



THE UNIVERSITY OF  
**CHICAGO**  
MEDICINE &  
BIOLOGICAL  
SCIENCES

# 56 F with HIV who presents with lethargy

Endorama 6/30/16  
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**Dr. Jain** does not have any relevant financial relationships with any commercial interests.

# HPI

- 56 F woman currently admitted for acute on chronic pancreatitis
- Recent, prolonged admission for Cryptococcosis meningitis (more details forthcoming)
- Noted to be lethargic and hyponatremic. 6 AM cortisol checked on back-to-back days:  
5/2 - 1.3 ug/dL  
5/3 - 2.1 ug/dL
- Endocrinology consulted for further management.

# Extended History

**PMH:** HIV/AIDS (CD4 12), Cryptococcosis, Pancreatitis, Heroin use

**Past surgical Hx:** Traumatic leg fracture with rod/pin placement

**Fam Hx:** Non-contributory

**Social History:** Heroin user, previously in a methadone clinic, last use was day of admission. EtOH 2-3x weekly, last use day before admission. Tobacco ½ ppd - 20 years

**Medications:** emtricitabine-tenofovir, lopinavir-ritonavir, raltegravir [compliance?], azithromycin, fluconazole, bactrim, tramadol, methadone

# Recent Admission

- Patient recently admitted 1/5 – 3/3 for cryptococcosis and cryptococcal meningitis requiring serial LPs and lumbar drain for elevated intracranial pressures.
- Completed 3 weeks of Amphotericin and transitioned to fluconazole. Also started on HAART during previous admission after found to have a CD4 count of 1.
- Discharged to rehab, returned home to live with daughter 3 weeks ago. Patient's daughter reports patient was doing well for one week, but then two weeks ago began complaining of back and leg pain, and has become increasingly more lethargic over last week.

# Physical Exam

Vitals T 36.7, BP 103/73, P 93, R 16, BMI 20.1

Gen: Alert, awake, no acute distress

HEENT: Oropharynx clear

Neck: No thyromegaly, no acanthosis nigricans

CV: Tachycardic, regular rhythm. No murmurs

Pulm: Normal respiratory effort, clear to auscultation

Abd: Soft, non-tender, no striae

MSK: Moving all extremities, no notable palmar crease darkness

Neuro/Psych: difficult to assess as patient nods head yes to all questions, does not respond to open-ended questions.

Skin: Warm, dry

# Other Labs/Imaging

1 PM: ACTH 22.1, Cortisol 1.5

128	100	17	100	4.0
4.4	17	1.8		
				2.6

**CT Head:** No evidence of intracranial hemorrhage, edema, or mass effect.

**CT Abd/Pel W:** Acute on chronic pancreatitis. Adrenal glands normal appearing

CODE: KABJUP to 773-245-0068

# ACTH Stim Test

	Time 0 → 250 ug cosyntropin	Time 30 mins	Time 60 mins
Cortisol (ug/dL)	1.0	2.9	4.0
ACTH	9.3		

# Etiologies?

## Etiologies of Adrenal Insufficiency in HIV

### **Primary**

Infections - CMV, Mycobacterium avium-intracellulare, TB, cryptococcosis, histoplasmosis, blastomycosis, toxoplasmosis, PCP

Malignancy – Kaposi sarcoma, non-Hodgkin lymphoma

**Secondary:** CMV, toxoplasmosis of the pituitary gland



# Adrenal Insufficiency and HIV

Often missed, as symptoms of AI are not dissimilar from HIV itself

Adrenal involvement is common in HIV/AIDS but doesn't necessarily correlate with symptoms or actual adrenal insufficiency

**Table 1. Autopsy studies of adrenal gland in HIV**

Reference	Number of Cases	CMV adrenalitis	Other Pathology <sup>a</sup>
Taper et al <sup>5</sup>	10	7	2
Guarada et al <sup>6</sup>	13	12	
Welch et al <sup>7</sup>	35	14	3
Glasgow et al <sup>8</sup>	41	21	13
Niedt et al <sup>9</sup>	54	29	
Bricaire et al <sup>10</sup>	88	44	9
Pulakhandam et al <sup>11</sup>	37	31	

<sup>a</sup> *M. tuberculosis, MAI, toxoplasmosis, cryptococcosis, KS, and adrenal infarction.*

