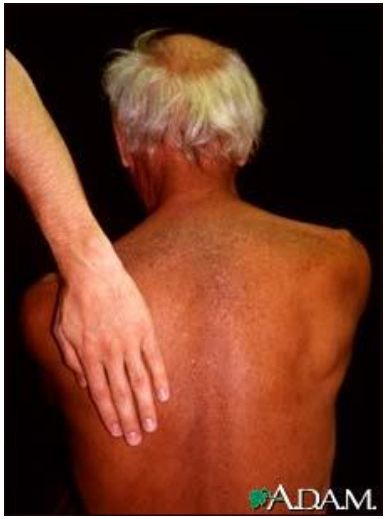
Baring the facts to uncover the naked truth: the stubborn puzzle



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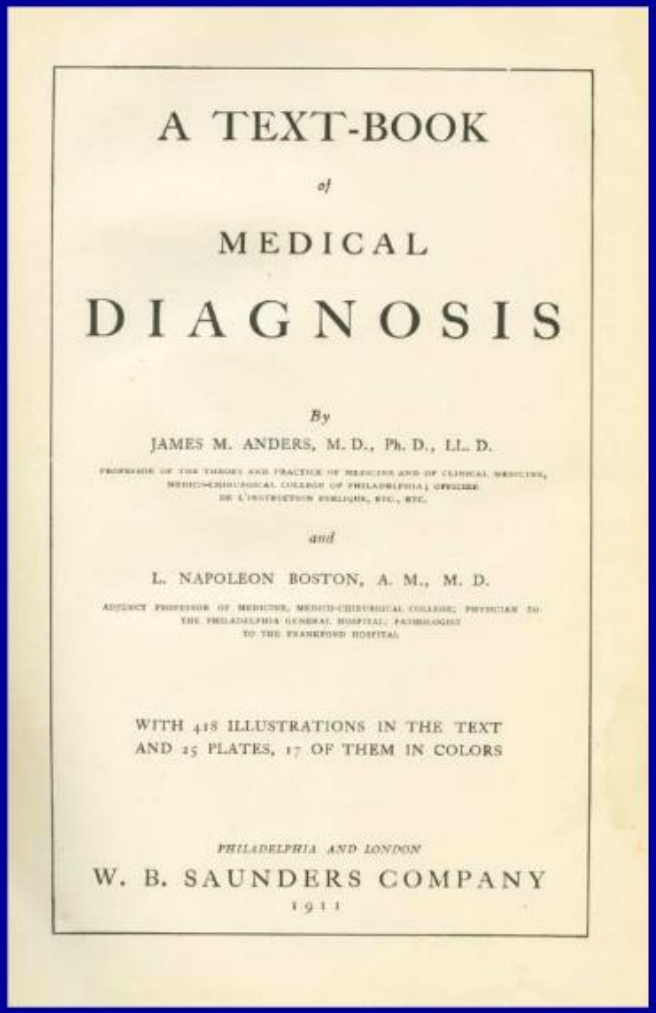
ESIM Clinico-pathological conference

06.02.2017



A TEXT-BOOK

of

MEDICAL

DIAGNOSIS

By

JAMES M. ANDERS, M. D., Ph. D., LL. D.

and

L. NAPOLEON BOSTON, A. M., M. D.

WITH 418 ILLUSTRATIONS IN THE TEXT
AND 25 PLATES, 17 OF THEM IN COLORS

PHILADELPHIA AND LONDON

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1911

"In endeavoring to trace the clinical features of a given disease to their source, use is made of the physical signs and modern laboratory methods of investigating disease, as well as of all data relating to the anamnesis. The marks of disease are often decidedly obscure, and for their detection the diagnostician must call into requisition the various instruments of precision contributed by science, e.g., the microscope, stethoscope, hemomanometer, and many others, as well as the helps furnished from the laboratory expert."

