The Pituitary Gland in Clinical Practice

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LUZERN

European Federation of Internal Medicine

1. Feedback control of hormone secretion

2. Pituitary function in critical illness

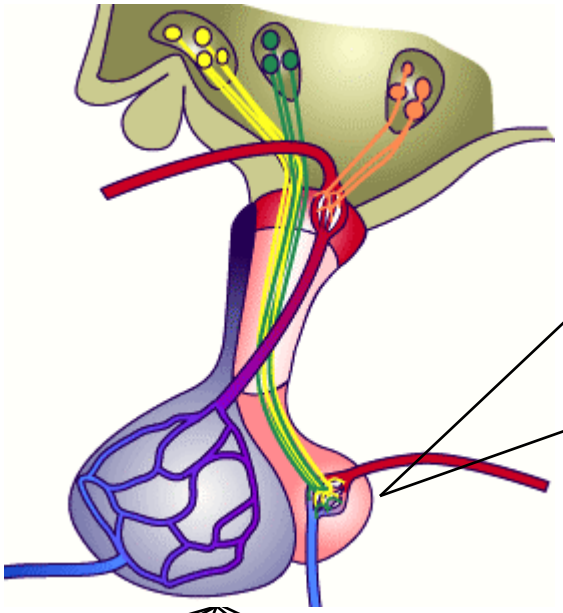
3. Diagnosis and treatment of (pan)hypopituitarism

4. Cushing's disease

5. Acromegaly

6. Prolactinoma

7.Disorders of ADH secretion



Oxytocin

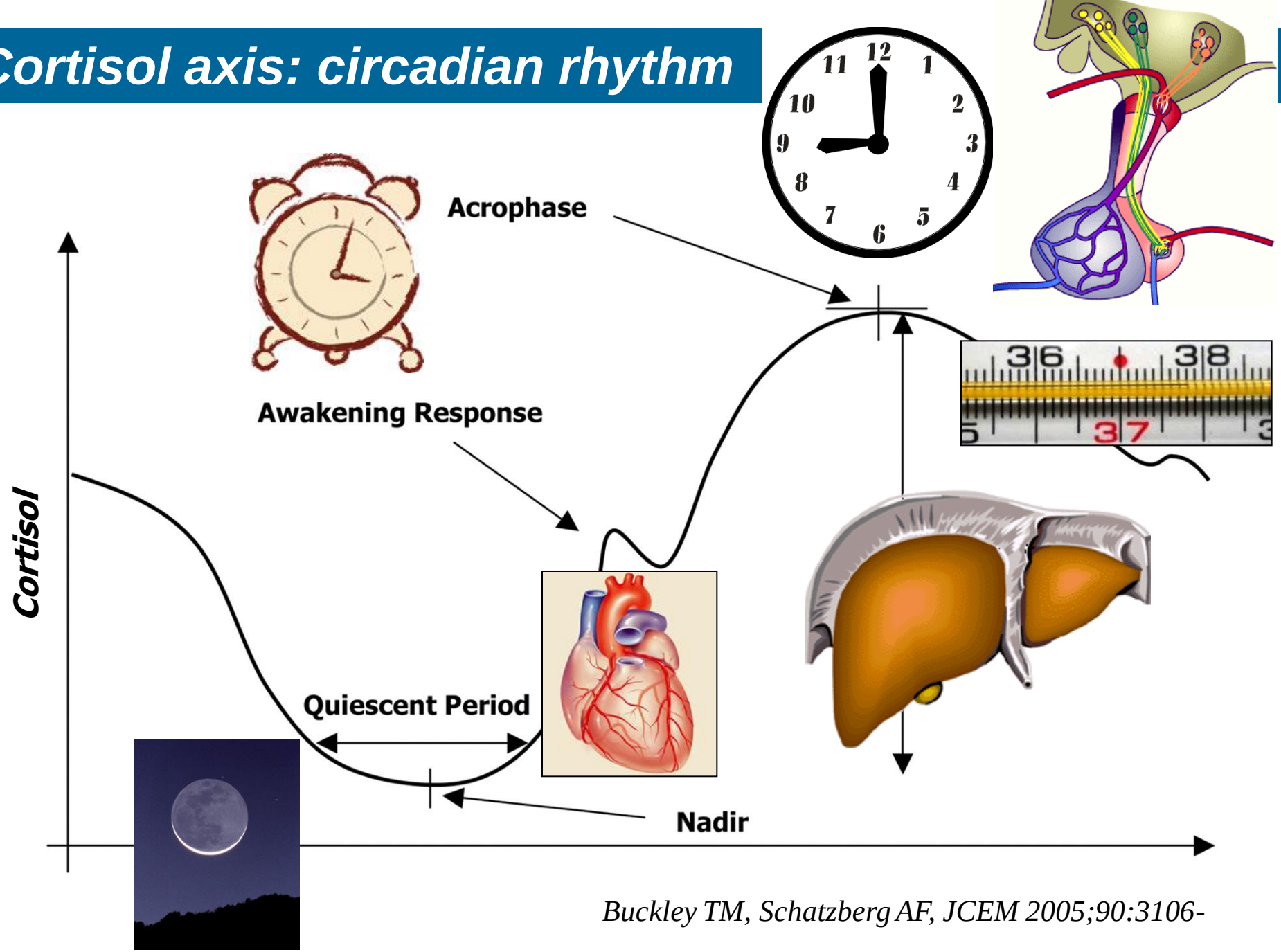
ADH

Na+/Osmol

ACTH TSH LH/FSH HGH Prolactin

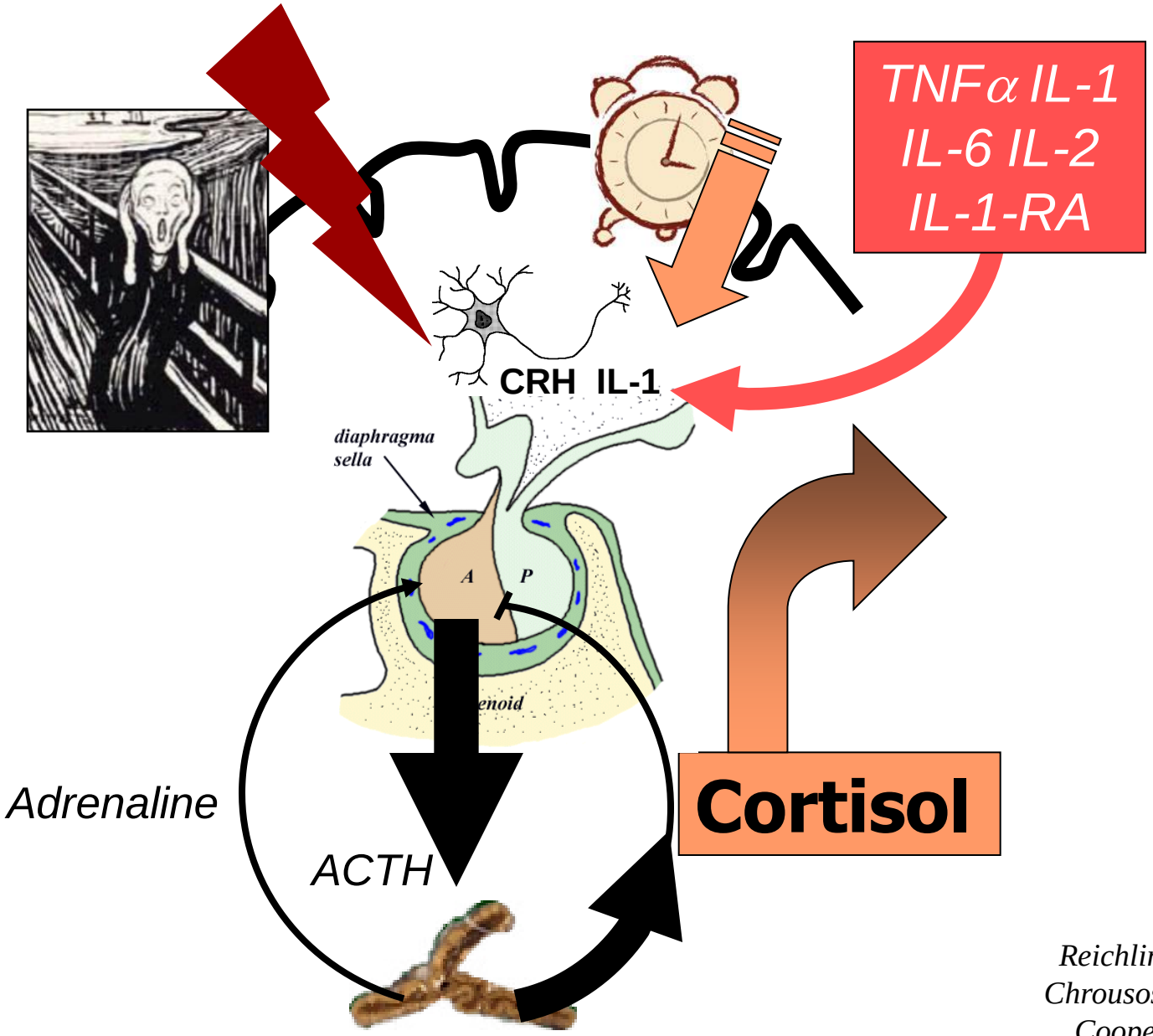
Cortisol *fT4* *Testosterone* *IGF-1*

Cortisol axis: circadian rhythm



Buckley TM, Schatzberg AF, JCEM 2005;90:3106-

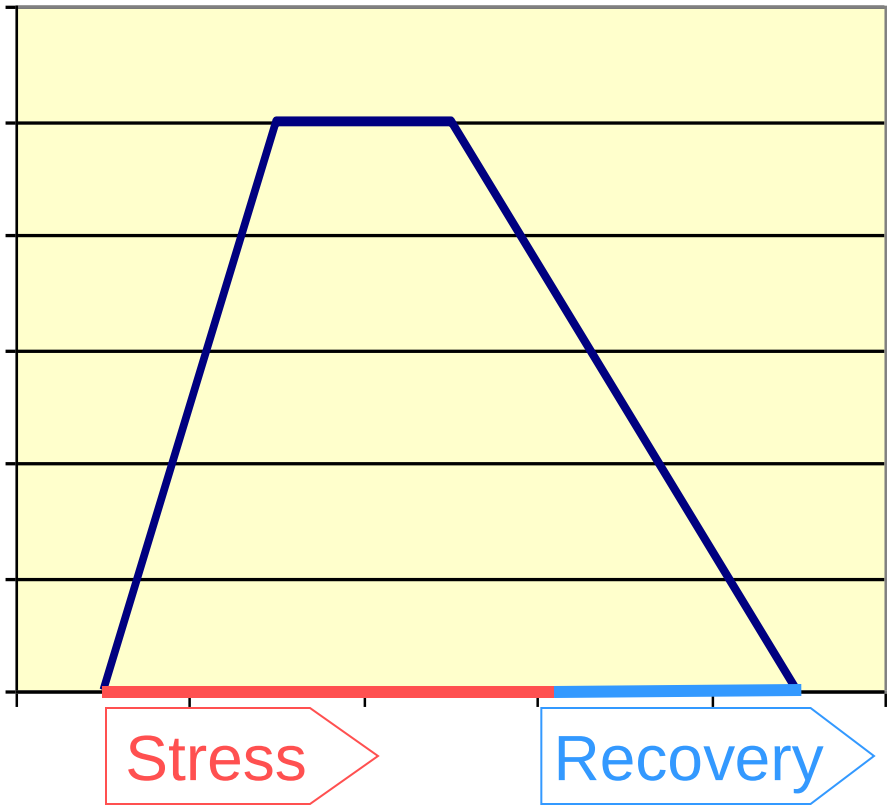
Cortisol axis

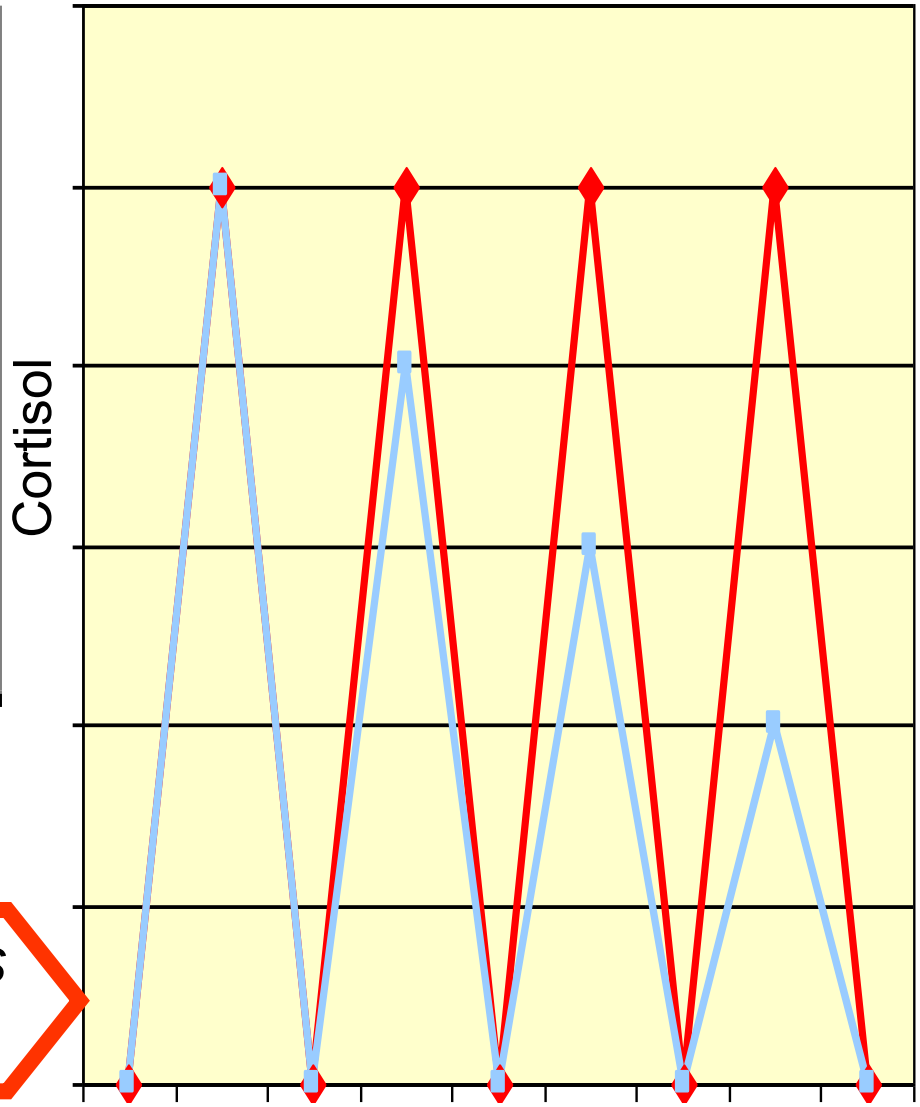


Reichlin, NEJM 1993;
Chrousos, NEJM 1995;
Cooper, NEJM 2003.

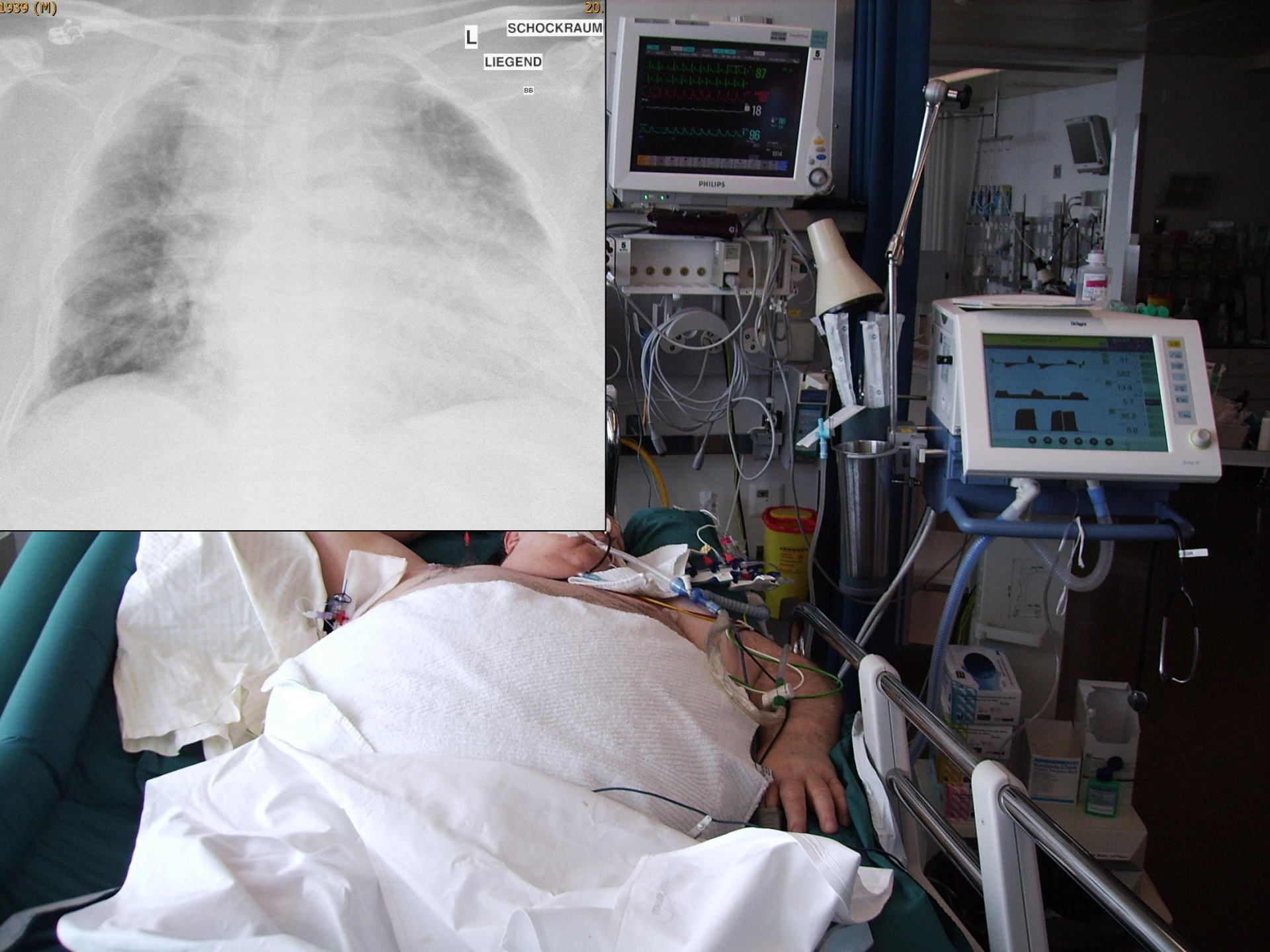
Protective and damaging effects of stress mediators