*Adapted from Masharani and Schambelan.<sup>14</sup>*

# Further work up?

FSH 33.4

LH 20.0

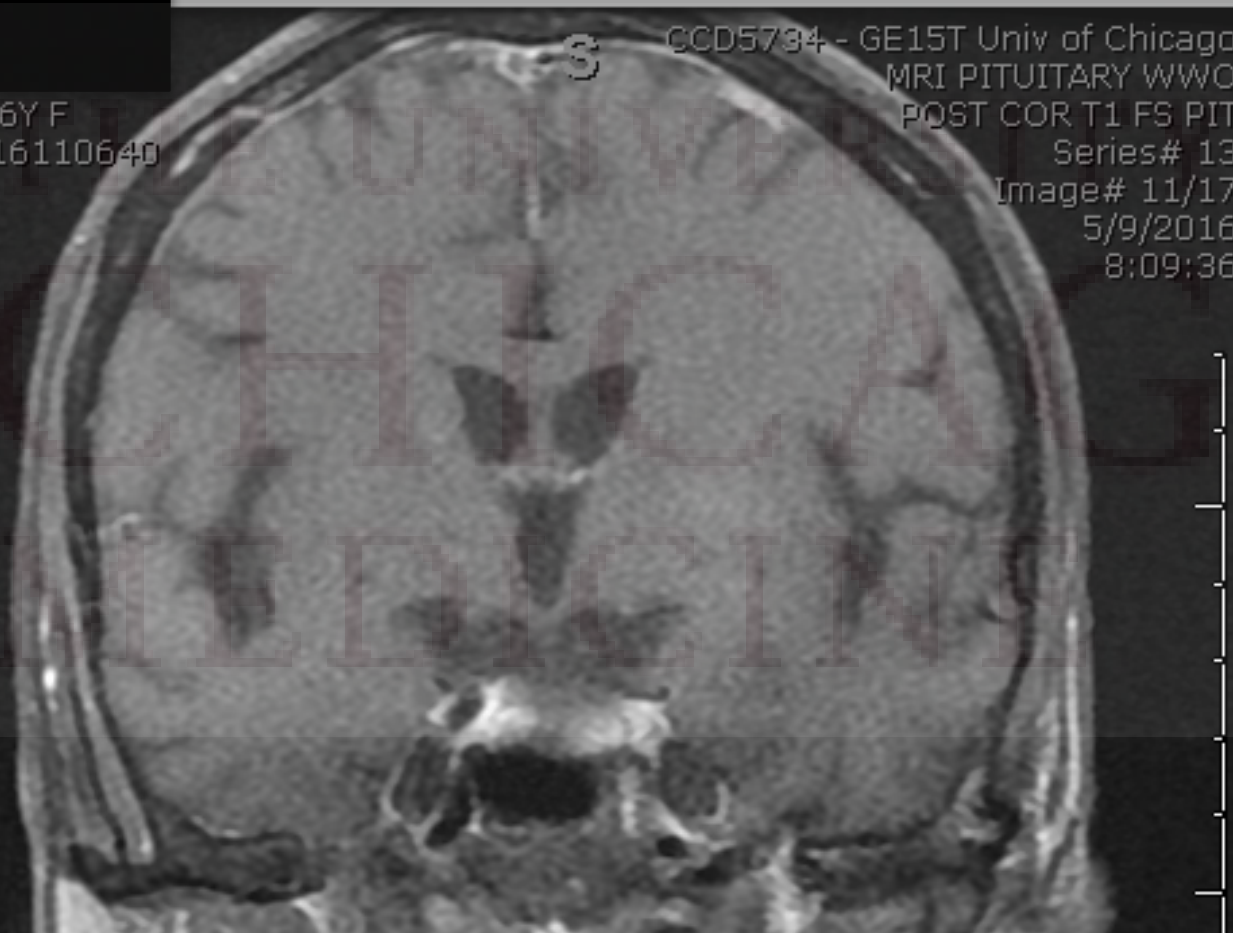
Prolactin 18.6

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# MRI Pituitary

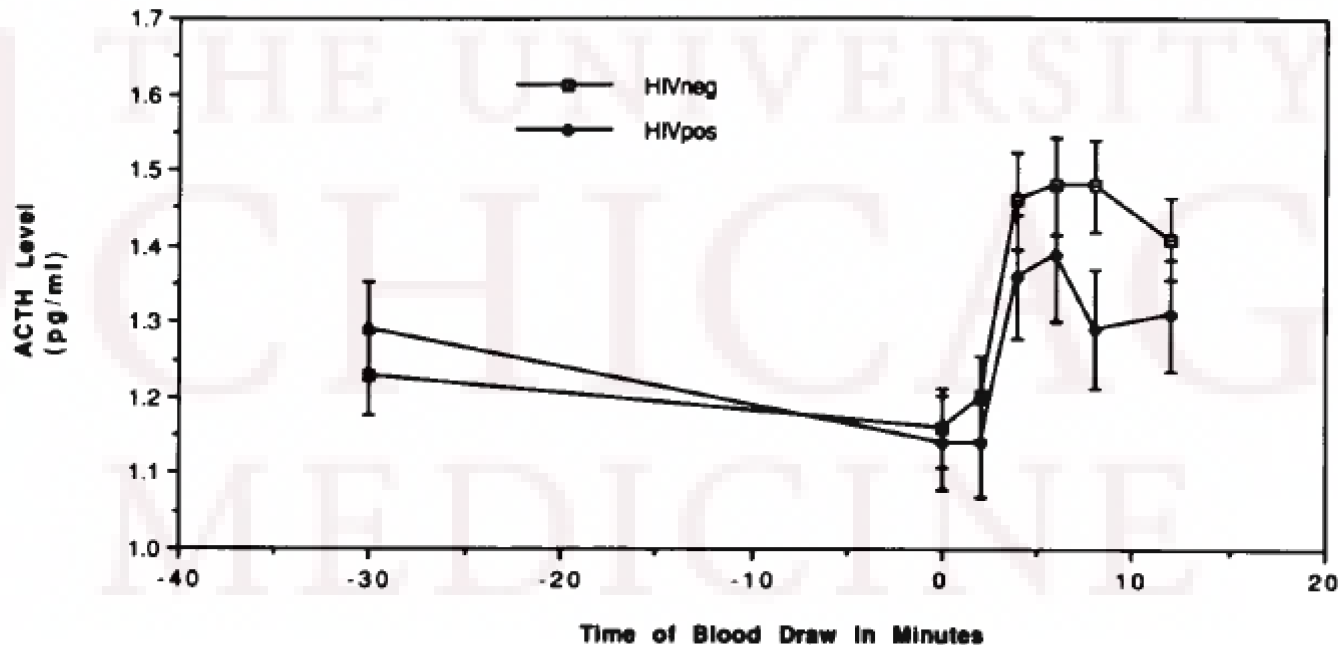
## **FINDINGS:**

The pituitary gland is appropriate in overall height and morphology. The infundibulum of the pituitary gland is midline. No suprasellar or intrasellar mass is identified. The