Anders, JM and Boston, LN. *A Textbook of Medical Diagnosis.* Saunders, 1911. p. 17.

www.slidegur.com/doc/1864662/clinical-pathology-conference

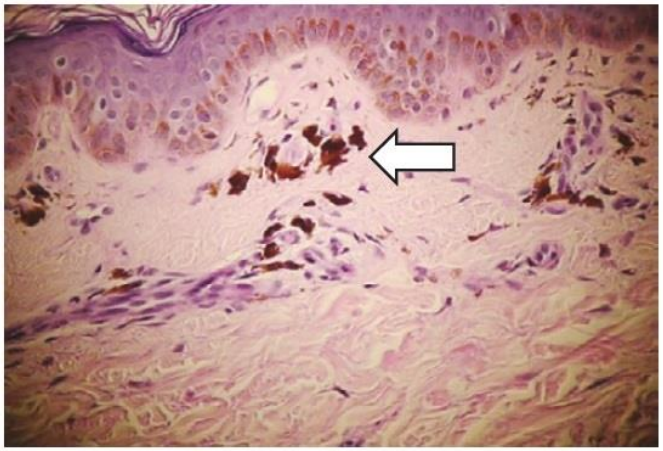
“Gut feeling”

- [..] an **“inexplicable gut feeling is an important diagnostic sign and a very good reason for seeking the opinion of someone with more paediatric expertise or performing additional testing”**
- Gut feeling should make three things mandatory:
  - conducting a full and careful examination;
  - seeking advice from a more experienced clinician;
  - providing the parent with safety netting advice.
- Clinicians should not ignore gut feeling and use it in decision making

http://www.bmj.com/press-releases/2012/09/25/doctors%E2%80%99-%E2%80%9Cgut-feeling%E2%80%9D-should-not-be-ignored

Ms. G.S., 50 y.o. woman

- 1st visit (Mar-2011) to general practitioner (GP) for mild respiratory viral infection
- GP asks the patient to undress – noticed **hyperpigmentation** of the back
- Referred for hip skin **biopsy** – no iron deposits

