**

- Hyperkalemia: 65% (only in primary AI)
- Hyponatremia: 90%
- Hypercalcemia: 6%
- BUN: ↑ (primary AI), normal or ↓ (secondary)
How to assess adrenal axis failure?
Case index patient 1

- Patient 75 years old treated for arteritis temporalis during 2 years
- Initial high dose medrol during two months, with tapering and followed by low dose medrol (6mg)
- Medrol is further decreased in order to stop glucocorticoids: 4mg every day and 4mg alternate days
- After 48h withdrawal: ACTH 6ng/l
  Cortisol 84µg/l

Is it safe to stop medrol?
Diagnosis of tertiary adrenal insufficiency

Case index patient 1

Will you perform:

- ITT (insulin induced hypoglycaemia)
- SST (short synacthen test 250 µg IM or IV)
- LDST (low dose synacthen test: 1 µg ACTH IV)
Laboratory diagnosis of adrenal insufficiency: dynamic testing

Component-provocative testing
• Low dose / high dose ACTH stimulation test
• Prolonged ACTH stimulation test
• CRH stimulation test

Integrated-provocative testing
• Insulin-induced hypoglycemia test
• Metapyrone test (not feasible in Belgium)
Non-provocative testing for adrenal insufficiency

Morning [cortisol]_{serum}:

- $> 150 \, \mu g/l$ excludes diagnosis
- $< 70 \, \mu g/l$ : “presumptive evidence of A.I.”
After 48h withdrawal of glucocorticoids

9 a.m. plasma cortisol (best correlation with peak cortisol after hypoglycaemia)

< 200 nmol/L (72,5 µg/L) deficiency

> 400 nmol/L (145 µg/L) OK

200 – 400 nmol/L provocative tests
Insulin-induced hypoglycemia test

Minimum 8 h fasting

Insulin I.V. (1 x repeat if necessary)
0.15 U / kg [0.1 - 0.25]

Adequate test: [glucose] < 40 mg/dl and symptoms of hypoglycemia (profuse perspiration, hunger, sleeping, ...), usually within 30-45 min after insulin adm.

Termination test: [glucose] < 40 mg/dl or seizure, chest pain, confusion (glucose I.V. and softdrink P.O.)
Insulin-induced hypoglycemia test - interpretation

Normal values:

- \([\text{Cortisol}] > 180-200 \, \mu g/l\)
- \([\text{ACTH}] > 150 \, \text{pg/ml}\)

\(\Delta [\text{Cortisol}]\) not important

(+): intact HPA
(-): adrenal insufficiency or inadequate hypo-test

Considered the golden standard for diagnosis of adrenal insufficiency
ITT? = “golden standard”

Peak cortisol values after significant hypoglycaemia
(< 40 mg/dl)

C.I.: - very young and old
  - diabetes?
  - Epilepsy, CVA, TIA
  - ischemic heart disease
Alternatives

- Glucagon-test (1 mg SC)
  measure cortisol + GH

- Metyrapone (2 gr per os)
  requires 11-desoxycorticisol assay

- Synacthen-test
Low/High dose ACTH stimulation test

**LOW DOSE**
1 µg/1,73 m² I.V. SYNACTHEN

**HIGH DOSE**
250 µg I.V./I.M. SYNACTHEN
Rationale for synacthen-test

- easy to perform
- bedside (IM or IV)
- 1 single measurement of cortisol after 30 minutes

But

NOT to use in acute post-surgery setting

Wait 4 weeks (4 weeks of ACTH withdrawal)
• “pass” on ITT
• peak cortisol value
• > 550 nmol/L (200 µg/l) on current assays

• “pass” on SST
• absolute 30’ cortisol value
• > 600 nmol/L (220 µg/l) on current assays for secondary adrenal insufficiency

• increment not used
Diagnosis of Adrenal Insufficiency

Meta-analysis of all available data

ACTH stimulation test in patients with primary adrenal insufficiency

Table 1. The 250-μg Cosyntrpin Stimulation Test in Patients with Primary Adrenal Insufficiency