cavernous sinuses are intact bilaterally. There is T1 and T2 signal hyperintensity centered in the right basal ganglia.

## **IMPRESSION:**

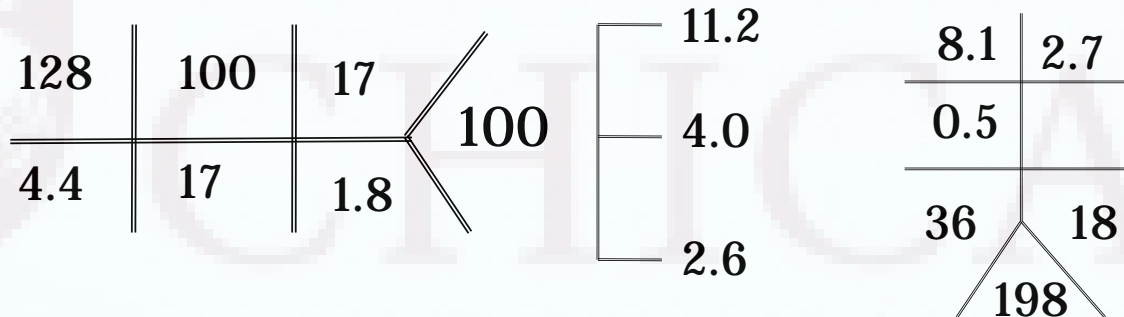
1. There is no pituitary mass or other abnormality that is appreciated.
2. A lesion is present in the right basal ganglia. It is not clearly defined on this exam. Given the suspicion for cryptococcal meningitis, this may be related to cryptococcal meningitis.