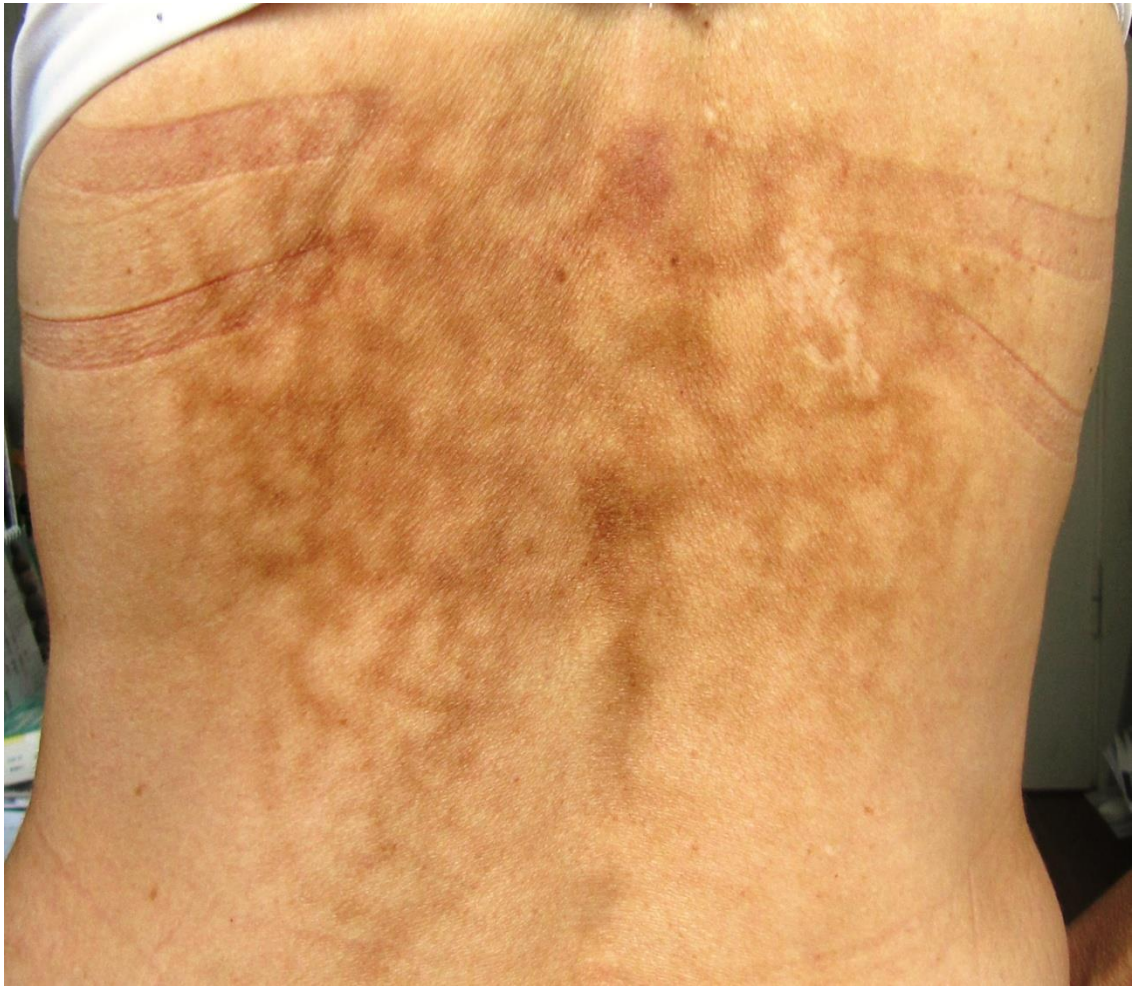


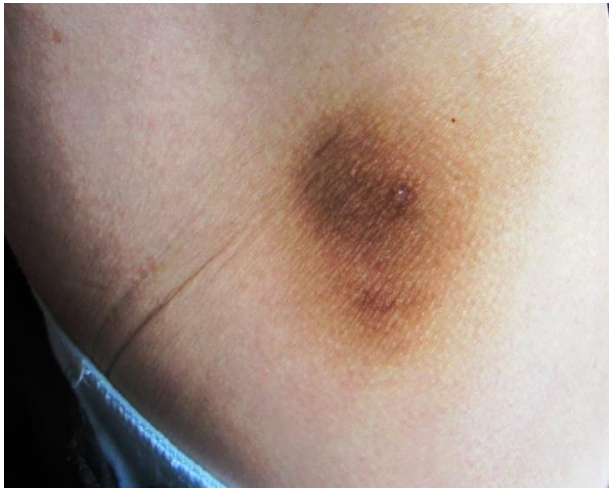
DOI: http://dx.doi.org/10.15605/jafes.030.02.12

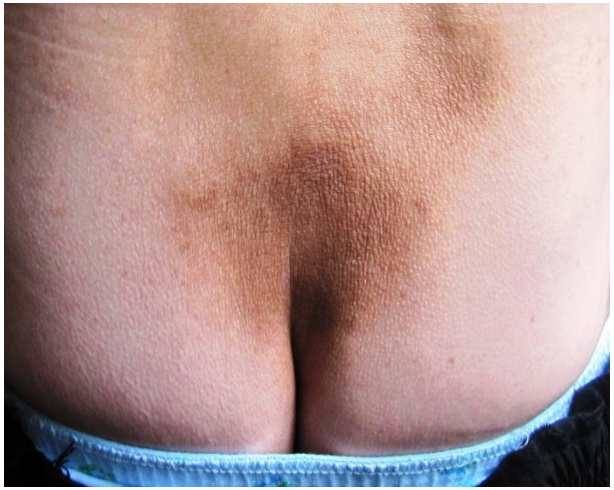
Ms. G.S., 50 y.o. woman (W 44 kg, H 151 cm, BMI 19.3 kg/m^2)