McEwen B, NEJM 1998;338;171-9



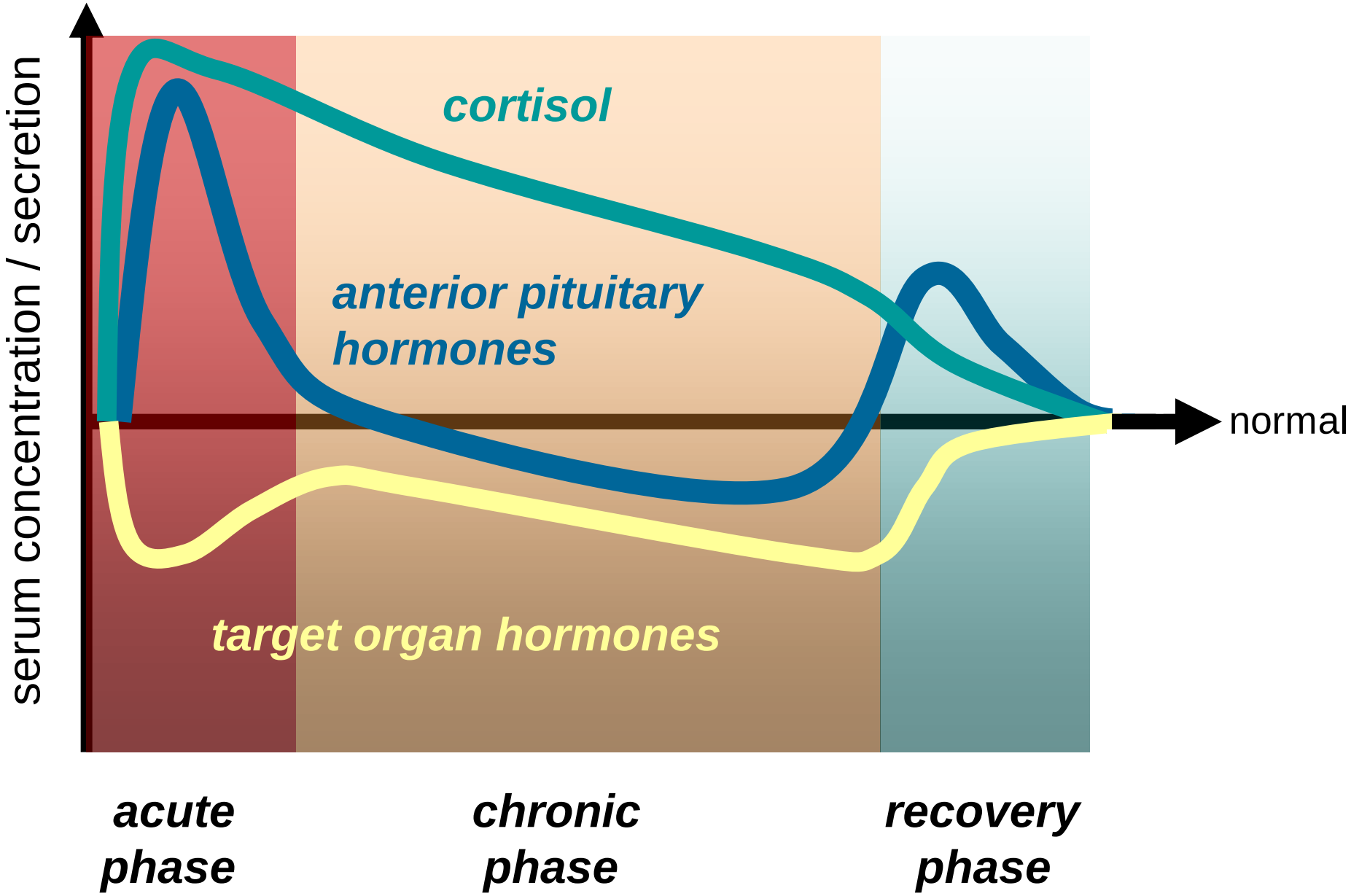


Allostatic load: *repeated hits and lack of adaptation*

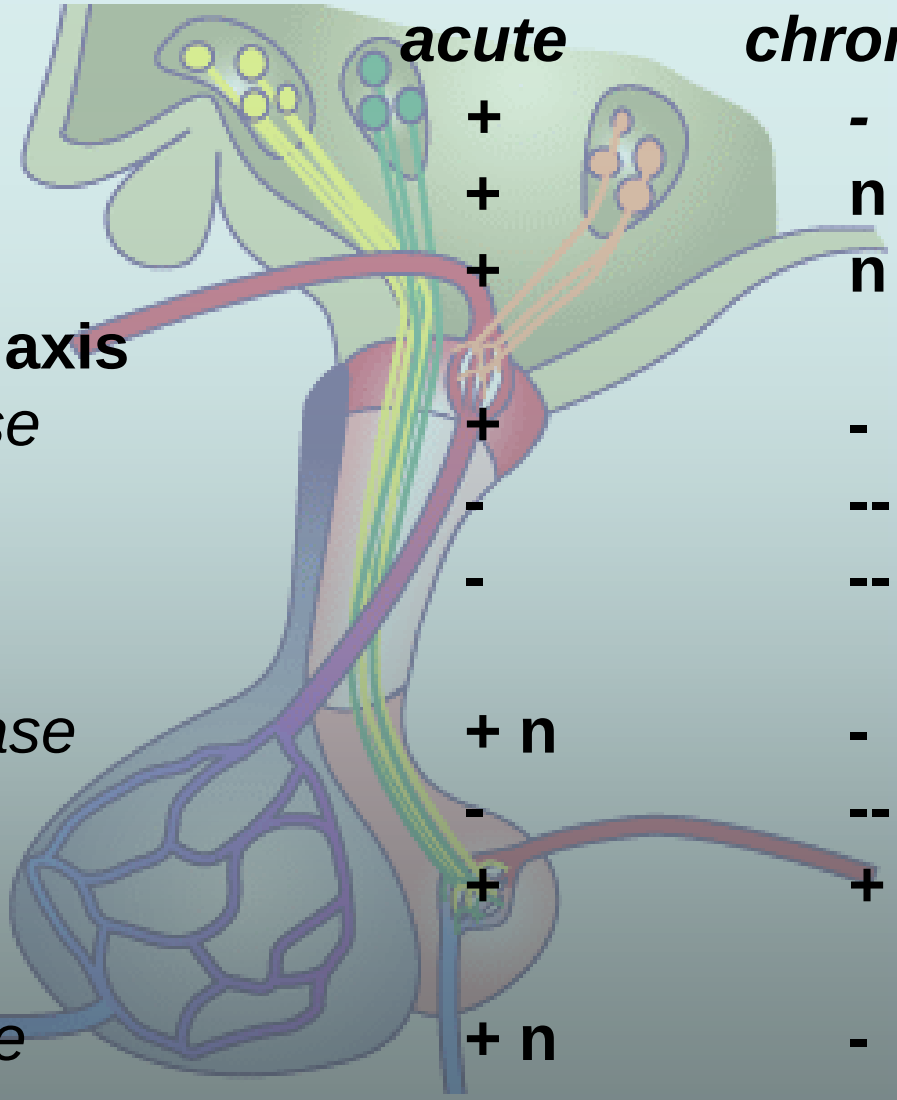

1939 (M)
20.
L
SCHOCKRAUM
LIEGEND
BB
PHILIPS

Pituitary dependent changes during critical illness

Van den Berghe, JCEM 1998;83:1827-



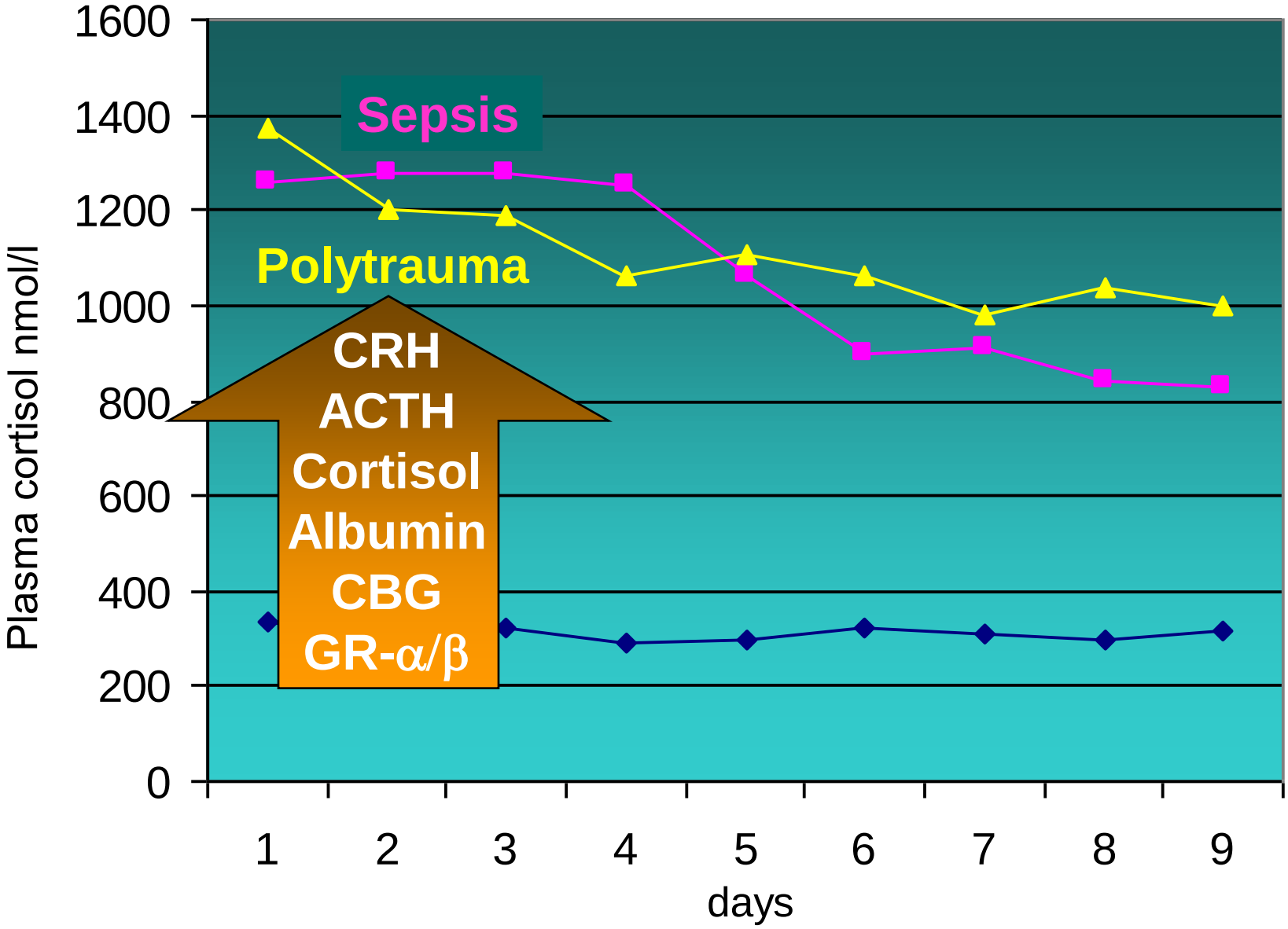
Acute and chronic neuroendocrine changes

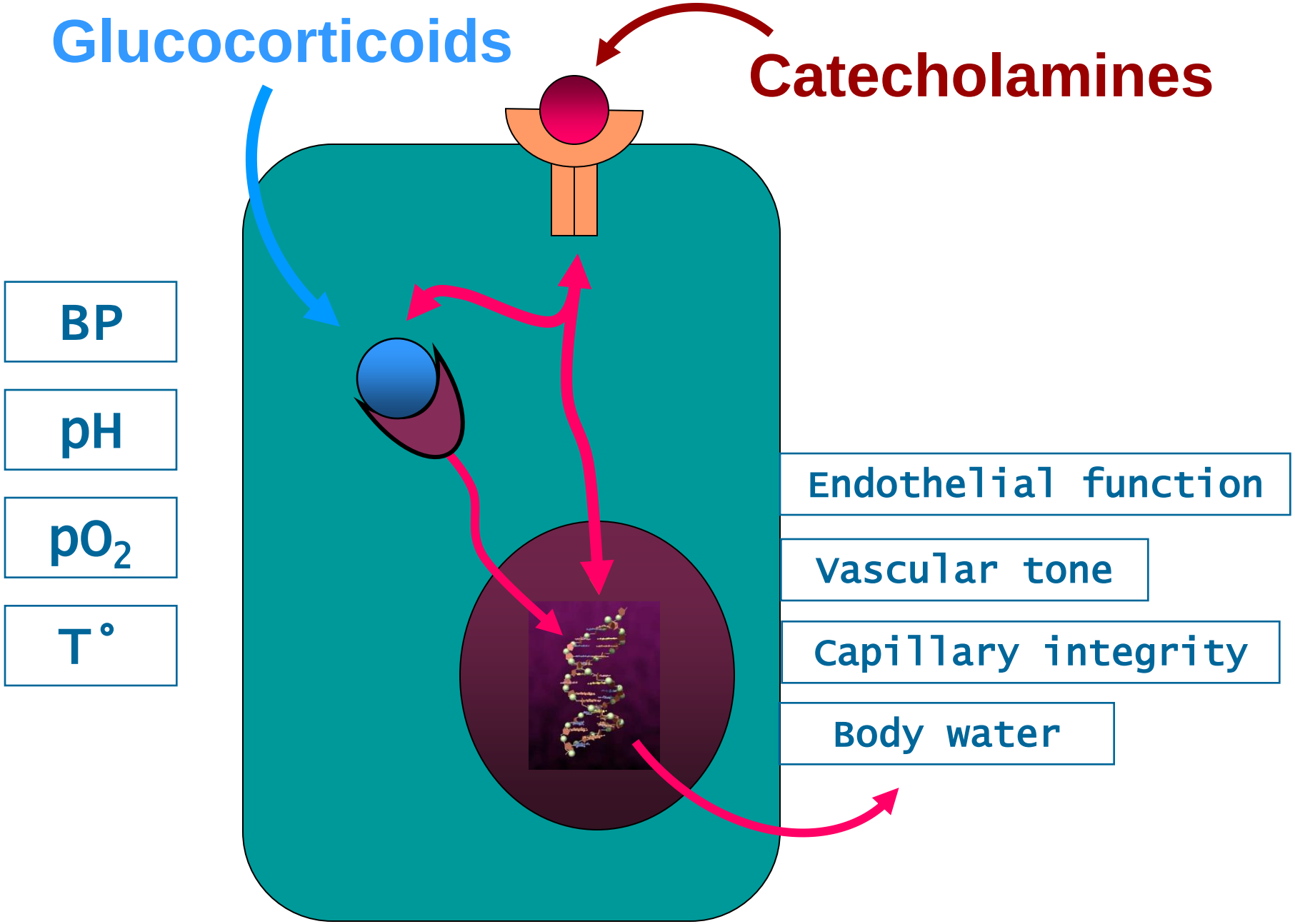


	acute	*chronic*
1. Cortisol axis		
-ACTH	+	-
-Cortisol	+	n
-CBG	+	n
2. Somatotropic axis		
-GH release	+	-
-IGF-1	-	--
-IGFBP-3	-	--
3. Thyroid axis		
-TRH release	+ n	-
-T3	-	--
-rT3	+	+
4. Gonadal axis		
-LH release	+ n	-
-Testosterone	-	--
-Prolactin	+	-

Plasma Cortisol during acute illness

Naito et al, JCEM 1991; Vermes et al, JCEM 1995; Lamberts et al, NEJM 1997



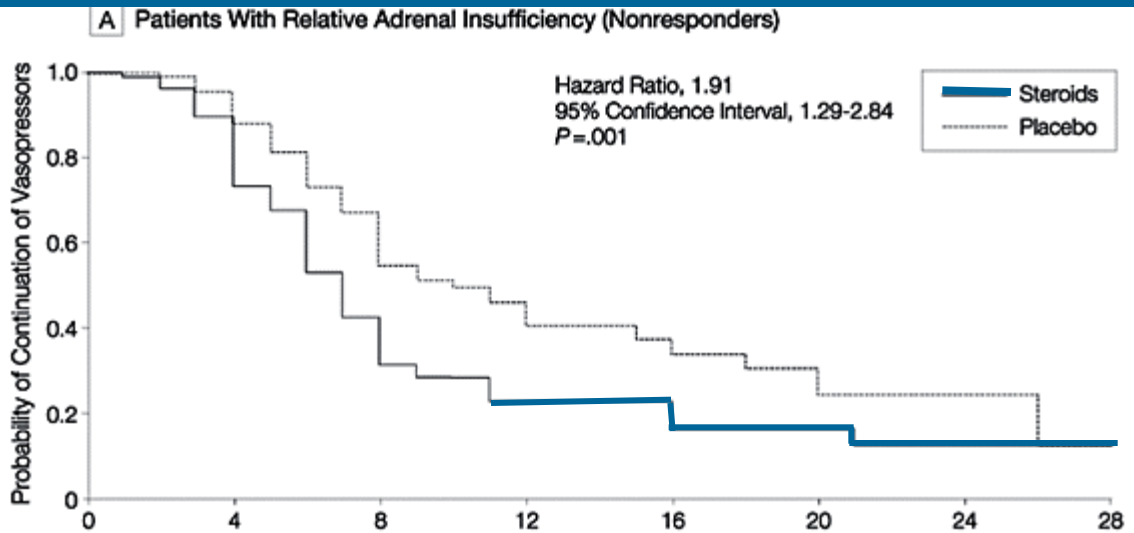


McEwen, NEJM 1998;338;171-

Effect of Treatment With Low Doses of Hydrocortisone and Fludrocortisone on Mortality in Patients With Septic Shock