# HPA Axis dysfunction?



**FIG. 2.** Plasma ACTH response to cold pressor challenge in HIV-1 infection (values are presented as log pg/ml of plasma). Time of blood draw is represented as the number of minutes before and after the immersion of each subject's hand in ice water.

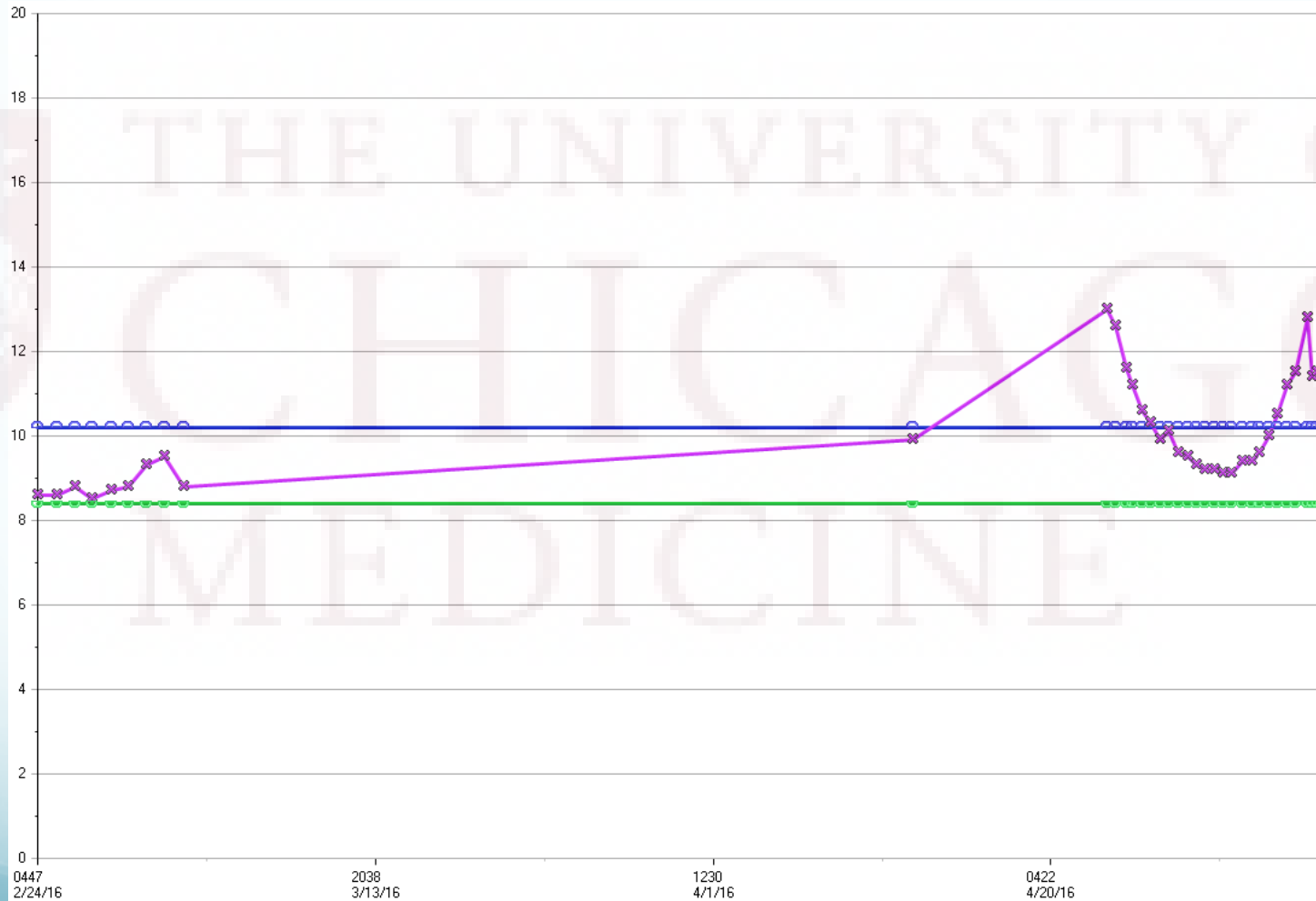
# About those labs...