<table>
<thead>
<tr>
<th>Study (Reference)†</th>
<th>Cosyntrpin Route and Time after Injection</th>
<th>Serum Cortisol Cutoff Level</th>
<th>Sensitivity§</th>
<th>Specificity§</th>
<th>Positive Likelihood Ratio‖</th>
<th>Negative Likelihood Ratio‖</th>
</tr>
</thead>
<tbody>
<tr>
<td>Speckart et al. (27)</td>
<td>IV, 60</td>
<td>415</td>
<td>100 (6/6)</td>
<td>100 (9/9)</td>
<td>&gt;100</td>
<td>0</td>
</tr>
<tr>
<td>Nelson and Tindall (14)</td>
<td>IV, 60</td>
<td>415</td>
<td>100 (7/7)</td>
<td>100 (69/69)</td>
<td>&gt;100</td>
<td>0</td>
</tr>
<tr>
<td>Oelkers et al. (28)</td>
<td>IM, 60</td>
<td>415</td>
<td>100 (41/41)</td>
<td>-</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Fiad et al. (29)</td>
<td>IV, 60</td>
<td>415</td>
<td>100 (12/12)</td>
<td>100 (55/55)</td>
<td>&gt;100</td>
<td>0</td>
</tr>
<tr>
<td>Kong and Jeffcoate (23)</td>
<td>IV, 60</td>
<td>415</td>
<td>75 (6/8)</td>
<td>-</td>
<td>8.3</td>
<td>0</td>
</tr>
<tr>
<td>Gonzalez-Gonzalez et al. (20)</td>
<td>IV, 60</td>
<td>415</td>
<td>82 (9/11)</td>
<td>100 (46/46)</td>
<td>&gt;100</td>
<td>0.18</td>
</tr>
<tr>
<td>Soule (30)</td>
<td>IV, 60</td>
<td>415</td>
<td>95 (35/37)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Speckart et al. (27)</td>
<td>IV, 30</td>
<td>415</td>
<td>100 (6/6)</td>
<td>88 (7/8)</td>
<td>8.3</td>
<td>0</td>
</tr>
<tr>
<td>Dhuhy et al. (13)</td>
<td>IM, 30</td>
<td>415</td>
<td>100 (5/5)</td>
<td>100 (12/12)</td>
<td>&gt;100</td>
<td>0</td>
</tr>
<tr>
<td>Oelkers et al. (28)</td>
<td>IM, 30</td>
<td>415</td>
<td>100 (41/41)</td>
<td>-</td>
<td>8.3</td>
<td>0</td>
</tr>
<tr>
<td>Kong and Jeffcoate (23)</td>
<td>IV, 30</td>
<td>415</td>
<td>89 (16/18)</td>
<td>-</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Gonzalez-Gonzalez et al. (20)</td>
<td>IV, 30</td>
<td>415</td>
<td>82 (9/11)</td>
<td>100 (46/46)</td>
<td>&gt;100</td>
<td>0.18</td>
</tr>
</tbody>
</table>

* IM = intramuscular; IV = intravenous.
† In six studies (13, 14, 20, 27–29), cases of typical Addison disease (proven by clinical criteria, low urine steroids levels, or high serum adrenocorticotropic hormone levels) were selected for cosyntrpin testing from outpatient clinics. Two studies (23, 30) are retrospective surveys of patients with suspected Addison disease who had cosyntrpin testing and were compared with historical controls. Control groups were historical (23, 28, 30), healthy volunteers (13, 14, 20), persons with nonendocrine illness (14, 27), or persons with suspected adrenal insufficiency with a normal metyrapone test result (29).
‡ Time after injection is when the serum cortisol is drawn in minutes after the 250-μg cosyntrpin injection.
§ Sensitivity is the percentage calculated from raw data (shown in parentheses) indicating the number of persons with positive cosyntrpin test results among true-positive persons. Specificity is the percentage calculated from raw data (shown in parentheses), indicating the number of persons with negative cosyntrpin test results among true-negative persons.
‖ Definitions of positive and negative likelihood ratios are shown in equation A2 in the Appendix (available at www.annals.org).
most of the patients with primary adrenal insufficiency had cortisol values $< 275$ nmol/L (100 µg/l)