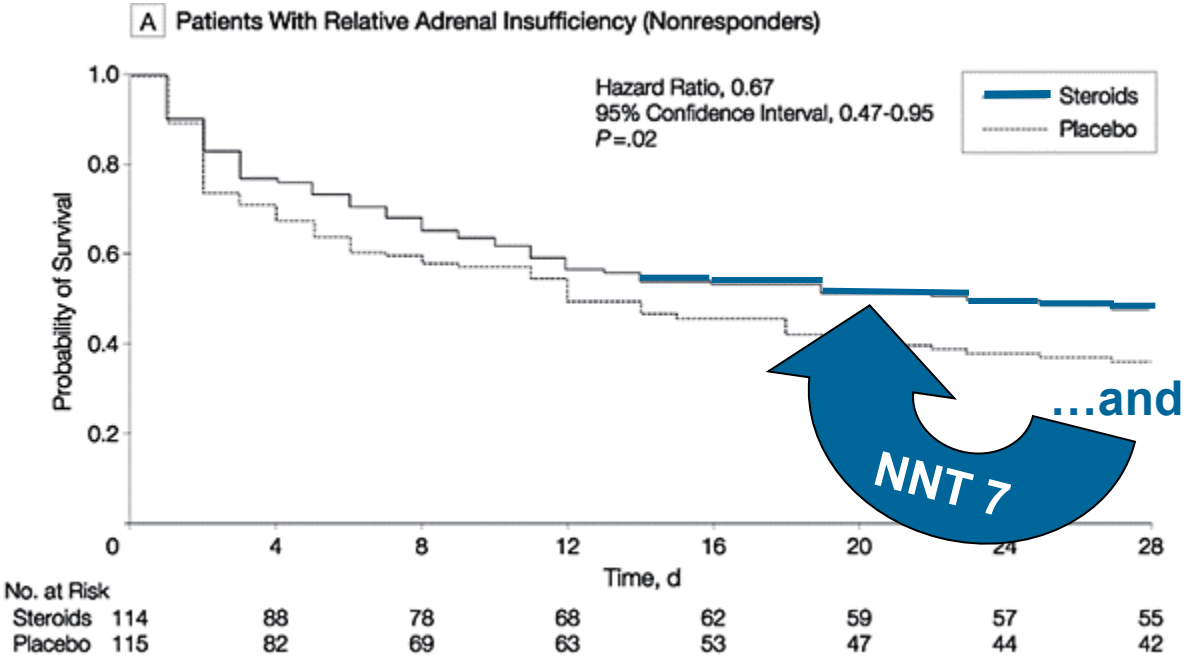
Annane D et al, JAMA 2002;288:862-

Vasopressors



19 ICUs
n=229
28 d-Mortality

Survival

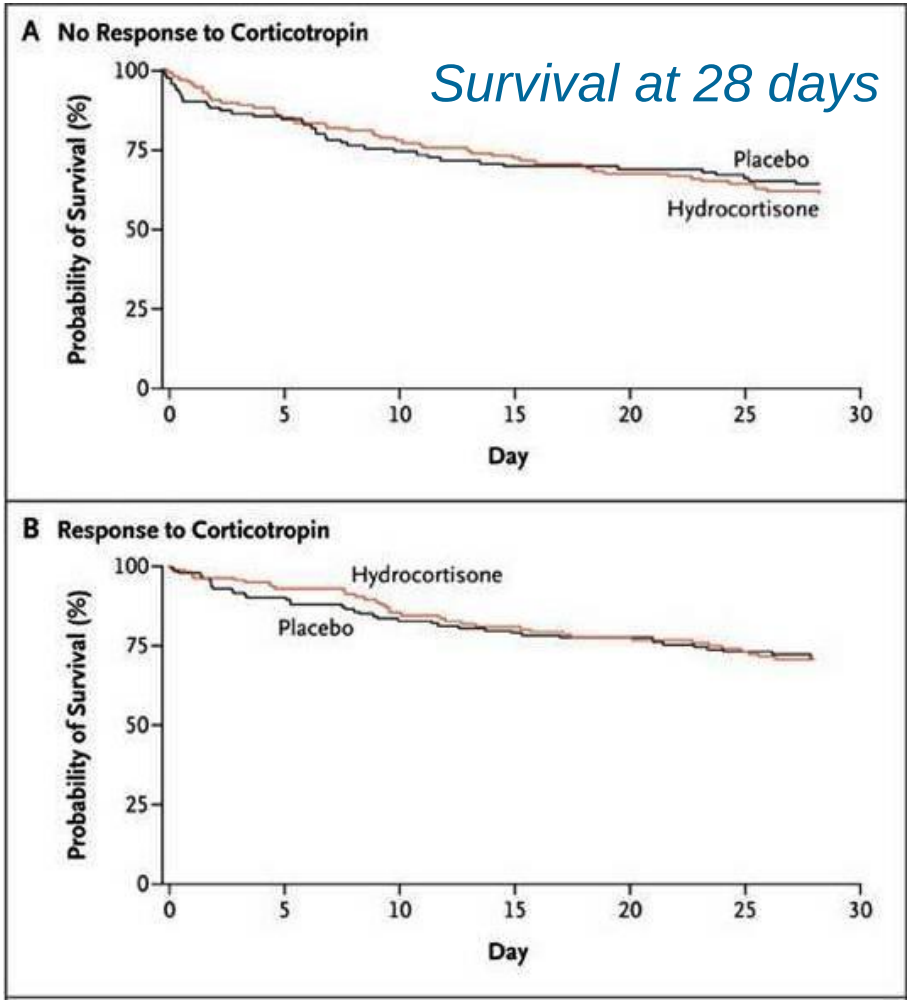


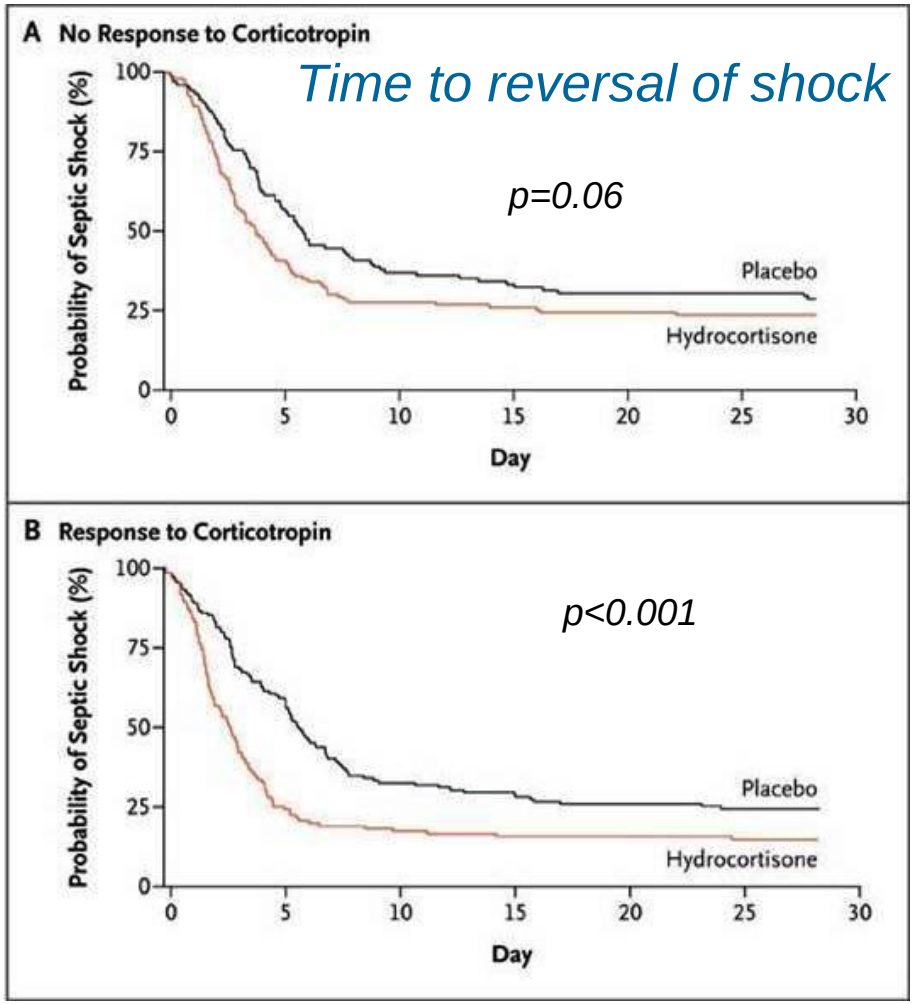
NNT 7

…and no side effects!

Hydrocortisone therapy for patients with septic shock *(CORTICUS study group) NEJM 2008;358:111-124*

Multicenter study: n=499 → 233 (46.7%) with no response to ACTH.





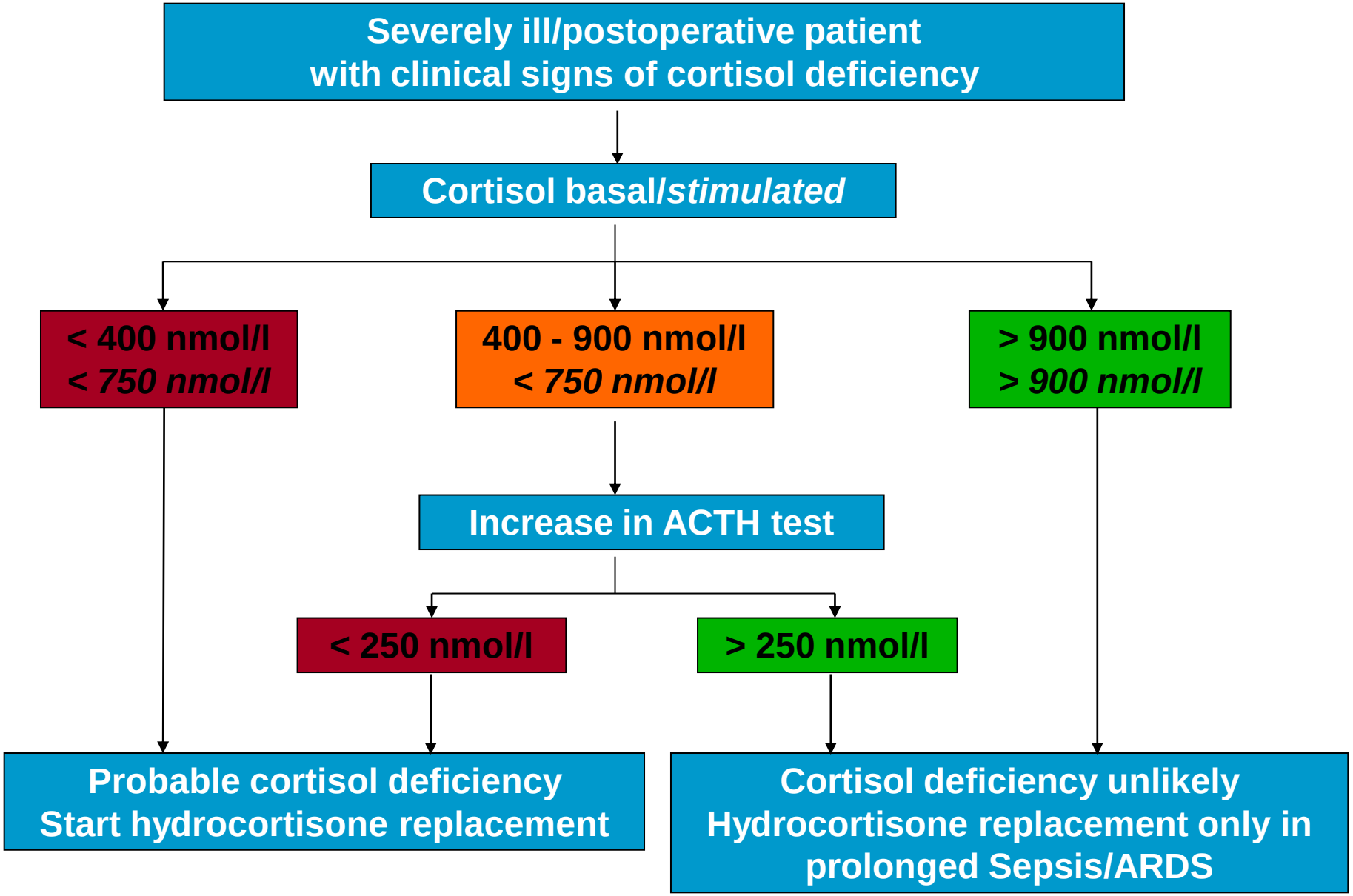
Hemodynamic instability

Abdominal pain

Fever

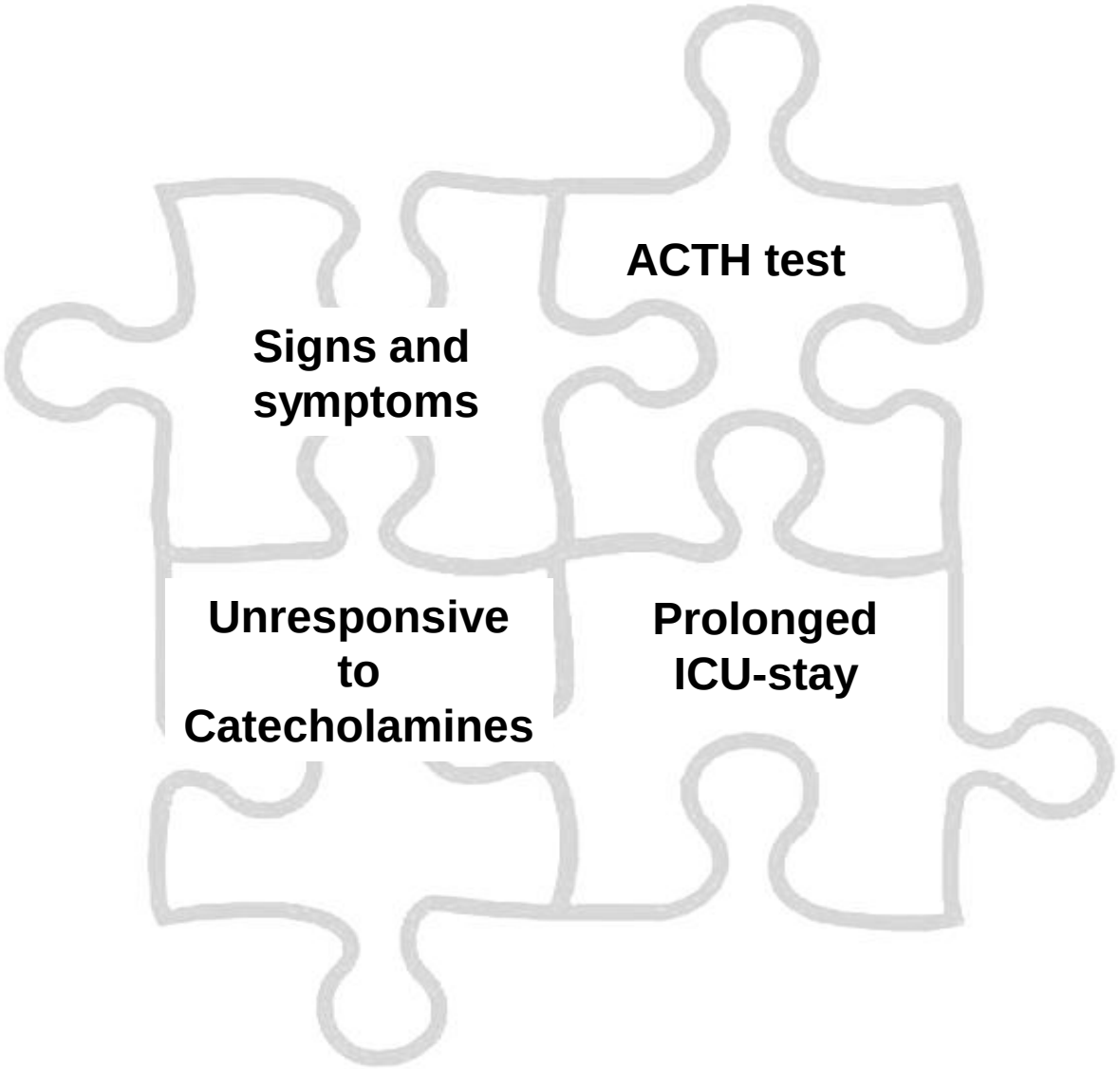
Apathy

Discrepancy between the anticipated disease severity and the state of the patient…



Swiss Medical Forum 2004;4:1187-1191

Hydrocortisone replacement in the ICU?



Hydrocortisone replacement in the ICU?