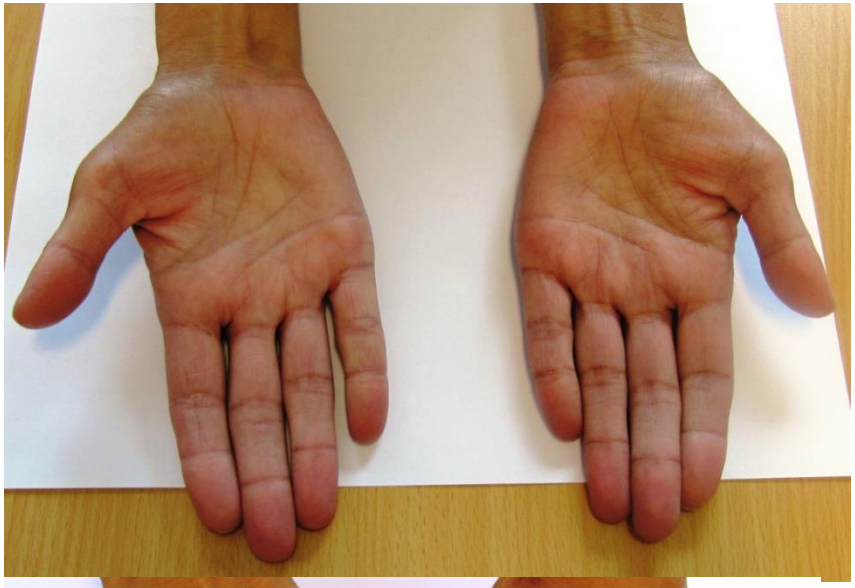
- **Mild diarrhea** (May-2011) – severe fatigue
- GP remembers adrenals –> **endocrinologist**

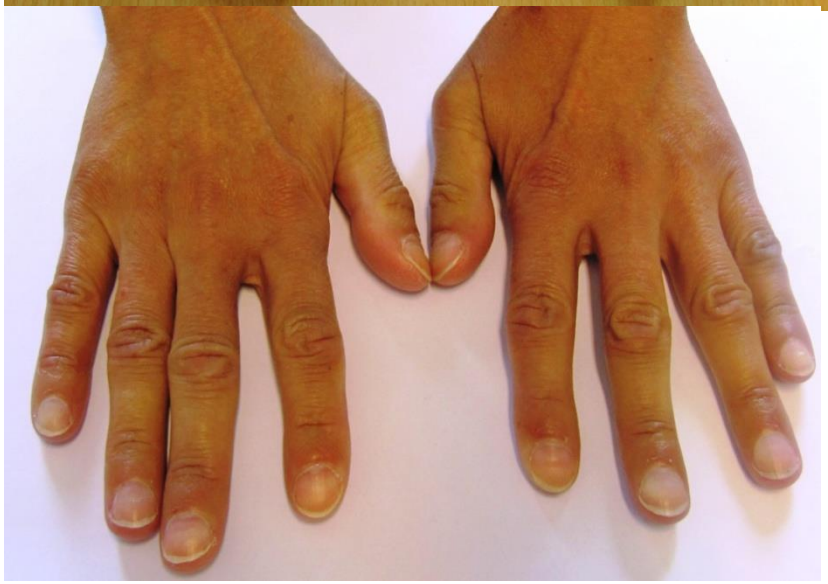
Ms. G.S., 50 y.o. woman



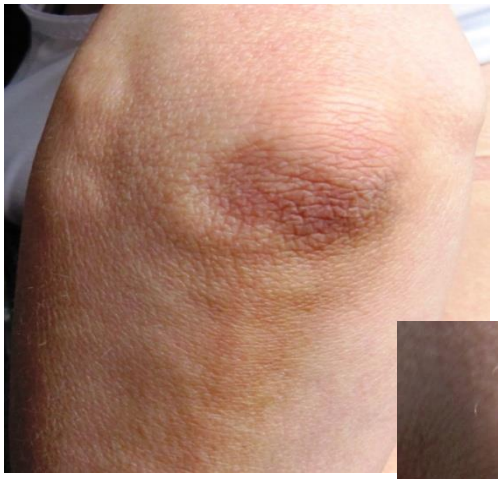


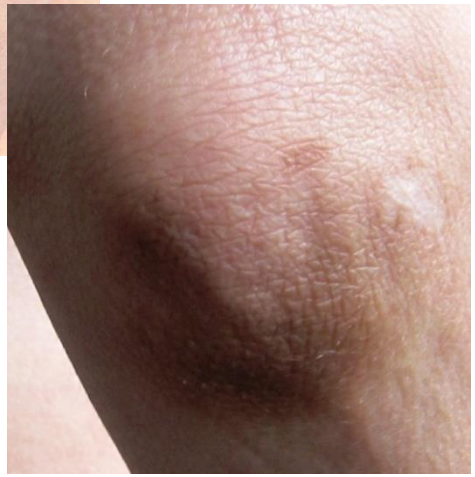






Ms. G.S.,
50 y.o. woman
(W 44 kg, H 151 cm, BMI 19.3 kg/m^2)