- cut-off of 415 nmol/L (150 µg/l)
  
  sensitivity 95 %  specificity 97.5 %

ROC cure: AUC 0.99

- use adjunctive tests: ACTH to confirm diagnosis
### Table 2. Usefulness of the 250-μg Cosyntropin Stimulation Test in Patients Who Are Taking Glucocorticoids or Have Pituitary Disease*

<table>
<thead>
<tr>
<th>Study (Reference)</th>
<th>Cosyntropin Route and Time after Injection</th>
<th>Serum Cortisol or Deoxycortisol Cutoff Level after Stimulation</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Positive Likelihood Ratio**</th>
<th>Negative Likelihood Ratio**</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>IV, 30</td>
<td>min</td>
<td>500</td>
<td>500</td>
<td>% (n/n)</td>
<td></td>
</tr>
<tr>
<td>Kehlet et al. (73)</td>
<td>IV, 30</td>
<td>ITT</td>
<td>90 (9/10)</td>
<td>87 (13/15)</td>
<td>6.9</td>
<td>0.11</td>
</tr>
<tr>
<td>Lindholm et al. (74)</td>
<td>IV, 30</td>
<td>MT</td>
<td>85 (29/34)</td>
<td>96 (54/56)</td>
<td>21.3</td>
<td>0.16</td>
</tr>
<tr>
<td>Cunningham et al. (75)</td>
<td>IM, 60</td>
<td>175</td>
<td>40 (8/20)</td>
<td>100 (15/15)</td>
<td>&gt;100</td>
<td>0.58</td>
</tr>
<tr>
<td>Lindholm and Kehlet (76)</td>
<td>IV, 30</td>
<td>500</td>
<td>73 (19/26)</td>
<td>99 (139/136)</td>
<td>73</td>
<td>0.27</td>
</tr>
<tr>
<td>Stewart et al. (77)</td>
<td>IM, 30</td>
<td>550</td>
<td>90 (9/10)</td>
<td>85 (51/60)</td>
<td>6.0</td>
<td>0.12</td>
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<tr>
<td>Hartzband et al. (78)</td>
<td>IV, peak</td>
<td>500</td>
<td>80 (8/10)</td>
<td>100 (13/13)</td>
<td>&gt;100</td>
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<tr>
<td>Jackson et al. (79)</td>
<td>IV, 30</td>
<td>550</td>
<td>69 (9/13)</td>
<td>100 (11/11)</td>
<td>&gt;100</td>
<td>0.31</td>
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<td>Tordjman et al. (80)</td>
<td>IV, 30</td>
<td>200</td>
<td>50 (8/16)</td>
<td>89 (33/37)</td>
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<td>Kane et al. (81)</td>
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<td>500</td>
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<td>69 (9/13)</td>
<td>3.2</td>
<td>0.00</td>
</tr>
<tr>
<td>Hurel et al. (16)</td>
<td>IV, 30</td>
<td>520</td>
<td>33 (20/60)</td>
<td>95 (101/106)</td>
<td>6.6</td>
<td>0.71</td>
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<tr>
<td>Rasmussen et al. (82)</td>
<td>IV, peak</td>
<td>550</td>
<td>81 (13/16)</td>
<td>91 (10/11)</td>
<td>9.0</td>
<td>0.21</td>
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<tr>
<td>Ammiri et al. (83)</td>
<td>IV, 30</td>
<td>550</td>
<td>47 (8/17)</td>
<td>85 (11/13)</td>
<td>2.6</td>
<td>0.65</td>
</tr>
<tr>
<td>Orme et al. (84)</td>
<td>IM, peak</td>
<td>500</td>
<td>83 (5/6)</td>
<td>60 (6/10)</td>
<td>2.1</td>
<td>0.28</td>
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<tr>
<td>Mukherjee et al. (85)</td>
<td>IM, 30</td>
<td>580</td>
<td>73 (5/7)</td>
<td>91 (10/11)</td>
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<td>Weinreb et al. (19)</td>
<td>IV, peak</td>
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<td>100 (20/20)</td>
<td>&gt;100</td>
<td>0.10</td>
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<tr>
<td>Mayenknacht et al. (18)</td>
<td>IV, 30</td>
<td>200</td>
<td>65 (15/23)</td>
<td>95 (20/21)</td>
<td>13.0</td>
<td>0.37</td>
</tr>
<tr>
<td>Bangar and Clayton (86)</td>
<td>IV, 30</td>
<td>550</td>
<td>85 (17/20)</td>
<td>96 (47/49)</td>
<td>21.2</td>
<td>0.16</td>
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<tr>
<td>Talwar et al. (87)</td>
<td>IV, peak</td>
<td>550</td>
<td>54 (7/13)</td>
<td>100 (11/11)</td>
<td>&gt;100</td>
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<tr>
<td>Abdu et al. (31)</td>
<td>IV, 30</td>
<td>500</td>
<td>100 (12/12)</td>
<td>90 (27/30)</td>
<td>10.0</td>
<td>0.00</td>
</tr>
<tr>
<td>Suliman et al. (88)</td>
<td>IV, 30</td>
<td>200</td>
<td>67 (10/15)</td>
<td>100 (36/36)</td>
<td>&lt;100</td>
<td>0.33</td>
</tr>
</tbody>
</table>