Patients on chronic steroid treatment

Patients with diagnosed or suspected hypocortisolism

„minor“ stress:
Fever, intermediate trauma, surgery with lokal or plexus anesthesia

Hydrocortisone per os (eg Hydrocortone MSD 40-40-20mg) or i.v. (z.B. Solu-Cortef 100mg)

After recovery back to usual dose in 1-2 days

„maior“ Stress:
Maior surgery, polytrauma, severe illness and sepsis

Chronic insufficiency:
Hydrocortisone i.v. 200mg/24h

acute insuffiziency:
Hydrocortisone i.v. 100mg Bolus + 200mg/24h

After recovery back to usual dose in 3-4 days

Septic shock:
„Catecholamine unresponsiveness“

Hydrocortisone i.v. 100mg Bolus + 200mg/24h + (Florinef 0.05mg/d)

After recovery back to replacement dose. ACTH-Test

1. Normal pituitary hormone secretion is controlled by feedback and rhythms
2. Appropriate stimulation of the cortisol axis is essential for survival in ICU.
3. (Relative) adrenal insufficiency is suspected by clinical signs and ACTH stimulation test.
4. Prolonged ICU stay, catecholamine resistance, and hemodynamic instability are suggestive for cortisol deficiency.
5. Hydrocortisone replacement is mandatory in these patients.

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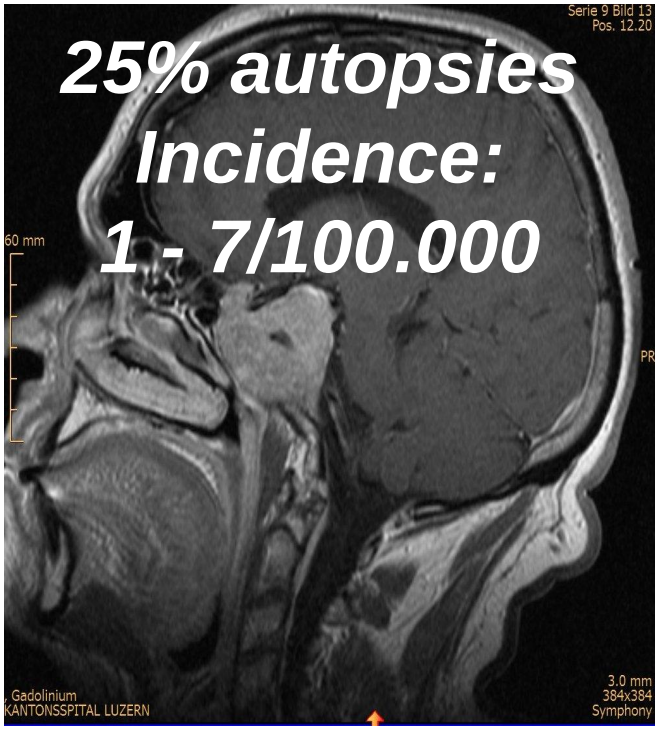
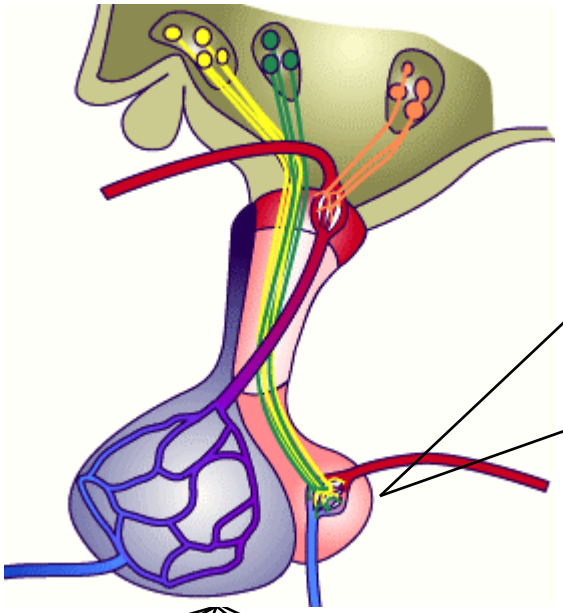
7.Disorders of ADH secretion



25% autopsies
Incidence:
1 - 7/100.000



Oxytocin

ADH

Na+/Osmol

ACTH **TSH** **LH/FSH** **HGH** **Prolactin**

Cortisol ***fT4*** ***Testosterone*** ***IGF-1***

Pituitary disorders ?

→ peripheral hormones !

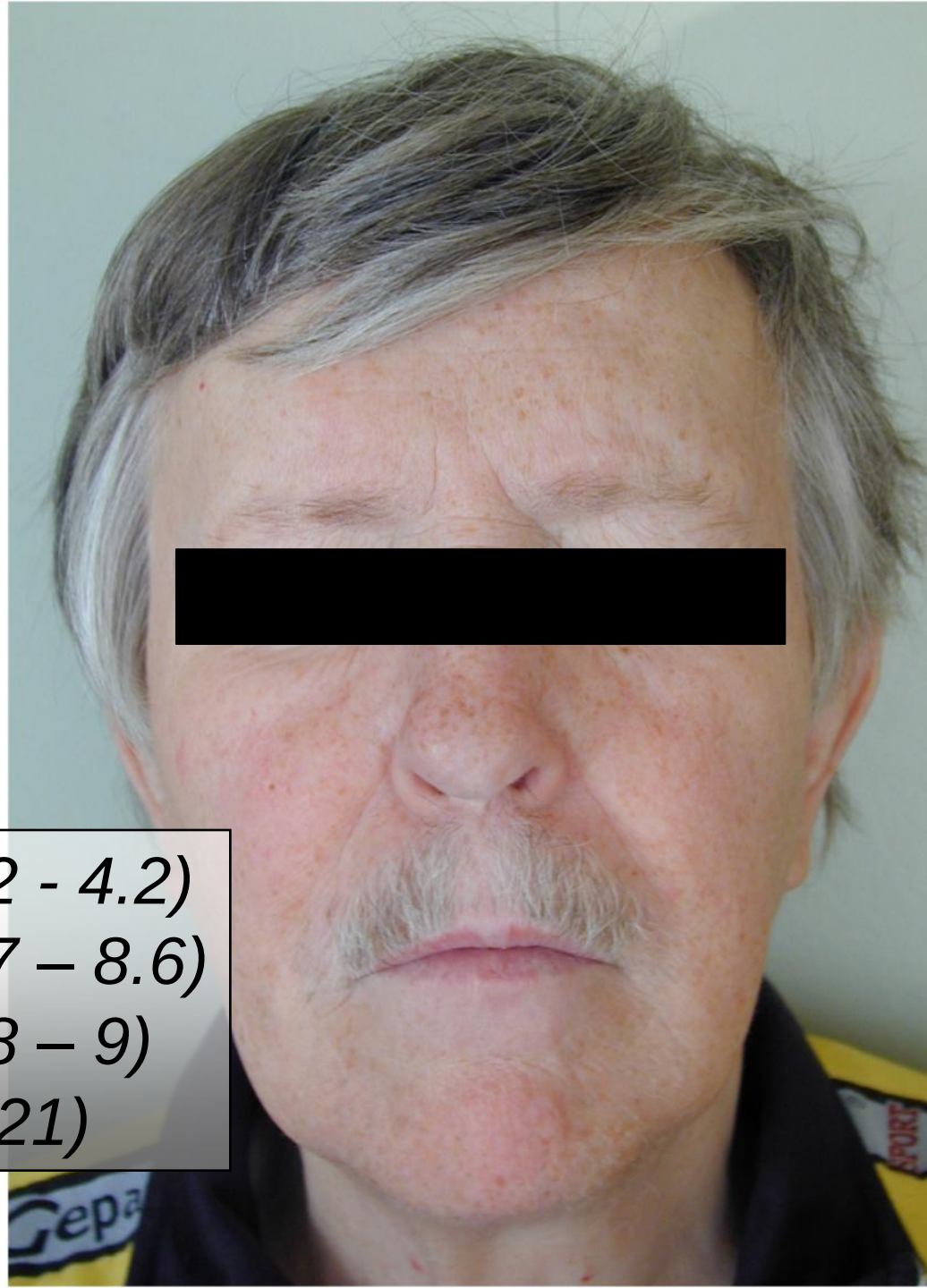
Mr K.J., 1934

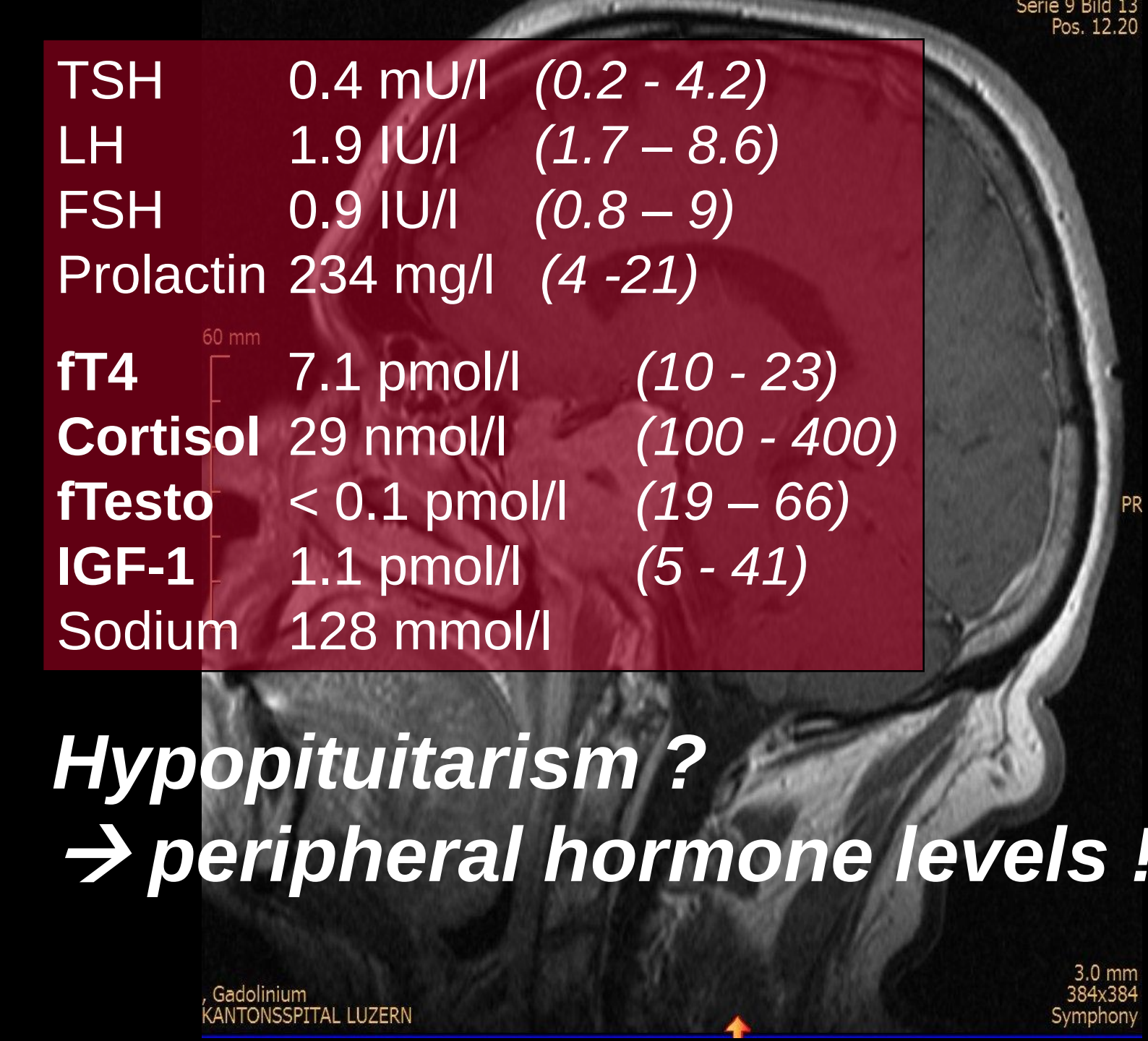
GCS 9, Temp 41°

Weakness, fatigue
Acute bronchitis

BP 70/40 mmHg
neck stiffness (+)
hemianopsia

TSH	0.4 mU/l	*(0.2 - 4.2)*
LH	1.9 IU/l	*(1.7 – 8.6)*
FSH	0.9 IU/l	*(0.8 – 9)*
Prolactin	234 μg/l	*(4 -21)*





TSH	0.4 mU/l	*(0.2 - 4.2)*
LH	1.9 IU/l	*(1.7 – 8.6)*
FSH	0.9 IU/l	*(0.8 – 9)*
Prolactin	234 mg/l	*(4 -21)*
fT4	7.1 pmol/l	*(10 - 23)*
Cortisol	29 nmol/l	*(100 - 400)*
fTesto	< 0.1 pmol/l	*(19 – 66)*
IGF-1	1.1 pmol/l	*(5 - 41)*
Sodium	128 mmol/l	

Hypopituitarism ?

→ peripheral hormone levels !

Mr W.H., 1965

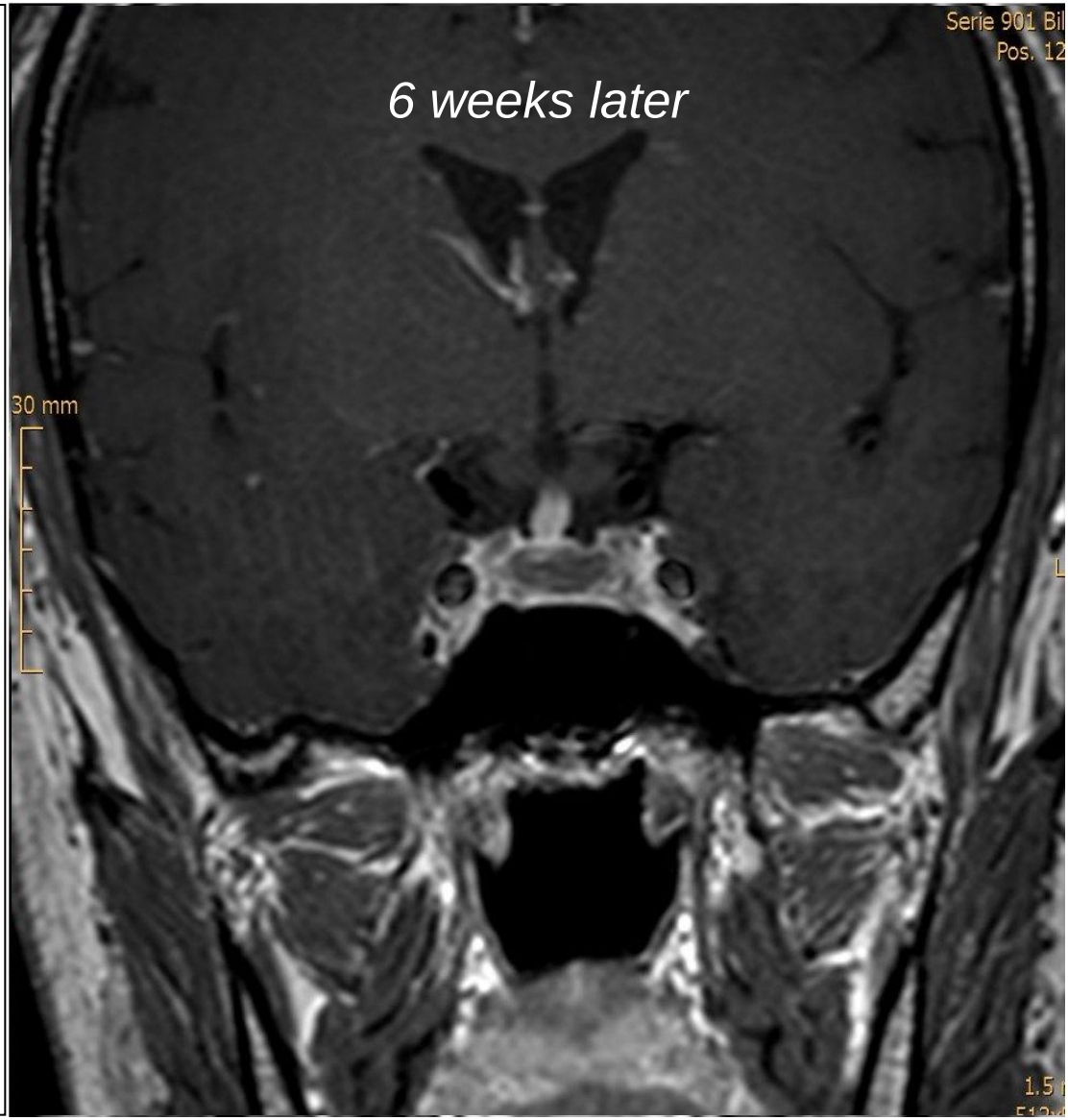
Admitted with acute onset of bitemporal headache, vomiting and collapse

→no focal deficits

→CT: no hemorrhage or ischemia

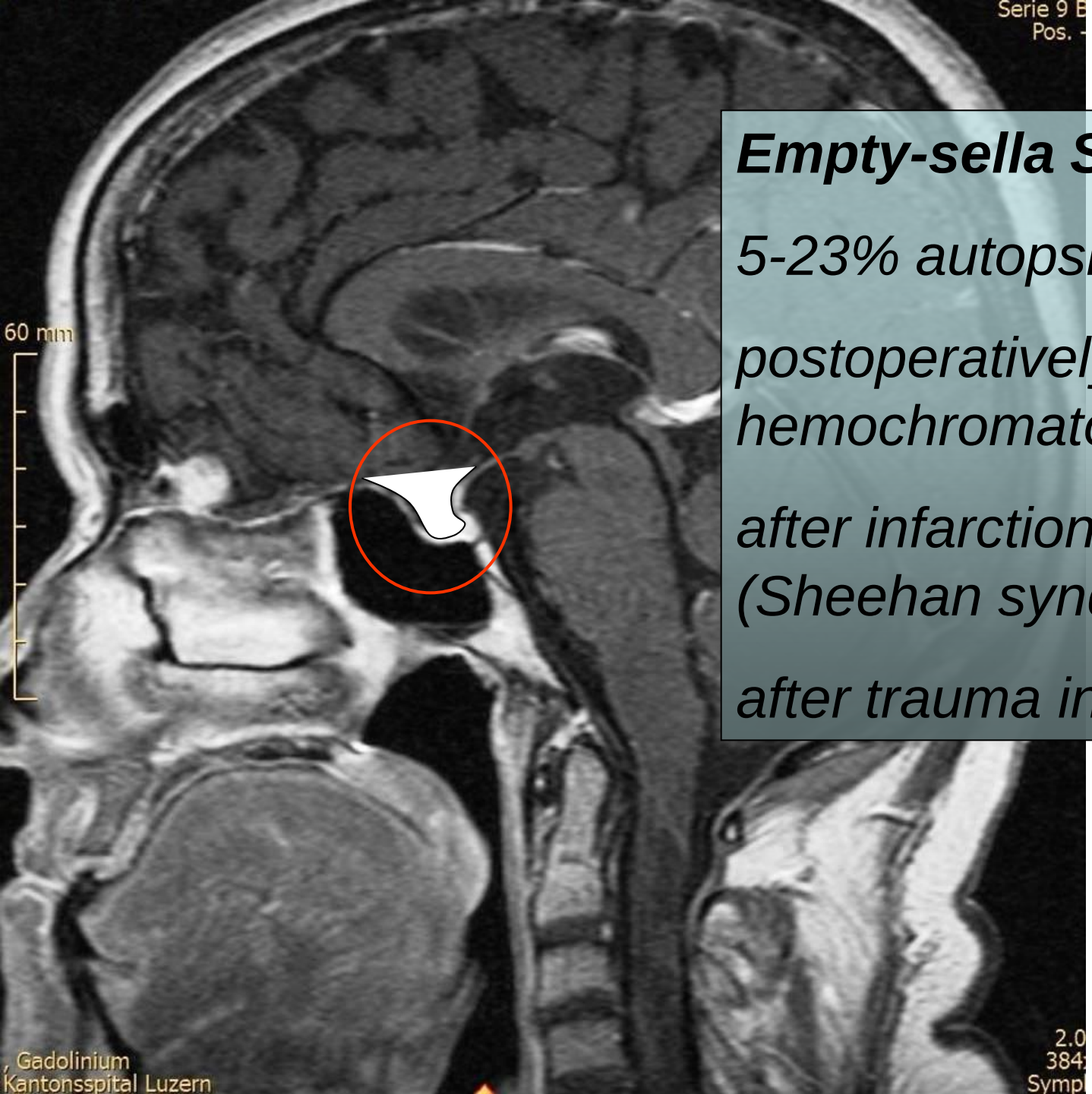
→LP: SAB excluded

→***MRI***



Pituitary apoplexy - a series of five cases *Burget L et al.*

Predominant features of pituitary apoplexy are acute onset of severe headache, a preexisting pituitary adenoma and permanent hypopituitarism. 4/5 patients in our series were women. Transsphenoidal pituitary decompression was necessary in 1/5 patients.