First visit (Jun 2011)

- **Darker face and palms**, nationality – European background
- No significant family history
- Single, no children, menopause since 2008
- Postal operator (indoors), no smoker, no EtOH
- **Medications** – risedronate, OTC Ca
- First examination – no other pathology
- HR 74x', **TA 85/60** mmHg, **no orthostatic** changes

First lab tests (Jun-2011)

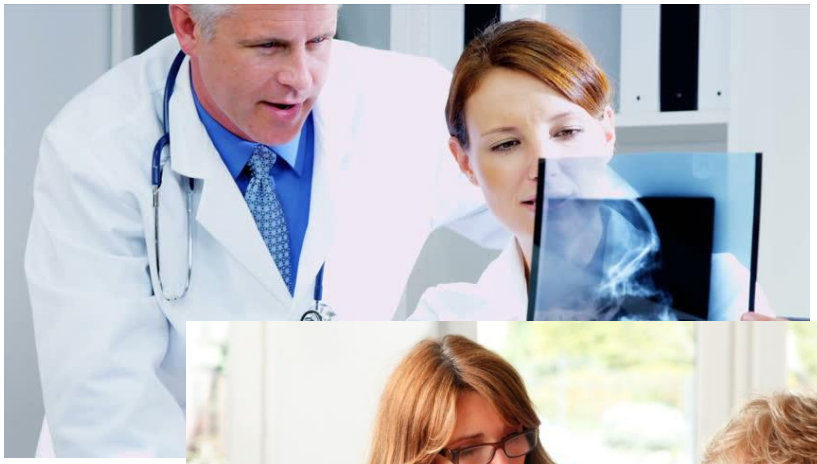
- **ACTH** – **218.1 pg/ml** (7.2-63.3)
- **Cortisol** (8AM) – **6.1 µg/dl** (3.7-19.4)
- **24h urinary cortisol** – **22.5 µg/24h** (4.3-176) (volume – 1.05 l)

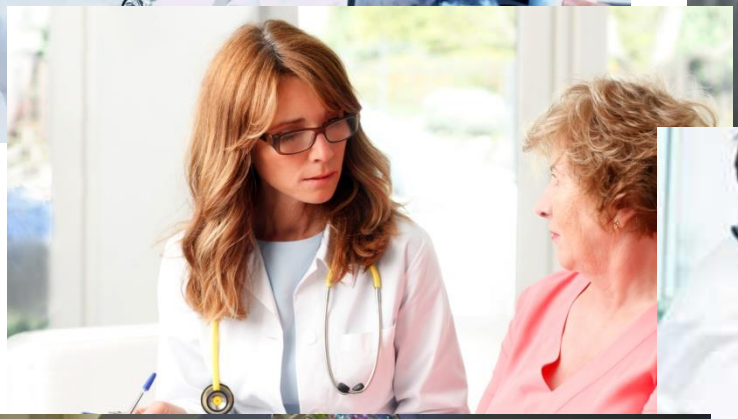
- **Diagnosis: Primary adrenal insufficiency**