* IM = intramuscular; ITT = insulin tolerance test; IV = intravenous; MT = overnight metyrapone test.
† All studies are prospective except two retrospective reviews (16, 86). In five studies, most of the patients with suspected adrenal insufficiency had excessive glucocorticoid exposure (75, 78, 81, 87, 88). Otherwise, patients with suspected adrenal insufficiency had known or suspected hypothalamic or pituitary disease. Two studies included consecutive patients (76, 83).
‡ Time after injection is when serum cortisol is drawn after the 250-μg cosyntropin injection. Peak denotes the time (usually 60 minutes) at which the serum cortisol level is maximal.
§ All MT values are for deoxycortisol. In one study (75), the MT cutoff level for deoxycortisol is 175 nmol/L, and in three studies (18, 80, 88), it is 200 nmol/L. In one study (80), if a postcosyntropin cortisol cutoff level of 500 nmol/L is applied, the sensitivity is only 6% (1/16); from the receiver-operating characteristic curve of Tordjman and colleagues (80), we have selected a cutoff level of 550 nmol/L, which yields a sensitivity of 50%.
¶ Sensitivity is the percentage calculated from raw data (shown in parentheses) indicating the number of persons with positive cosyntropin test results among true-positive persons (as defined by a metyrapone or insulin tolerance test). Specificity is the percentage calculated from raw data (shown in parentheses), indicating the number of persons with negative cosyntropin test results among true-negative persons.
** Definitions of positive and negative likelihood ratios are shown in equation A2 in the Appendix (available at www.annals.org).

www.annals.org
• a higher cortisol cutoff 500 (180) to 600 (220)nmol/l (µg/l)) should be applied?

• when specificity is set at 95 % the ROC curve yields a sensitivity of 57 % (CI 44 % - 71 %)

• positive likelihood ratio = 11.5 (CI 8.7 – 14.2)

• negative likelihood ratio = 0.45 (CI 0.30 – 0.60)
Thus with specificity of 95% a positive test (fail the test) substantially increases the likelihood for secondary adrenal failure.

Result influenced by pretest probability of disease:
- patients on moderate and high dose G.C. for ≥ 3 months (50%)
- in patients with macroadenoma of the pituitary transsphenoidal surgery radiotherapy ~30%
- after treatment of Cushing’s disease ~60%
• a negative test ("pass" test) only modestly decreases the likelihood for secondary adrenal insufficiency
• if pretest probability low or recent onset failure → consider additional evaluation with test with better sensitivity (ITT)
• **Low Dose S.T.**
• recent reviews compare both tests
• ROC curves comparable
• requires IV administration and timed blood sampling for peak cortisol response
Figure 1. Summary receiver-operating characteristic (SROC) curves for high-dose (250-μg) and low-dose (1-μg) cosynotropin tests in secondary adrenal insufficiency.