GGT 179 (RR 11-163)

What other workup do you want?

# Calcium Trend



# Workup?

PTH 7

25-OH Vitamin D 13

PTHrp: 0.3 (WNL, Normal <2.0)

1,25-OH Vitamin D: Pending

SPEP/UPEP: No monoclonal protein

CODE: KABJUP to 773-245-0068



# Cryptococcus and hypercalcemia

- Case report of cryptococcal pneumonia leading to hypercalcemia over 40 months
- In that case, 1,25-OH Vitamin D had mean value of 40 (normal 15-50 pg/mL)
- Hypothesized it was not higher due to increased clearance, as 1,25-OH Vit D is important in maturation of lymphocytes

# Hypercalcemia and Granulomatous infection associated with HIV

- Can sometimes be associated with the start of HAART / immune reconstitution syndrome (IRIS)
  - Theorized that HAART allows HIV-infected patients to form functional granulomas
- Mycobacterium (Tuberculosis, Mycobacterium avium, etc), Brucellosis, nocardia, syphilis, toxoplasmosis, CMV, fungal infections (Cryptococcus, Candidiasis, Sporotrichosis, Histoplasmosis, Aspergillosis, Blastomycosis, etc)

# Imaging

CT CHEST ABDOMEN PELVIS WO

## **IMPRESSION:**

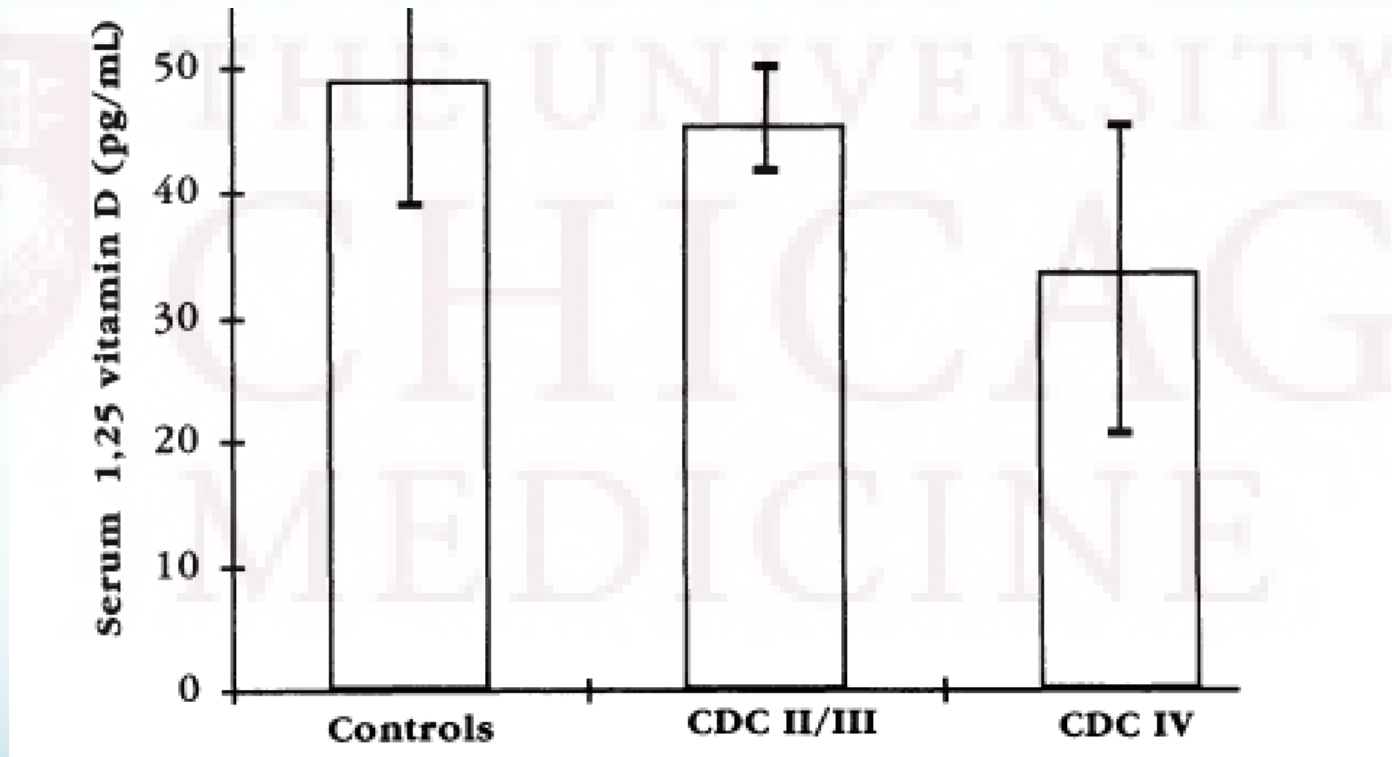
- 1. No peripancreatic fluid collection or pseudocyst as clinically questioned. Findings of chronic pancreatitis.**
- 2. Small left pleural effusion and associated atelectasis.**
- 3. Mildly prominent retroperitoneal lymph nodes are unchanged and can be seen in the setting of AIDS.**