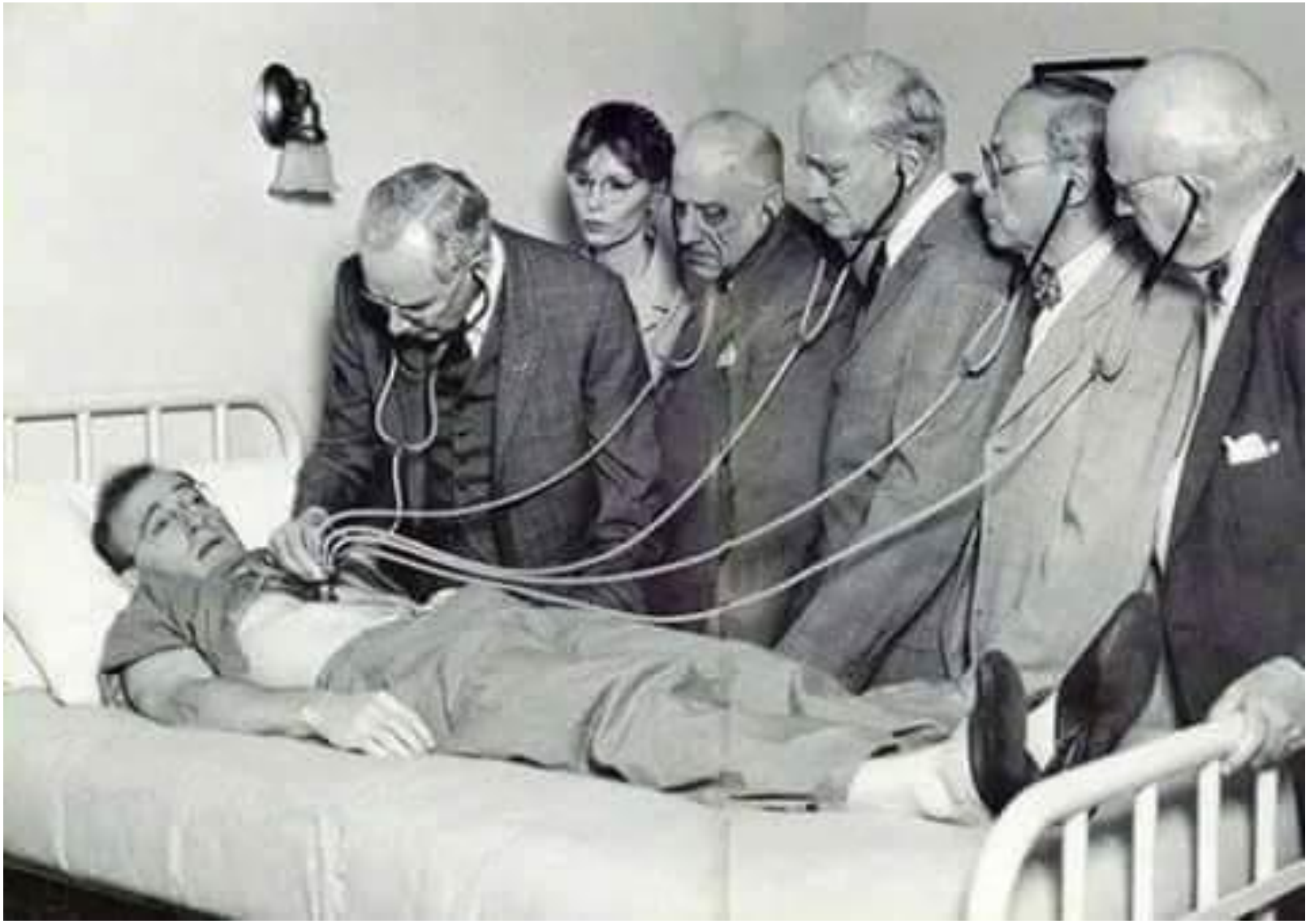
Confirmation of diagnosis

ACTH stimulation tests:

- No need for insulin hypoglycaemia test
- No possibility for tetracosactide/cosyntropin (*Synacthen* test)







Additional history

- **Frequent recurrent respiratory infections** and paranasal sinusitis (her mother's words: *"ты гнилая"* = "*you are foul*")
- **Failure to thrive**, small stature, underweight
- **Abdominal bloating**, **diarrhea exacerbated by fatty food**
- **Tolerates milk**

History (2002-2011)

- **FGS (2002, 2003, 2011)**
  - atrophic gastritis
  - duodenal reactive lymphoid hyperplasia
  - low mucosal plasma cell count
  - lymphoma excluded (immunochemical staining)
- **Common variable immunodeficiency (2003)**:
  - **IgA↓↓**, IgG, IgM, C3, CD4 ↓,
  - CD3, CD8, CD19 ↑
- **Colonoscopy (2011**) – similar findings to FGS