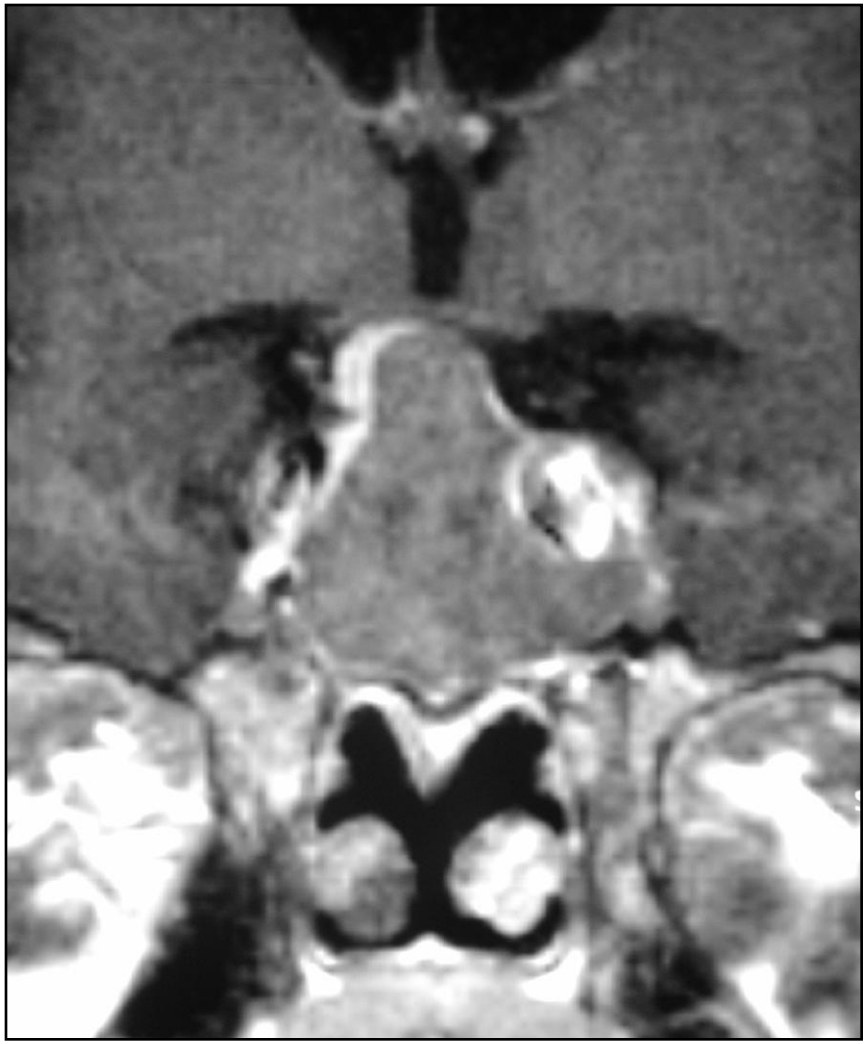
Empty-sella Syndrom

5-23% autopsies

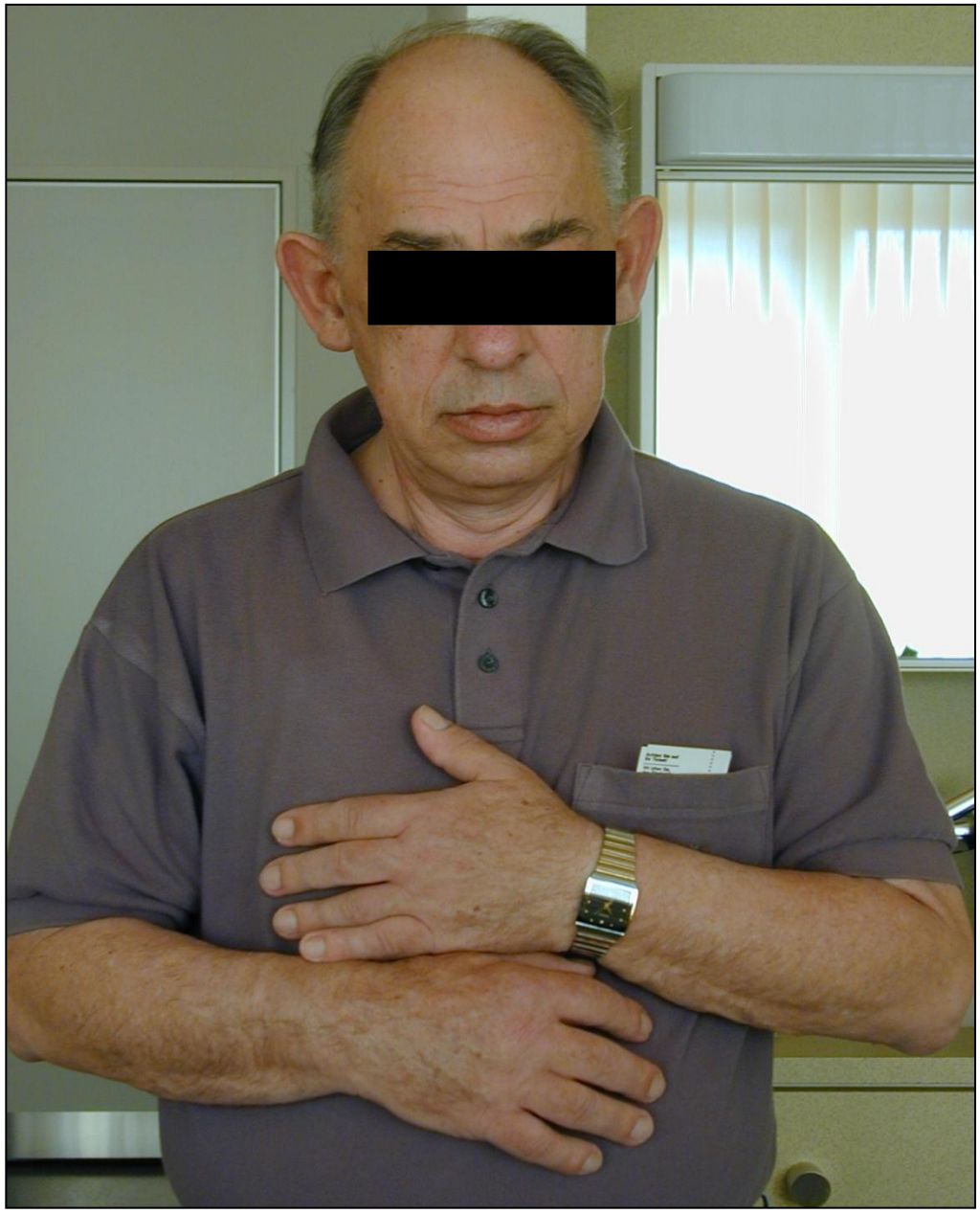
postoperatively/Radiatio/ hemochromatosis

after infarction/hemorrhage (Sheehan syndrome)

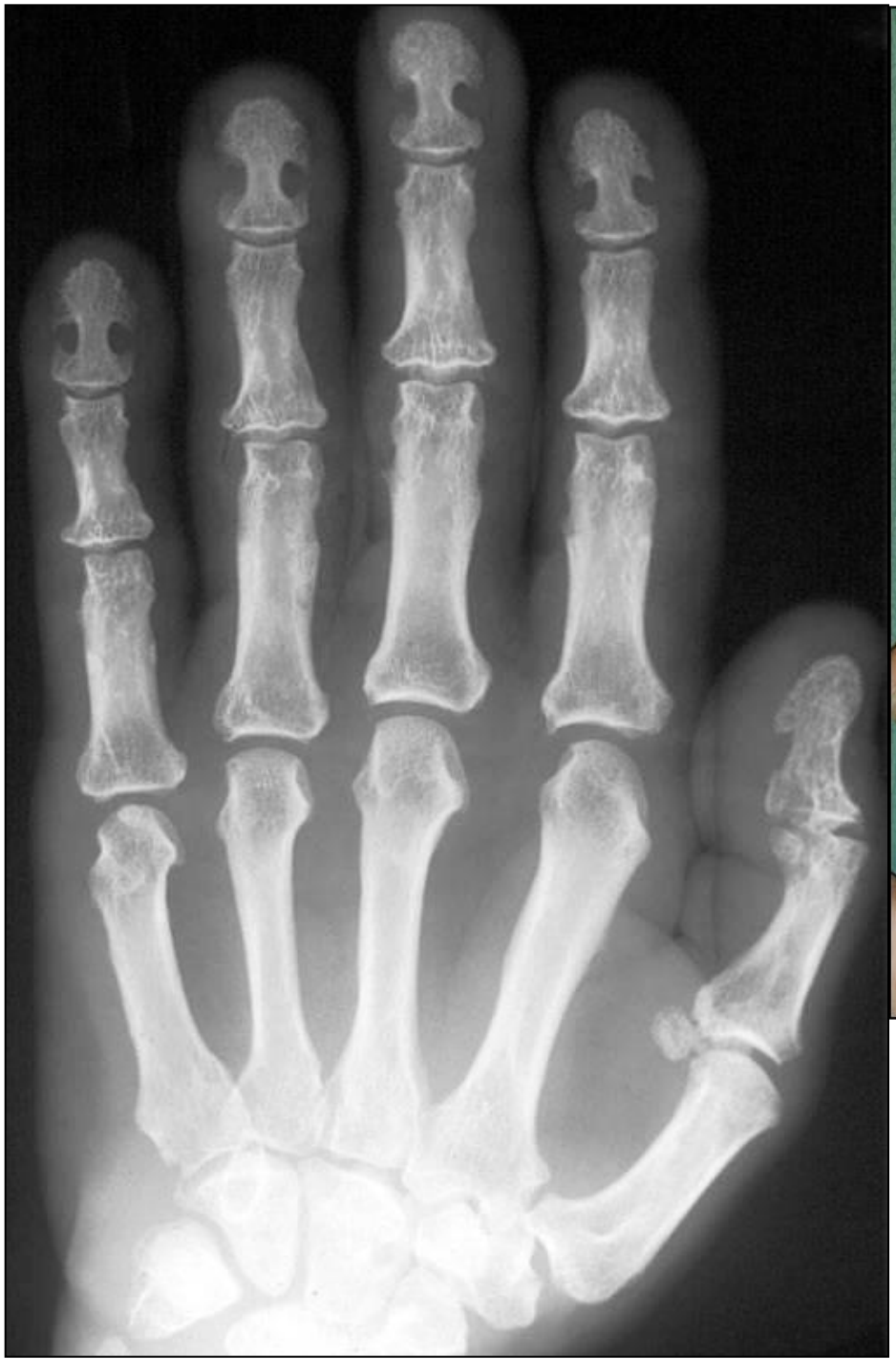
after trauma in 15%

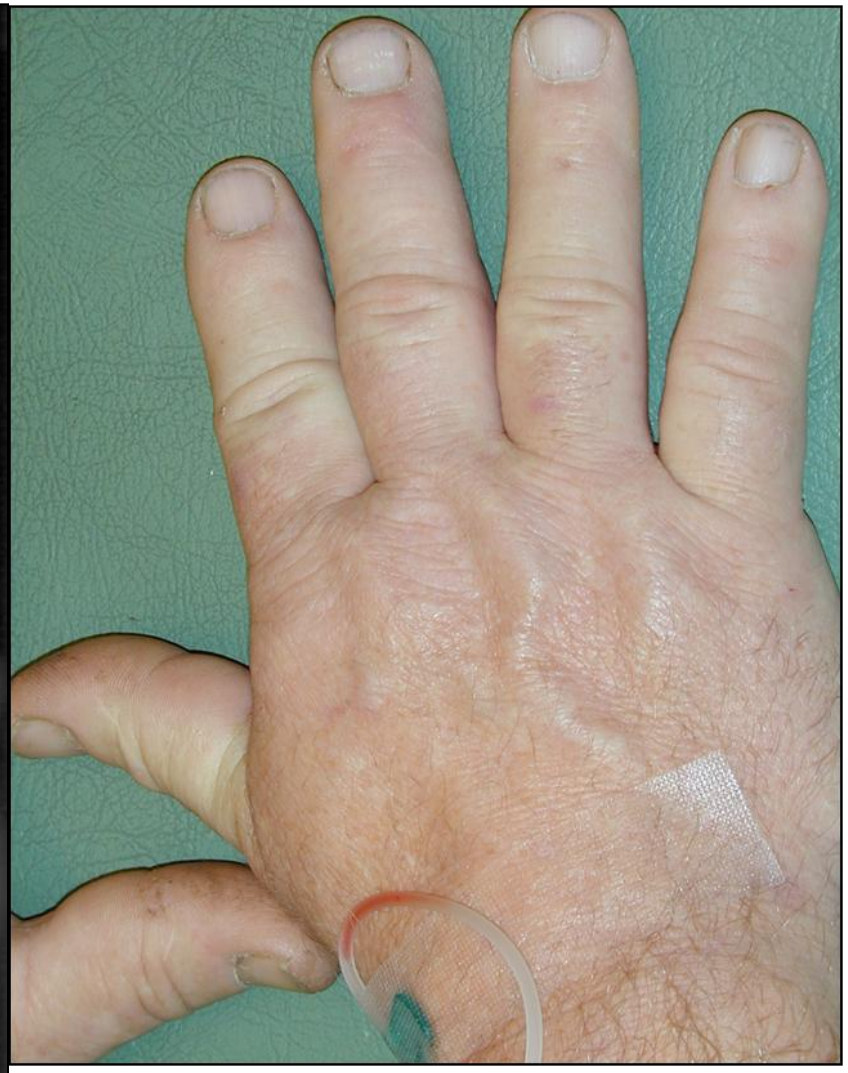


IGF-1: 234 nmol/l
(normal 5 – 41)