- No granulomas!

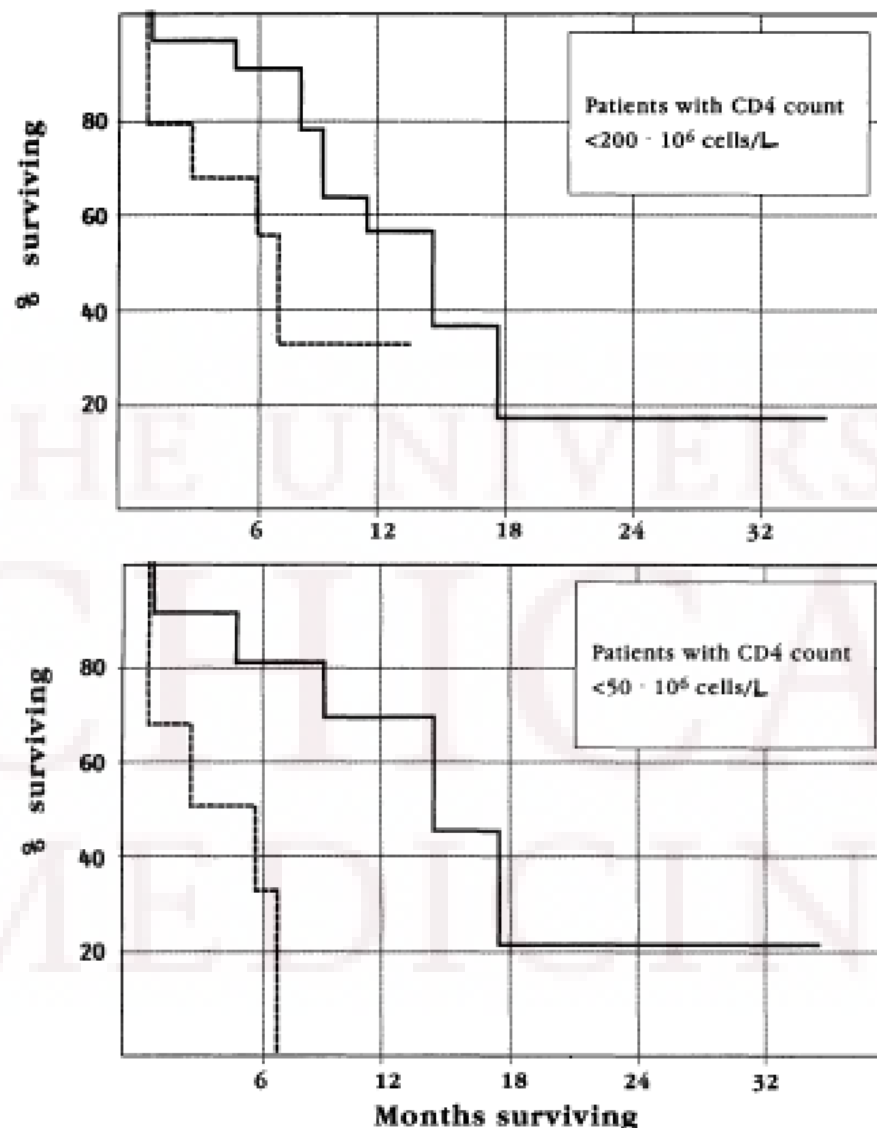
# Clinical Course Continued

- After discharge: 1,25-OH Vitamin D = 27 (RR 18-78)
- However, due to issues with getting an adequate sample for this lab, calcium had normalized (c8.7) by the time this was checked.