History (2008-2011)

- **Osteoporosis (2008):**

  T-score -2.8SD in lumbar vertebrae

- **Hypocalcaemia (2008, 2011)**

	Apr-2008	Jun-2011
Ca^{2+} (2.1- 2.55 mM/l)	**1.17**	**1.6**
PTH (15-68 pg/ml)	**95**	**135.8**

- **ECG** – no pathology (QTc 437ms)
- **ANA, ENA, dsDNA, SAA – neg.**

Lab tests (Jun-2011)

- **Full blood count: Leu 16.000**, **Eo 0.887** (<0.4), **Hb 9.89** g/dl, slight macrocytic anemia
- **Urinalysis** – no pathology
- **Biochemistry** (no changes in other electrolytes):
  - **Ca 1.6** mM/l (2.1-2.55), **PTH 135.8** pg/ml (15-68)
  - No changes in lipids, liver enzymes, creatinine
- **24 h urinary calcium** – **4.2** mg/24h (100-300)

Lab tests (Jun-2011)

- **B_{12} vitamin 77.03** pg/ml (191-663)
- **25(OH) D_3 vitamin 4** ng/ml (20-55)
- **Glu** 3.41 mM/l, **HbA1c** 4.6%, **C-peptide** 0.694 ng/ml
- **IgA 0.03** (0.7-4), **IgM 0.1** (0.4-2.3), **IgG 1.78** (7-16) g/l

Hormones and antibodies (ab)

- **TSH** – 2.64 µIU/ml (2.34-4.94)
- **FT4** – 1.05 ng/dl (0.7-1.48) - **euthyroid**
- **LH** – 61.57 µIU/ml (7.7-58.5), **FSH** – 92 µIU/ml (25.8-134.8), **menopause** – 3 years
- **Anti-thyroid peroxidase** (TPO) ab – **negative**
- **Anti-adrenal** ab – **negative**
- **Anti-ovarian** ab – **positive**
- **Transglutaminase IgA/IgG** - **negative**

Radiology

- **Abdominal, thyroid USG** – no pathology
- **Chest X-ray** – bronchiectasis, bilateral hilar calcification
- **Head CT** – no pathology
- **Abdominal CT:**
  - small adrenals (left< right)
  - no calcification, no tumors
  - mesenterial lymphadenopathy

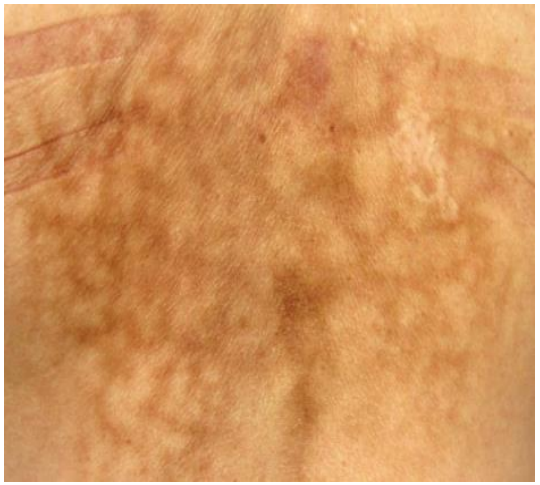
Diagnosis

- **Primary adrenal insufficiency**
- **Hypocalcemia with secondary hyper-PTH** (vitamin D deficiency, intestinal malabsorption)
- **Secondary osteoporosis**
- **Common variable immunodeficiency (CVID)**

- **Autoimmune polyglandular syndrome?**

Treatment

- **Hydrocortisone** – 10 mg (8AM) + 5 mg (3PM)
- **Calcitriol** ($1,25(OH)_2$ D_3 vit.) – 0.5 µg x2 1 week followed by **cholecalciferol** 2000IU=3 drops
- **Calcium** (citrate) – 1000 mg/day
- **Risedronate** – 35 mg/week
- Diet, activities
- Main worry – "**but my skin?"**



Stubborn puzzle?