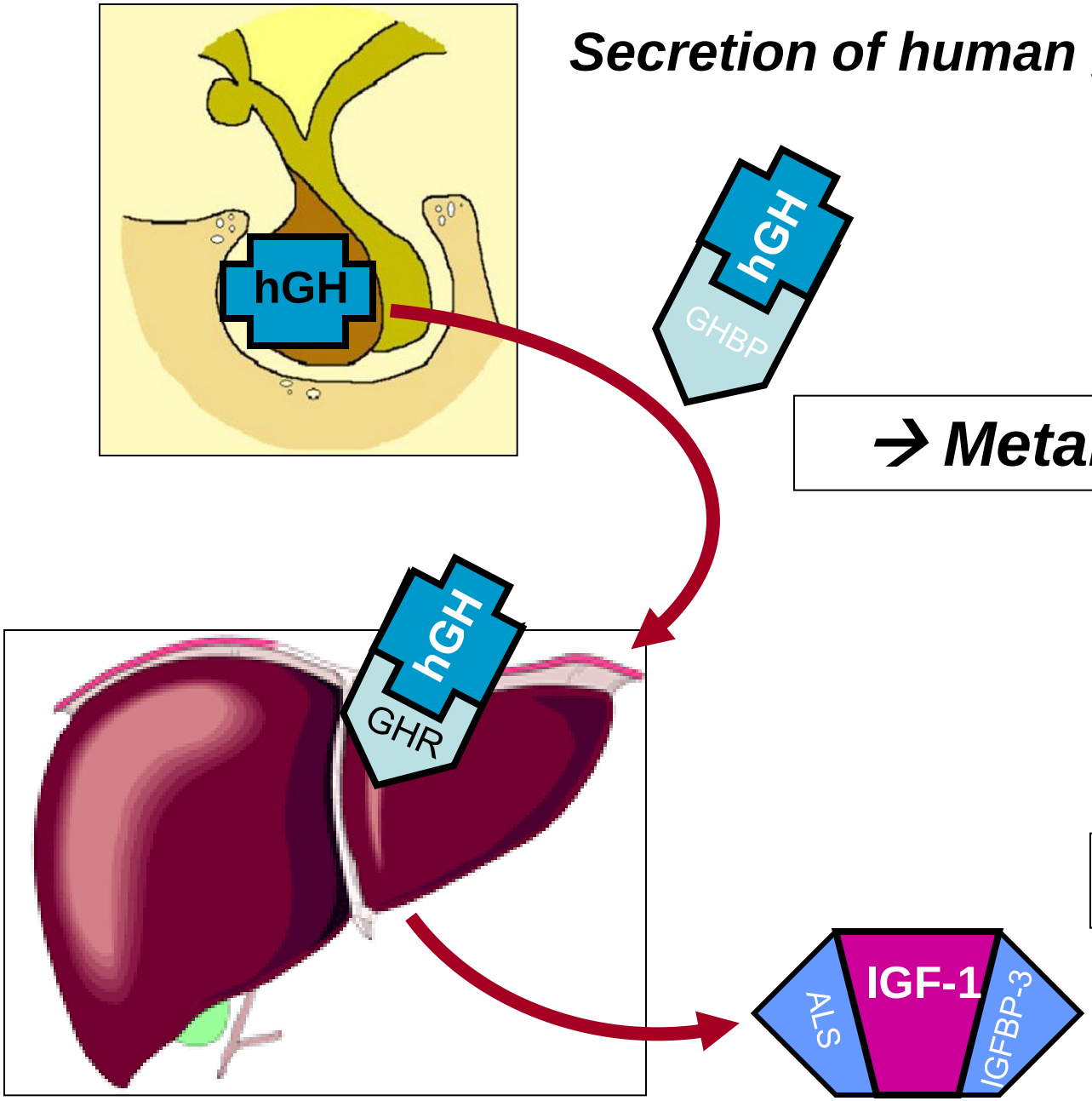
2004





handshake…“

Secretion of human growth hormone

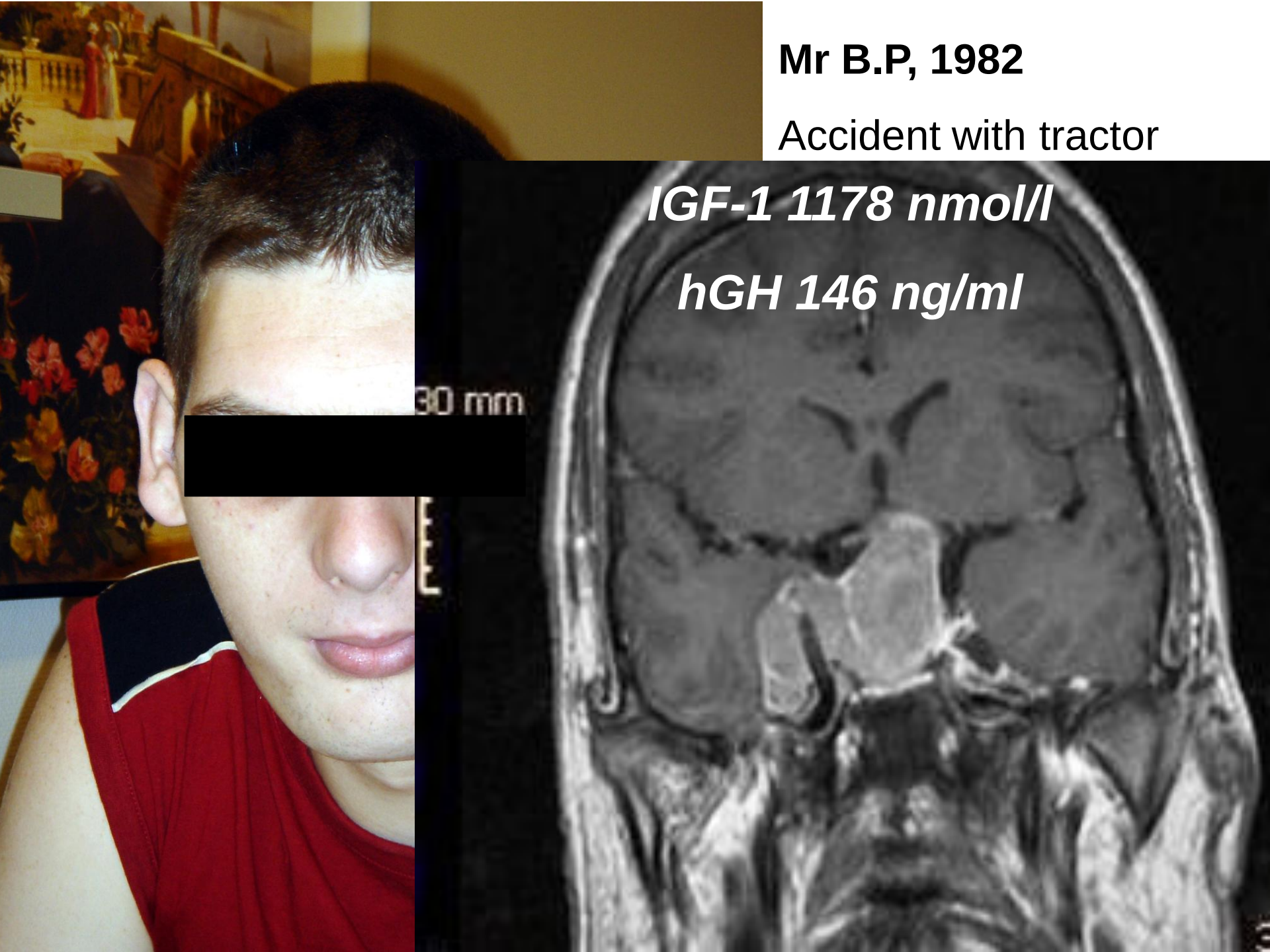


→ Metabolic effects

→ GROWTH

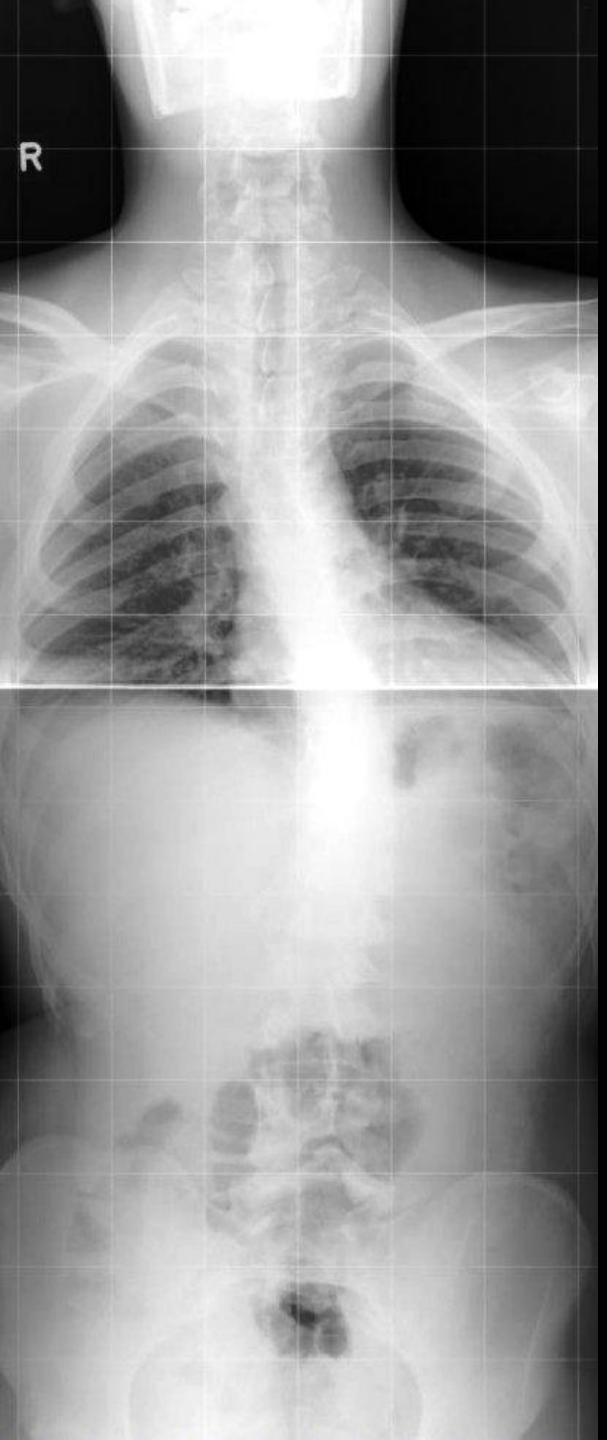
Mr B.P, 1982

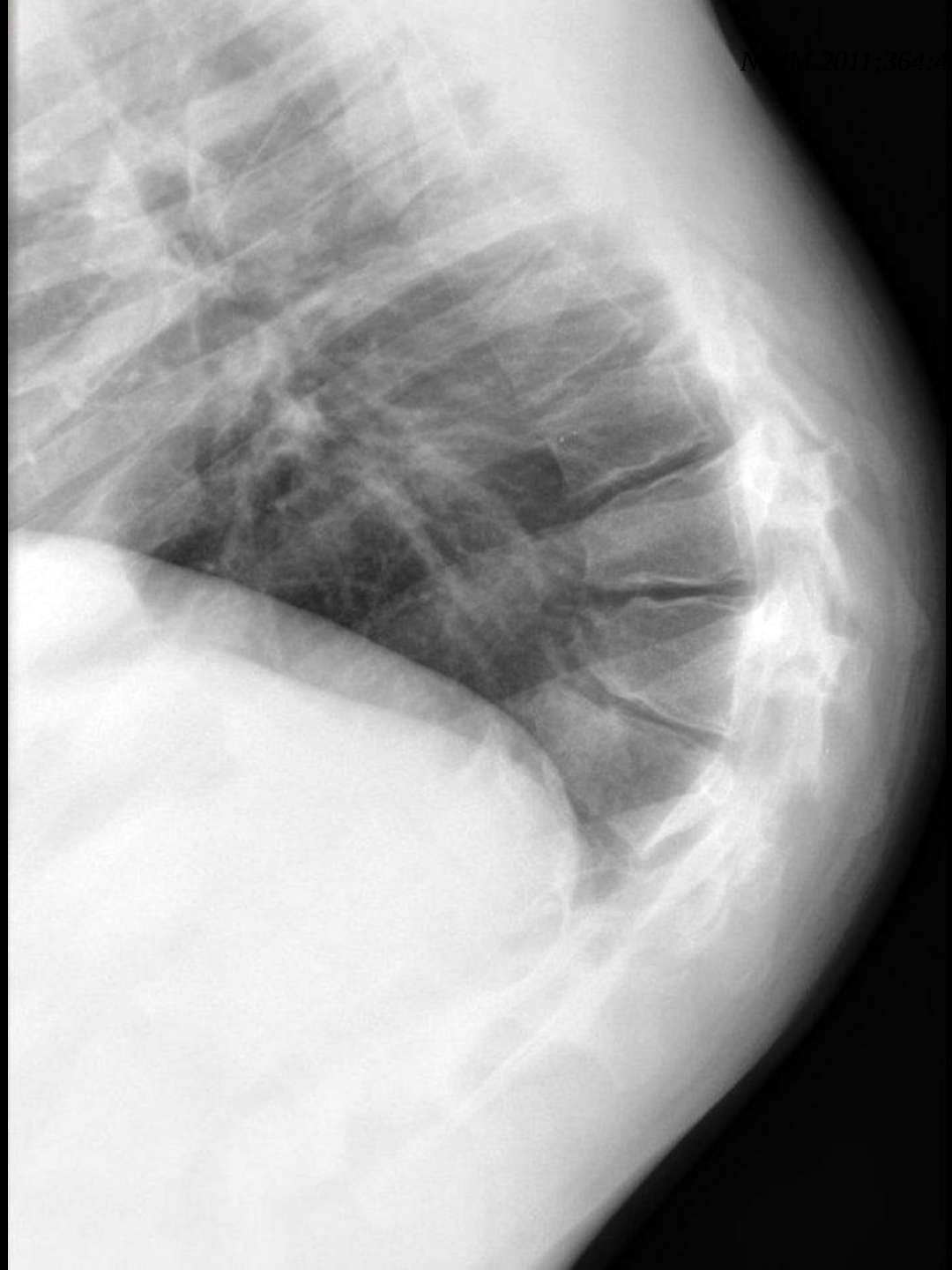
Accident with tractor



IGF-1 1178 nmol/l

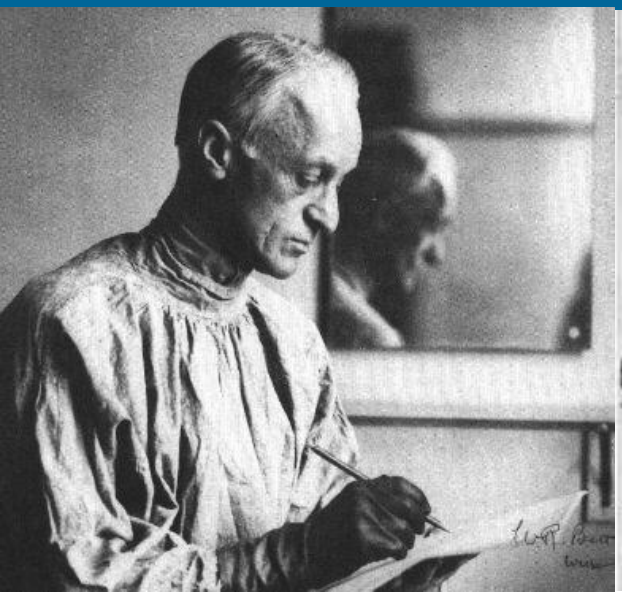
hGH 146 ng/ml

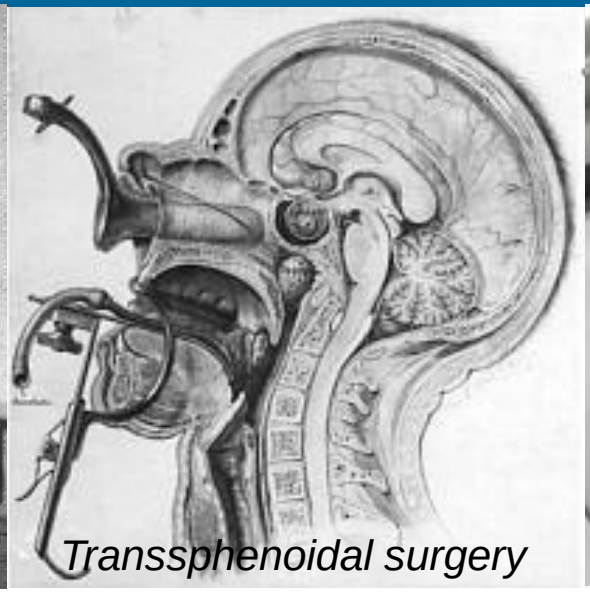




NEJM 2011;364:4

Treatment of acromegaly





Medical therapy:

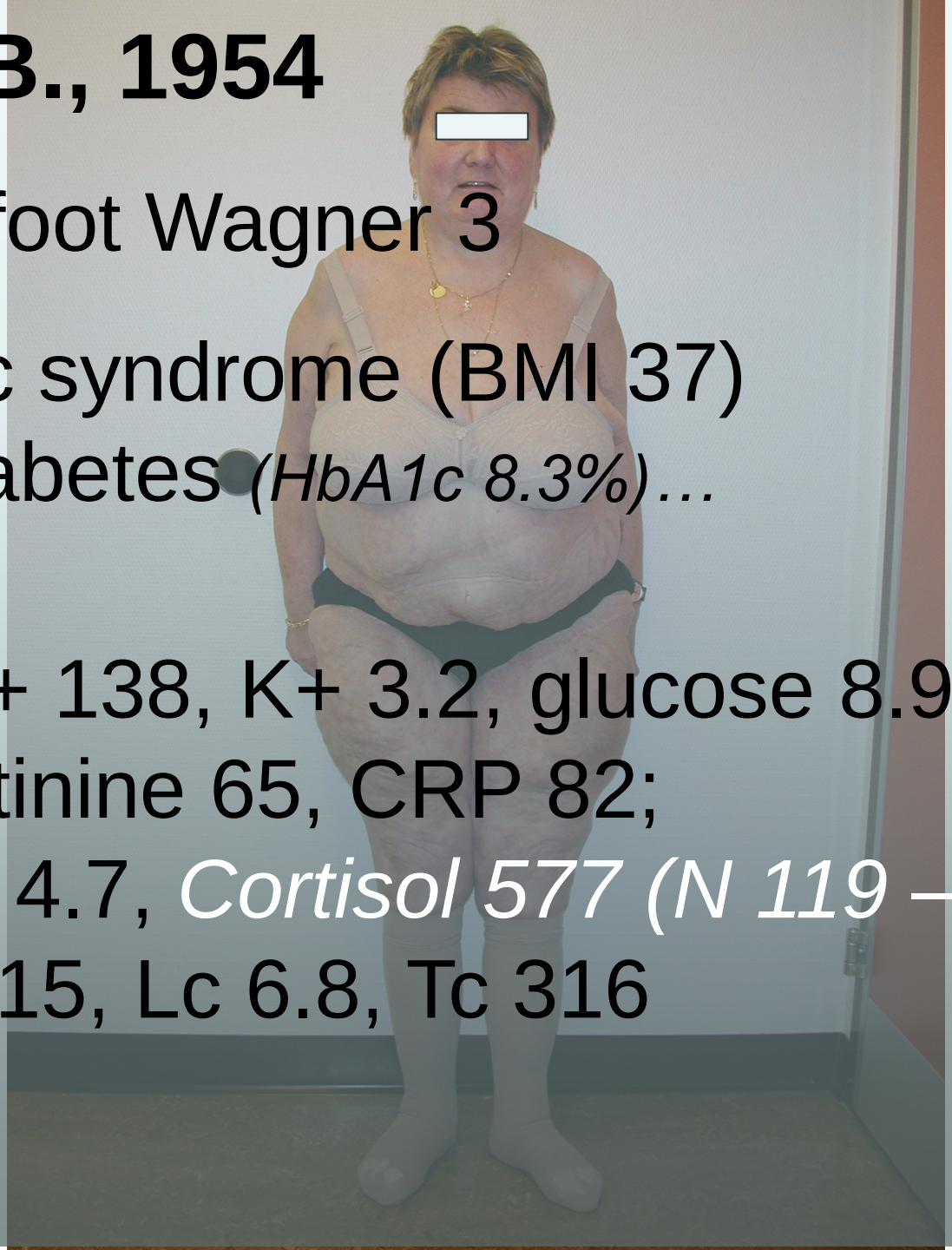
Somatostatin receptor ligands (Sandostatin® LAR, Somatuline®)
GH receptor antagonist (pegvisomant - Somavert®)
Dopamine agonist (cabergoline)

AIM: normal IGF-1 and random hGH < 2.5 ng/ml (< 0.4 ng/ml)

and… replacement therapy of the other axes!