The SROC curve for the high-dose cosynotropin test was derived from SROC analysis of 20 independent studies (Table 2), where each point (white circles) represents an individual study. The SROC curve for the low-dose cosynotropin test was derived from 9 independent studies (Table 4), where each point (white squares) represents an individual study.
Low/High dose ACTH stimulation test - EBM


<table>
<thead>
<tr>
<th></th>
<th>Specificity</th>
<th>Sensitivity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Primary A.I.</td>
</tr>
<tr>
<td>250 µg</td>
<td>95 %</td>
<td>97 %</td>
</tr>
<tr>
<td>1 µg</td>
<td>95 %</td>
<td></td>
</tr>
</tbody>
</table>
Problems SST:

- limited sensitivity in secondary adrenal failure
  primary adrenal insufficiency: specificity 95 % - sensitivity of 97.5 %
  secondary adrenal insufficiency: specificity 95 % - sensitivity of 57 %
- do not use in recent onset adrenal insufficiency
- cortisol cutoff (500 to 600 nmol/L 180-220 µg/l)
  600 nmol/L ↑ sensitivity
  ↓ specificity
- additional evaluation if test passed, with mild or recent onset adrenal insufficiency
Proposal for suspected chronic adrenal insufficiency

Suspected chronic adrenal insufficiency

250-μg cosyntropin stimulation test

+ →

8 a.m. plasma ACTH

Increased ACTH →

Primary adrenal insufficiency

Decreased or normal ACTH →

Secondary adrenal insufficiency

Specific diagnostic tests to determine cause

Mild primary or secondary adrenal insufficiency

Severe prolonged chronic adrenal insufficiency excluded

- →

Severe prolonged chronic adrenal insufficiency excluded

Suspicion of mild or recent-onset chronic renal insufficiency

+ →

Test for mild primary or secondary adrenal insufficiency (ACTH level, insulin tolerance test, metyrapone test)

- →

Longitudinal clinical follow-up
Index case 2

How will you treat your patient?

- HC 20 – 10 mg
- HC 10 – 5 mg
- HC 10 – 5 – 5 mg
- HC 10 – 10 mg
- Other?
Replacement therapy of adrenal failure

• daily production of cortisol = 10 mg/day

• make replacement as physiological as possible

• how to monitor treatment?
Normal cortisol physiology

- cortisol - 90% plasma protein bound (CBG)
  - “free” cortisol: 1 nmol/L (lowest) (0.04 µg/l)
    100 nmol/L (highest) (36µg/l)

- cortisone = inactive metabolite of cortisol
- $11\beta$-HSD$_2$ ($11\beta$-hydroxysteroid dehydrogenase type 2) mainly kidney
  
  cortisol $\rightarrow$ cortisone

- $11\beta$-HSD$_1$ ($11\beta$-hydroxysteroid dehydrogenase type 1) adipose tissue, liver, brain, bone
  
  cortisone $\rightarrow$ cortisol ("amplifies cortisol effect in target tissues")

  obesity: $\uparrow$ $11\beta$-HSD$_1$ in adipose tissue
  liver: $\uparrow$ $11\beta$-HSD$_1$ in metabolic syndrome ($\uparrow$ neoglucogenesis)

  $11\beta$-HSD$_1$ K-O mice: resistant to cognitive impairment

  $\uparrow$ age: $\uparrow$ $11\beta$-HSD$_1$ in bone: more susceptible to effects on bone
tissue-specific roles of circulating cortisol and cortisone in mediating normal physiological GC effects
Diurnal and ultradian rhythmicity of GC secretion