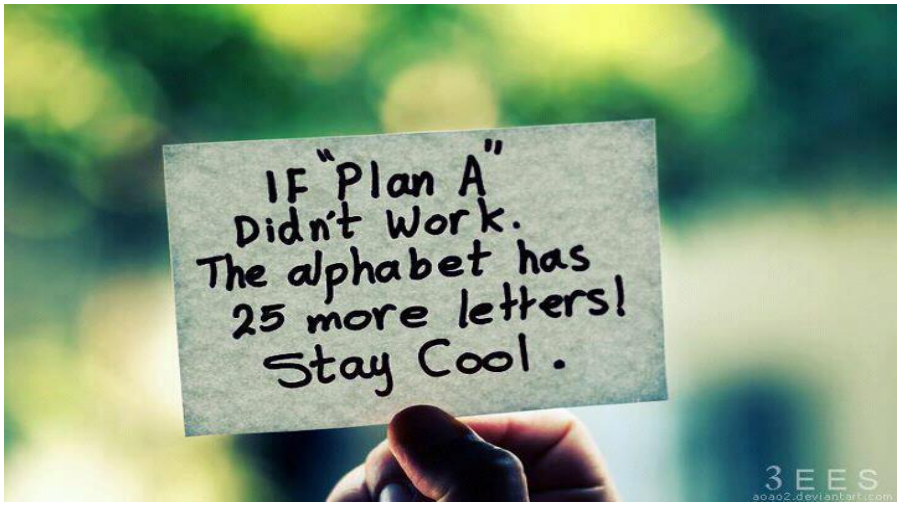
- CVID only?
- CVID + adrenal insufficiency?
- CVID + APS-4? (APS-2?)
- CVID + adrenal insufficiency + celiac disease?

- ACTH/cortisol/Ca/PTH/D vit level monitoring
- To do: Antiparietal cell ab? Endomysial ab?

Autoimmune Polyendocrine Syndromes

- **APS-1** – hypoAdren + hypoPTH +candidiasis
- **APS-2** – hypoAdren + chrThyr + T1DM + hypoGonad
- **APS-3** – chrThyr + 2 other <u>except</u> hypoAdr/T1DM
- **APS-4** – 2 or more other organ-specific AID

APS-3/4 =APS-2



APS and CVID

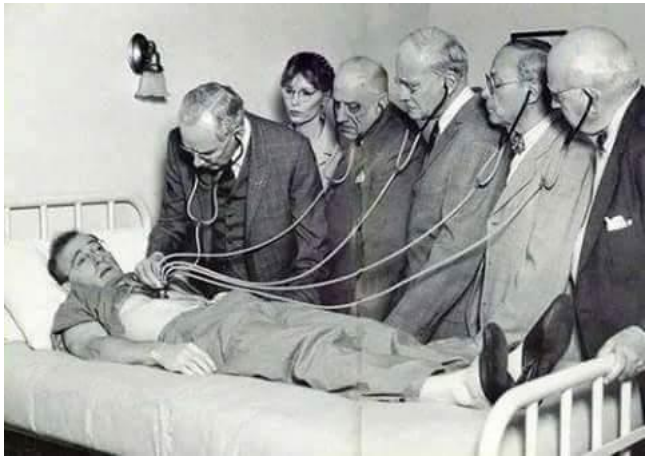
- Coexistence of APS-3 and CVID may be due to autoimmunity and the association of both conditions with human leukocyte antigen (HLA).
- **Clinical tip** - antibodies return negative due to CVID!

Literature list (for further reading)

- www.eje-online.org/content/161/1/11.full.pdf (review on APS)
- http://www.nature.com/nrendo/journal/v6/n5/full/nrendo.2010.40.html (review on APS)
- http://emedicine.medscape.com/article/124398-overview (coexistance of APS and CVID)
- http://www.worldallergy.org/professional/allergic_diseases_center/suspected_immune_deficiency/ (review on immunodeficiencies)
- http://www.bloodjournal.org/content/99/8/2694 (autoimmunity in human primary immunodeficiency syndromes)

Take home messages

- Listen to your patients
- *A capite ad calcem* inivestigation
- Trust your “gut feelings”
- “Take your hat, but don’t take your head off in front of all consultants”
- Use the internist broader view to problems



Thank you!