1. If hypopituitarism is suspected always check peripheral hormone levels.
2. Main causes are macroadenoma, apoplexy, hemochromatosis or trauma.
3. Acromegaly → bulky sweaty handshake and elevated IGF-1.
4. Treatment consists of transsphenoidal surgery, octreotid-analoga and pegvisomant.

Mrs G. B., 1954



Diabetic foot Wagner 3

Metabolic syndrome (BMI 37)
type 2 diabetes *(HbA1c 8.3%)…*

Lab: Na+ 138, K+ 3.2, glucose 8.9,
creatinine 65, CRP 82;
TSH 4.7, *Cortisol 577 (N 119 – 440)*
Hb 115, Lc 6.8, Tc 316

24h urinary free cortisol:

527 nmol *(N < 265)*

Salivary cortisol 11 pm:

32.8 nmol/l *(N < 8.3)*

8.00: ***33.2****, 16.00:* ***35.9***

Plasma cortisol at 8 am after 2 mg Dexamethason at 11 pm:

422 nmol/l

ACTH?

Salivary cortisol – an alternative to serum cortisol determinations in dynamic function tests

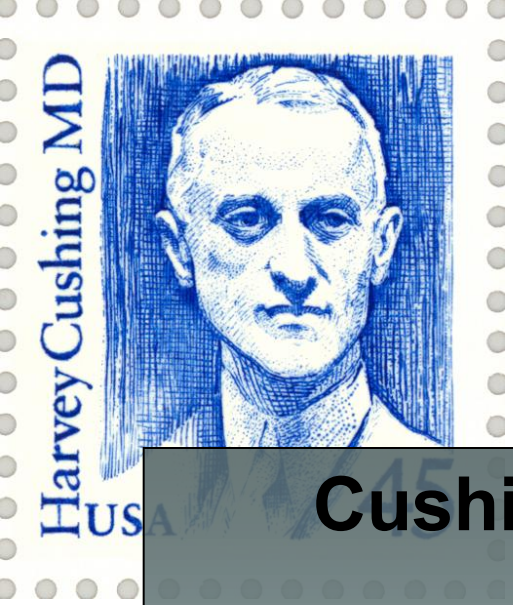
Aardal-Eriksson E et al, Clin Chem Lab Med 1998;36;215-22;

Gozansky WS et al, Clin Endocrinol 2005;63;336-41

1. Saliva is obtained in Salivette® Sarstedt
2. Frozen for at least 24h at $\leq$ -20° C
3. Luminescence Immuno-assay (IBL, Cortisol LIA®)
4. CV: 4.4 to 7.7%
5. Prednisolone crossreactivity: 57%
6. Sensitivity/specificity > 95%

Salivary cortisol = free Cortisol

Plasma cortisol = 90% CBG + 7% Albumin + **1-3% free**



„…diabetes in bearded woman…“

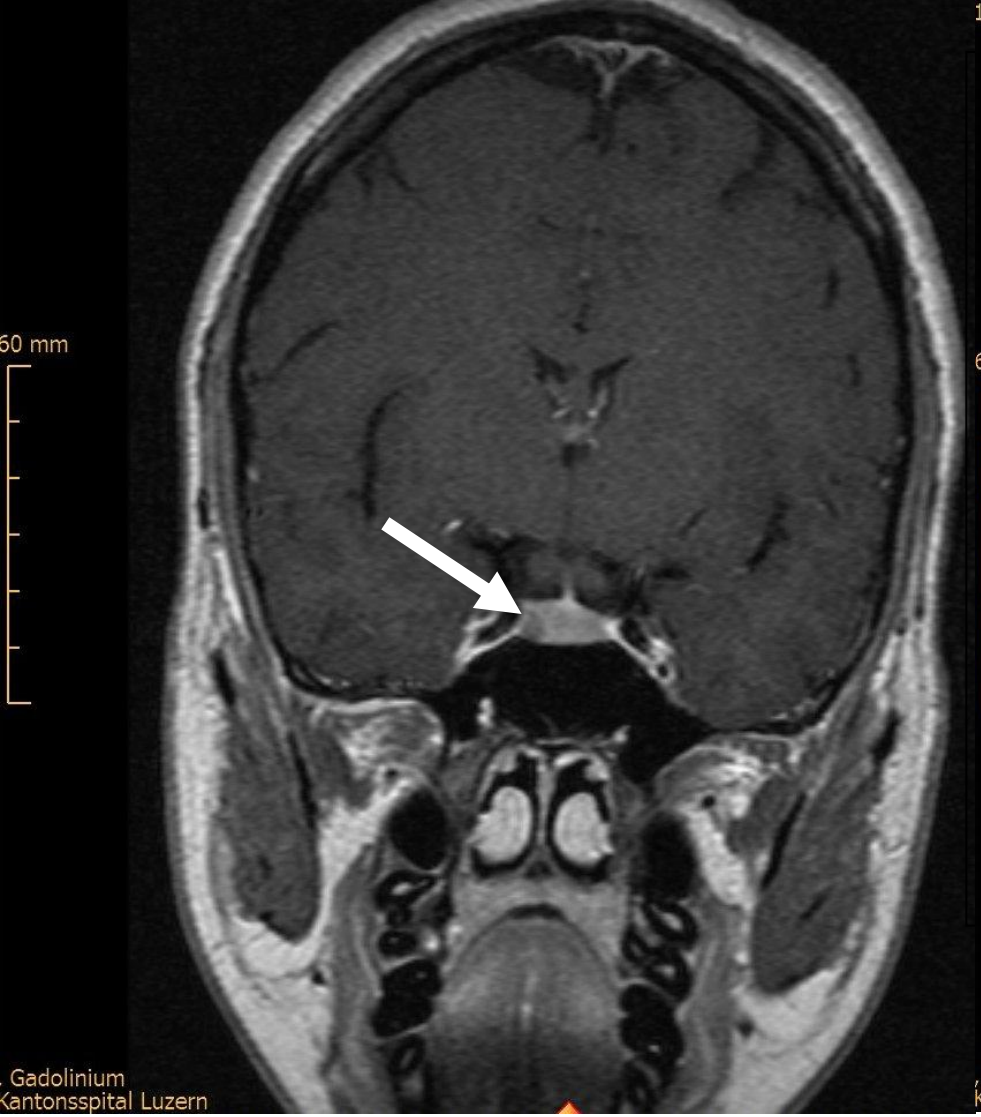
Cushing‘s Syndrom (Hypercortisolism)

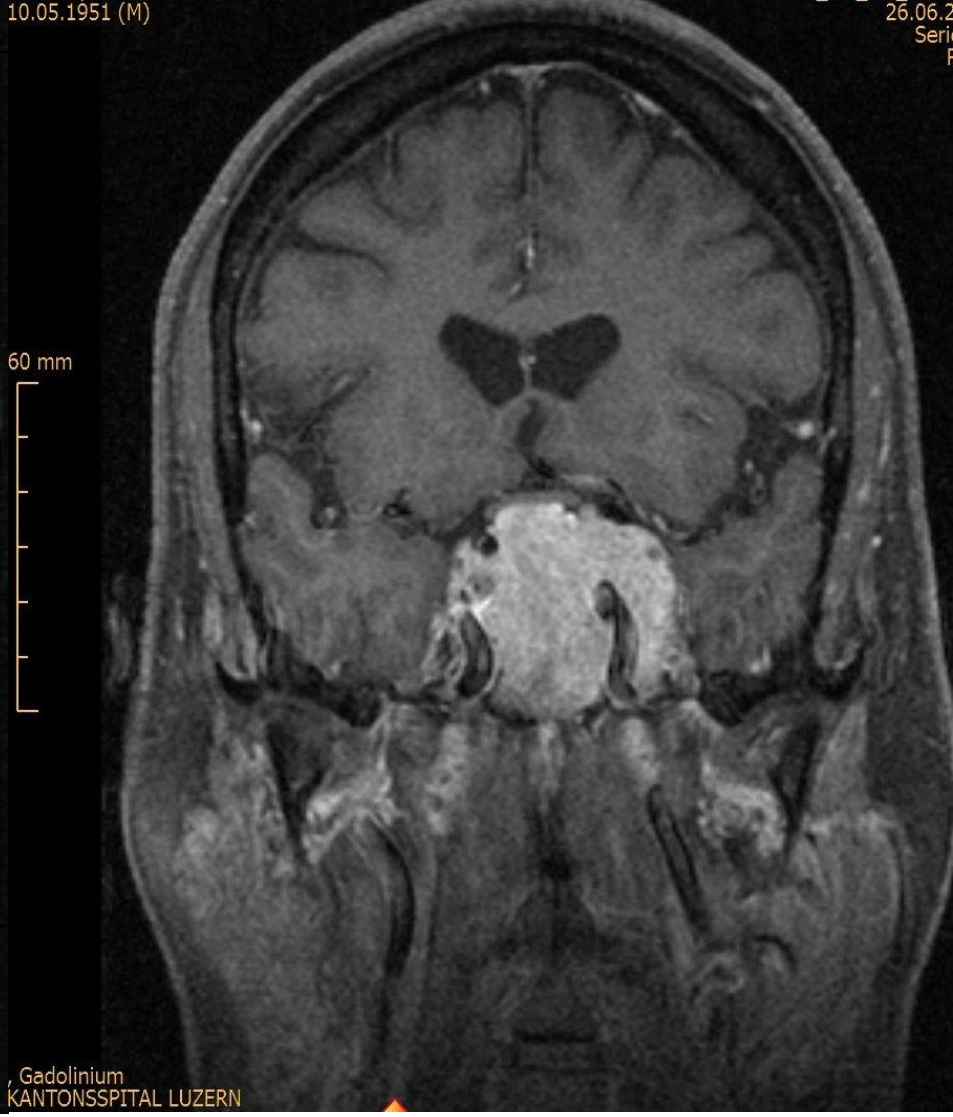
Incidence: 2 - 10 per Million
0.2 - 0.3 adrenal carcinoma

Localisation: adrenal = pituitary >> ectopic/ carcinoma/(Carney-Complex, McCune-Albright)

Sex: adrenal adenoma (women)

Mortality: 50% / 5 years!





Microprolactinoma

Tx: Cabergoline 2x0.5 mg/w

Prolaktin: **19.0 μg/l**

Macroprolactinoma

quinagolide 150 μg/d

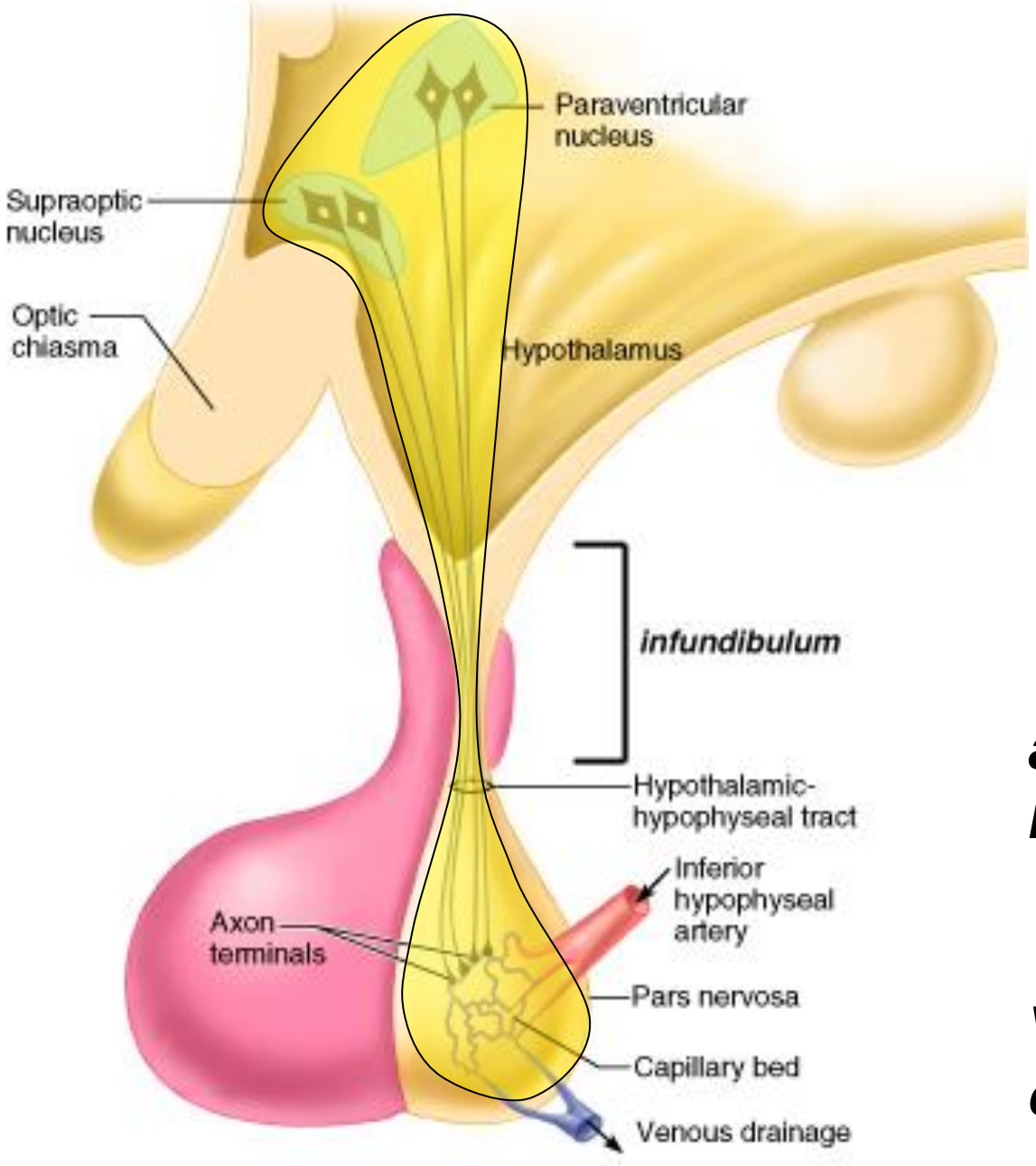
1180 μg/l

Pregnancy
stress, physical activity
kidney failure
postprandial, smoking...

estrogens
neuroleptics, antidepressants
phenytoin
cocaine, methadone, opiate..

Macroprolactinemia (big-big)

1. Cushing‘s syndrome: striae rubrae, hirsutism + „metabolic syndrome"
2. Best screening method for hypercortisolism → salivary cortisol at midnight
3. Stepwise evaluation: ACTH ?
4. Pituitary hypercortisolisms without adenoma → BIPSS
5. "Flat gonadal axis“ (i.e.amenorrhea/ galaktorrhea in women, and loss of libido/erection in men) → prolaktinoma?