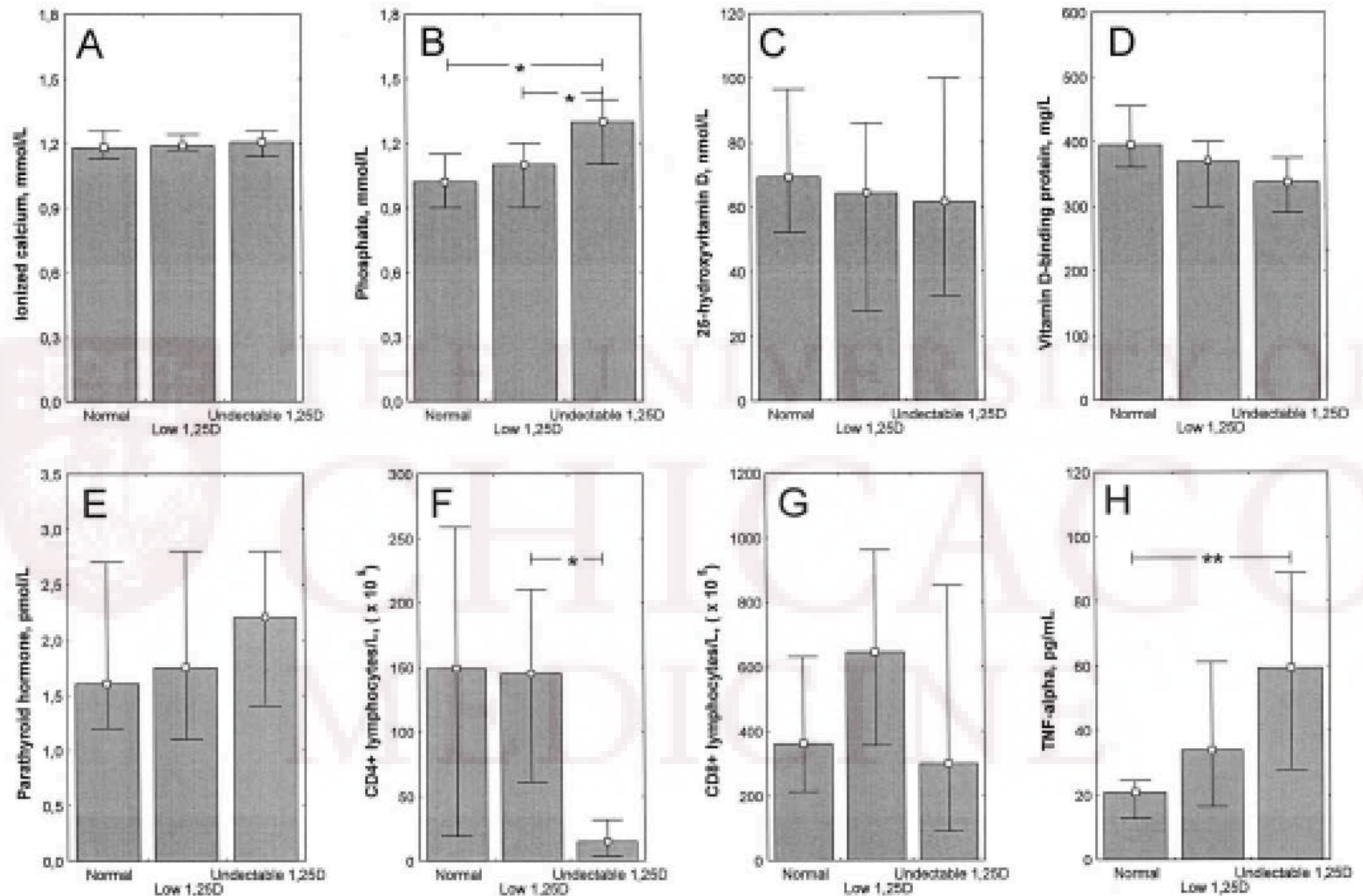
# 1,25 Vitamin D levels in HIV



Haug et al. Subnormal serum concentration of 1,25-Vitamin D in Human Immunodeficiency Virus Infection: Correlation with degree of immune deficiency and survival. J Inf Dis 1994