- **diurnal rhythm:** peak before wakening
  nadir at ± midnight

- **pulsatile ultradian rhythm:** varying pulses throughout the day
• pulsatility: a way to achieve tissue specificity?
  continuous prolonged vs. intermittent short exposure to GC may have different effects on steroid responsive hepatic enzymes f.i. Tyrosineaminotransferase

• pulsatility: effect on GR (GC receptor expression)
  prolonged exposure: ↓ GR
Normal pregnancy:

• $11\beta$-HSD$_2$ highly expressed in the placenta to term
  “barrier” to the passage of maternal GC
  only GC not inactivated: dexamethasone

• avoid dexamethasone for the purpose of the “mother” in pregnancy
Replacement therapy

- cortisol = hydrocortisone = most physiological drug of choice = natural substrate for $11\beta$-HSD$_2$
- normal production = 10 mg/day
- mimick diurnal rhythm:
  - last dose in the afternoon (5 p.m.) rather than evening
  - we cannot mimick ultradian pulsatility (“daily hassles”)
- late afternoon dose: low receptor occupancy overnight
- twice daily doses: supraphysiological cortisol concentrations post dose (“day curves”)
Assessment of GC replacement therapy

• UFC (urinary free cortisol) is influenced by the distribution of the dose
  ↑ UFC twice daily compared to three times daily (without change in total dose)

• no “gold standard” for assessing GC replacement dose daily curves: risk for over treatment
  ACTH: always high in the morning, suppresses after HC

• clinical assessment (Arit et al, Clinical Endocrinology, 2006)

Structured assessment of signs and symptoms
Clinical assessment of the glucocorticoid replacement therapy

<table>
<thead>
<tr>
<th>Quality of glucocorticoid replacement score signs and symptoms</th>
<th>Suggestive of under-replacement</th>
<th>Suggestive of over-replacement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td>Insomnia</td>
<td></td>
</tr>
<tr>
<td>Loss of energy</td>
<td>Recurrent infections</td>
<td></td>
</tr>
<tr>
<td>Reduced strength</td>
<td>Lumbar back pain</td>
<td></td>
</tr>
<tr>
<td>Muscle pain</td>
<td>Increased appetite</td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>Truncal obesity</td>
<td></td>
</tr>
<tr>
<td>Weight loss (&gt; 3 kg)</td>
<td>Weight gain (&gt; 3 kg)</td>
<td></td>
</tr>
<tr>
<td>Hyperpigmentation</td>
<td>Peripheral oedema</td>
<td></td>
</tr>
<tr>
<td>Fasting glucose &lt; 3.3 mmol/l, hypoglycaemic symptoms</td>
<td>Fasting glucose &gt; 5.6 mmol/l</td>
<td></td>
</tr>
<tr>
<td>Decreased serum sodium or increased serum potassium</td>
<td>Increased serum sodium or</td>
<td></td>
</tr>
<tr>
<td>Blood pressure (sitting):</td>
<td>decreased serum potassium</td>
<td></td>
</tr>
<tr>
<td>Systolic blood pressure &lt; 100 mmHg, diastolic blood pressure &lt; 60 mmHg</td>
<td>Systolic blood pressure &gt; 140 mmHg, diastolic blood pressure &gt; 90 mmHg</td>
<td></td>
</tr>
</tbody>
</table>
**Fig. 1** Algorithm for treatment of the glucocorticoid-deficient patient. Patients should be reassessed at 6–8 week intervals while their treatment is optimized.

Glucocorticoid-deficient patient:
start hydrocortisone $10 + 5$ mg daily

Review need for other hormone replacement therapy

Primary hypoadrenalism: fludrocortisone

Secondary hypoadrenalism: assess other axes and replace as indicated

Is the patient feeling well? → YES

NO

Explore other causes (based on history and examination)
Consider TDS split e.g. hydrocortisone $10 + 2.5 + 2.5$ mg daily

Is the patient feeling well? → YES

NO

Consider increased dose of hydrocortisone e.g. $10 + 5 + 5$ mg daily

Is the patient feeling well? → YES

NO

Consider ‘day curve’ assessment of serum cortisol