ADH

V1

arteries
liver

↓

Vaso-constriction

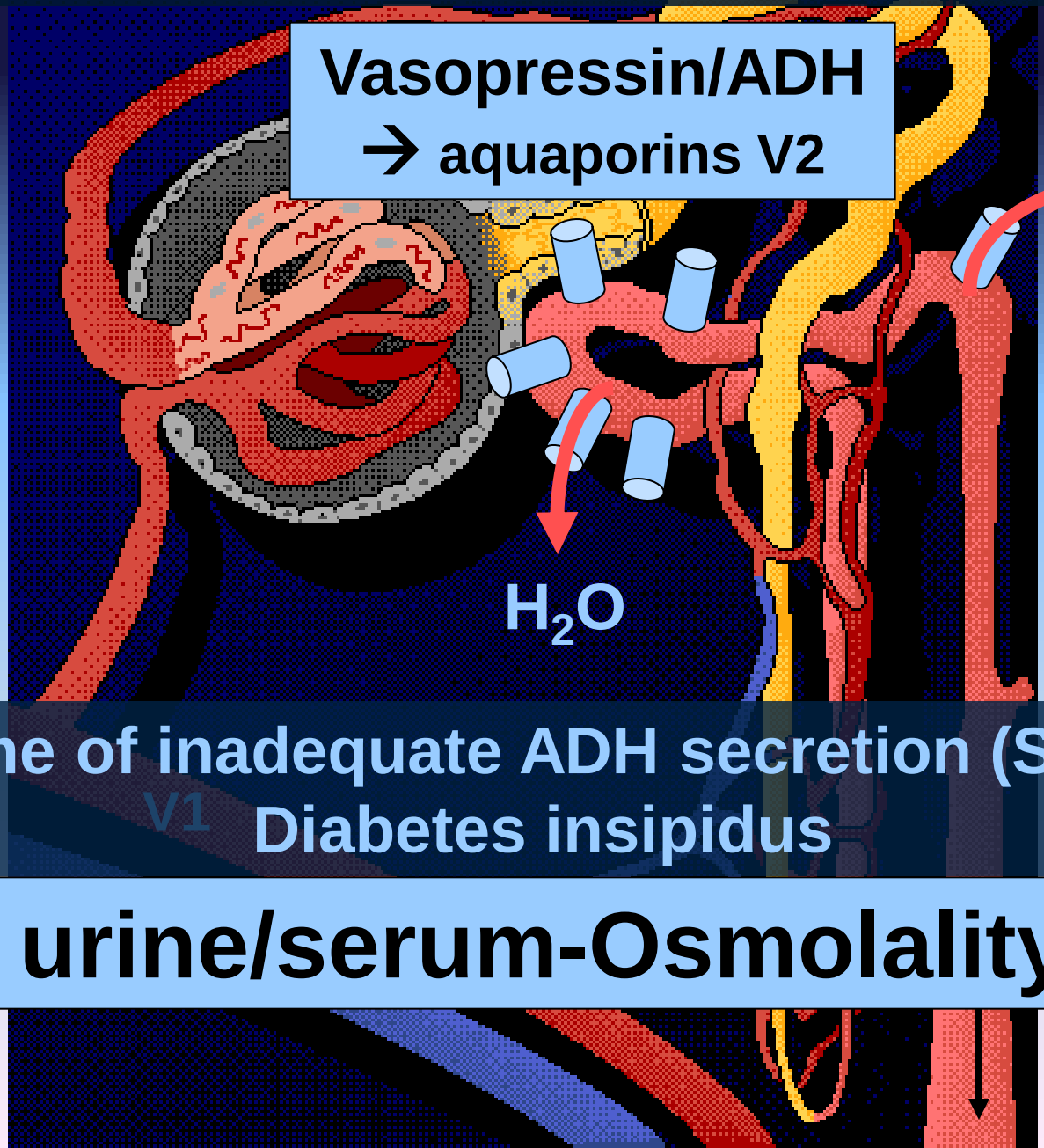
V2

renal tubule

↓

H_20-reap-sorption

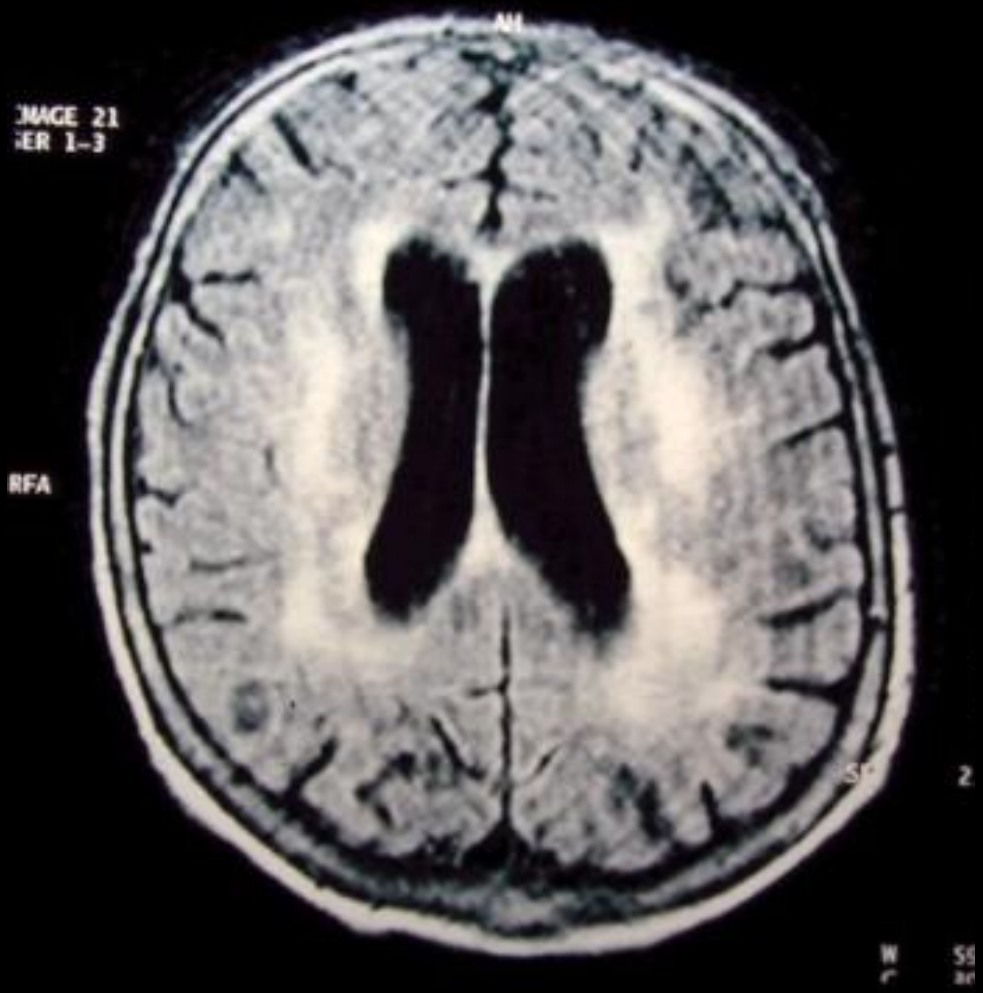
Renal effects of ADH/Vasopressin

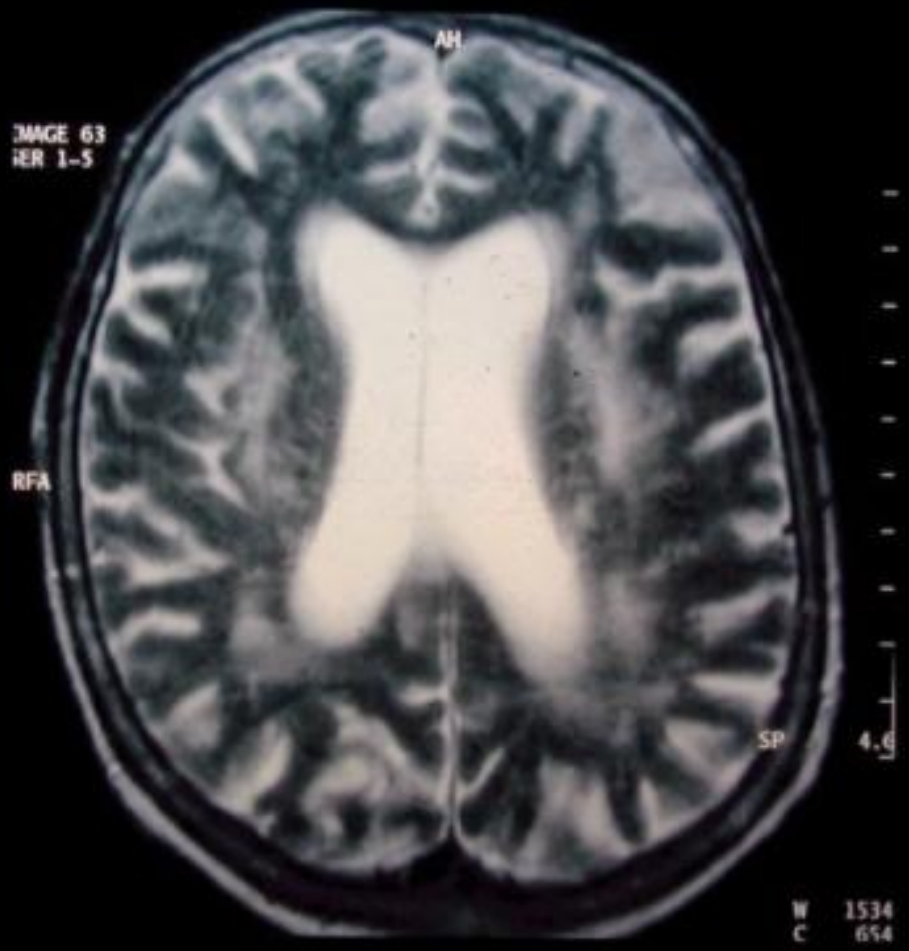


Syndrome of inadequate ADH secretion (SIADH) *vs.* Diabetes insipidus

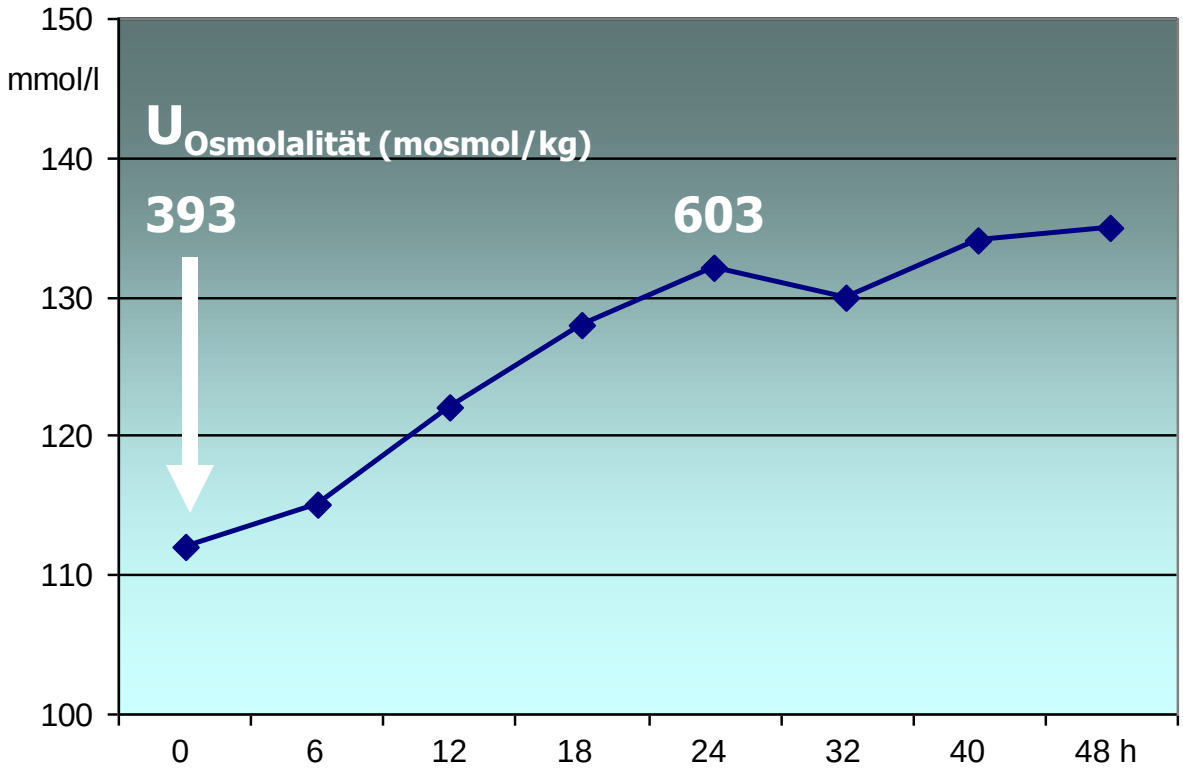
urine/serum-Osmolality

Mrs B.A, 1937: Sodium 112 mmol/l
osmolality i.S. 248 / i.U. 393 mosmol/kg





Follow-up: Na^+



SIADH =

S-Na^+ and -Osmo ⇩
(<280 mosmol/kg)

U-Osmo ⇧
(>100 mosmol/kg)

Euvolemia
Normal kid/adr/thyr

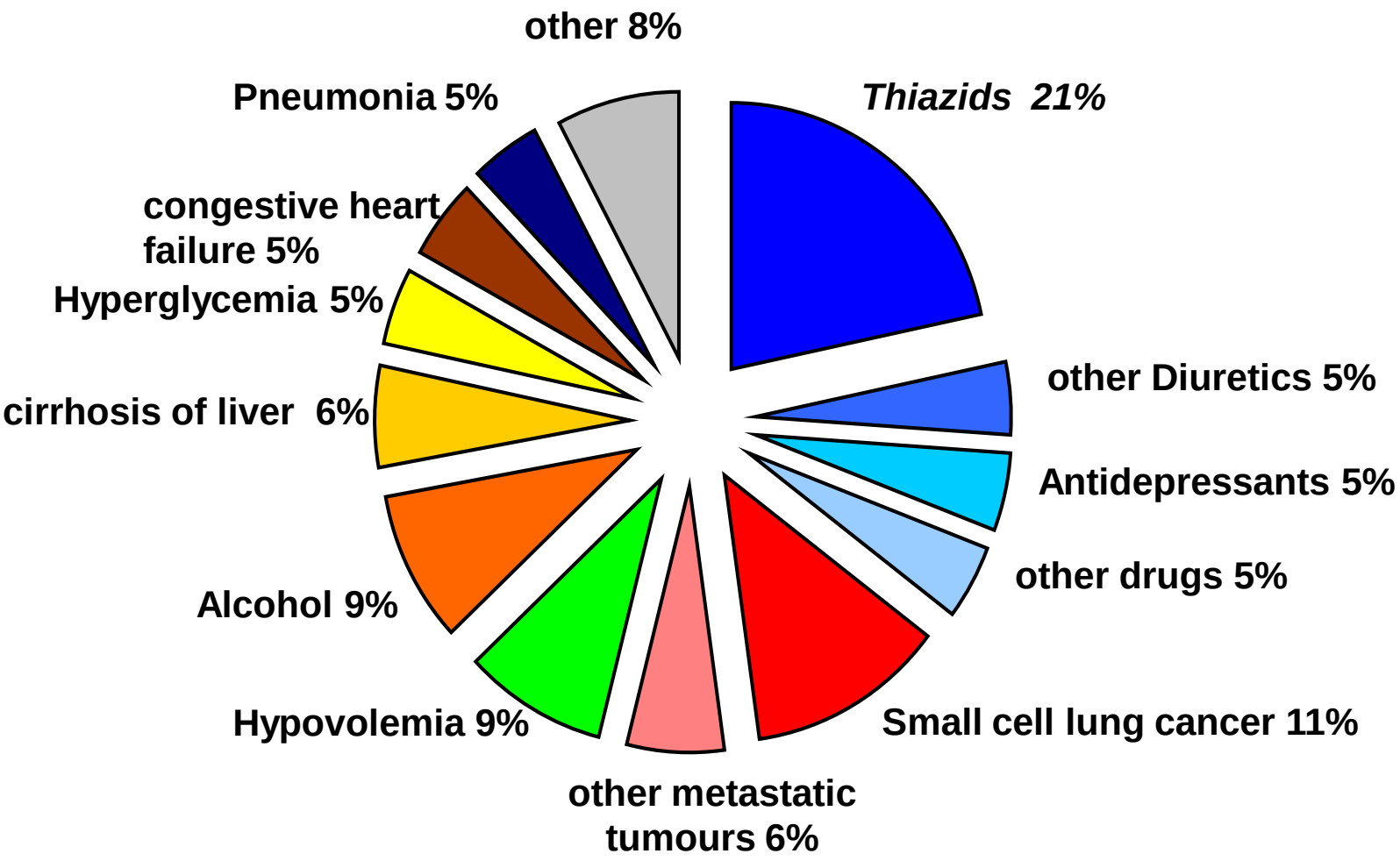
slow correction:

stop drugs, fluid restriction (0.8L/d)

NaCl 0.9% slowly i.v. → maximum increase of sodium 12 mmol/l 24h!

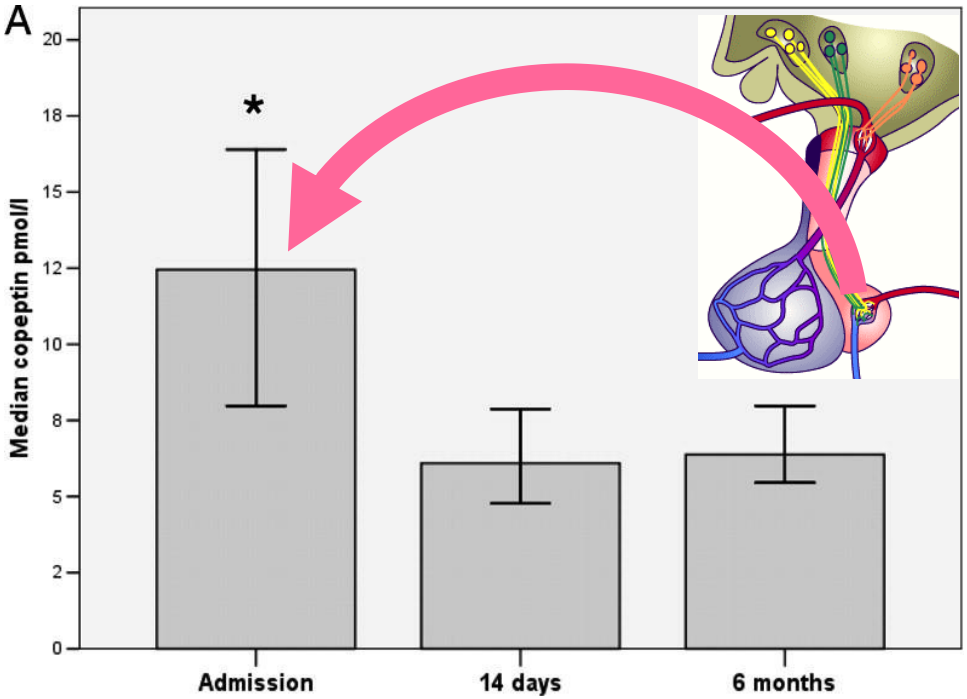
Medical tx: Urea, Lithium, Demeclocyclin

Retrospective analysis of severe hyponatriemia (n=65)



Copeptin in acute illness

Copeptin concentrations in patients with AECOPD (n=167)



Stolz D, Christ-Crain M et al, Chest 2007;131:1058-