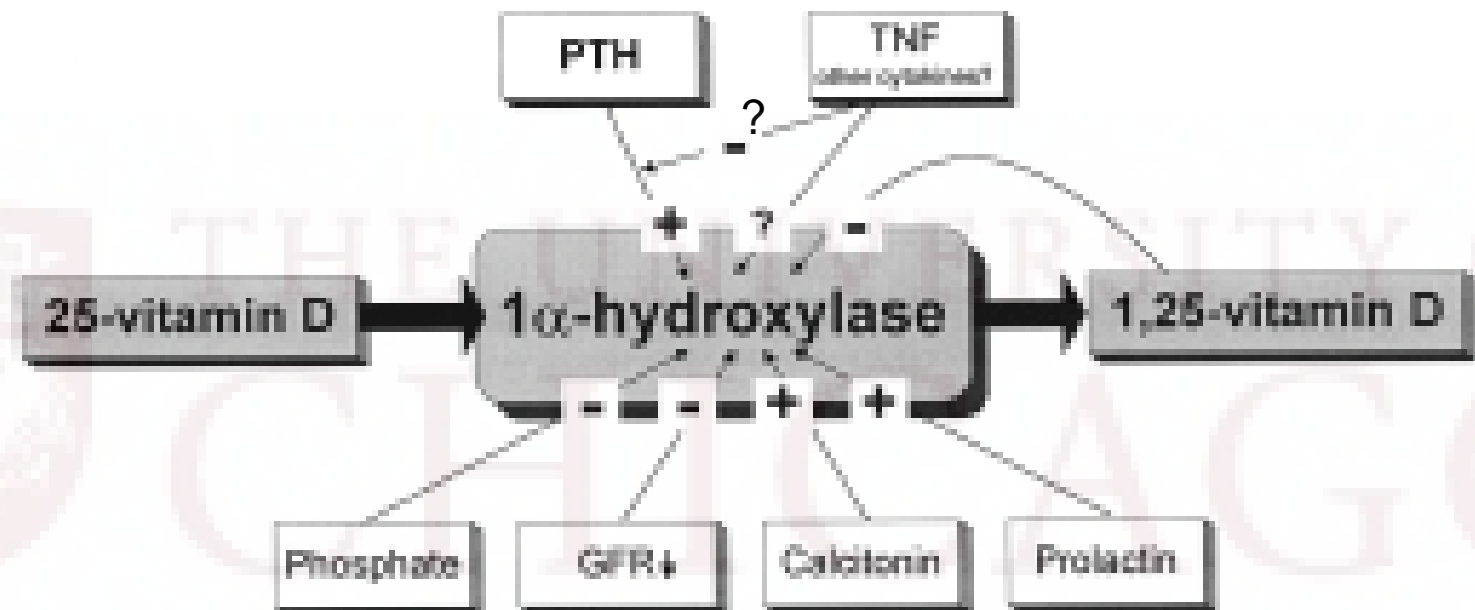


**Figure 2.** Kaplan-Meier plots of patient survival times according to serum levels of 1,25D. -----, group with levels <25 pg/mL ( $n = 9$ ); —, group with levels >25 pg/mL ( $n = 44$ ). Differences between groups in patients with CD4<sup>+</sup> cell counts of <200 × 10<sup>6</sup>/L ( $P < .05$ ) and patients with CD4<sup>+</sup> cell counts of <50 × 10<sup>6</sup>/L ( $P < .01$ ) were determined with log rank tests.



**FIG. 1.** Serum levels of vitamin D-related parameters, calcium-related parameters, and immunological parameters in HIV-infected patients with undetectable, low (below the 25th percentile of reference values), and normal serum levels of 1,25-(OH)<sub>2</sub>D. \*, Significant difference between the groups at the 5% level ( $P < 0.05$ ). \*\*, Significant difference between the groups at the 1% level ( $P < 0.01$ ).



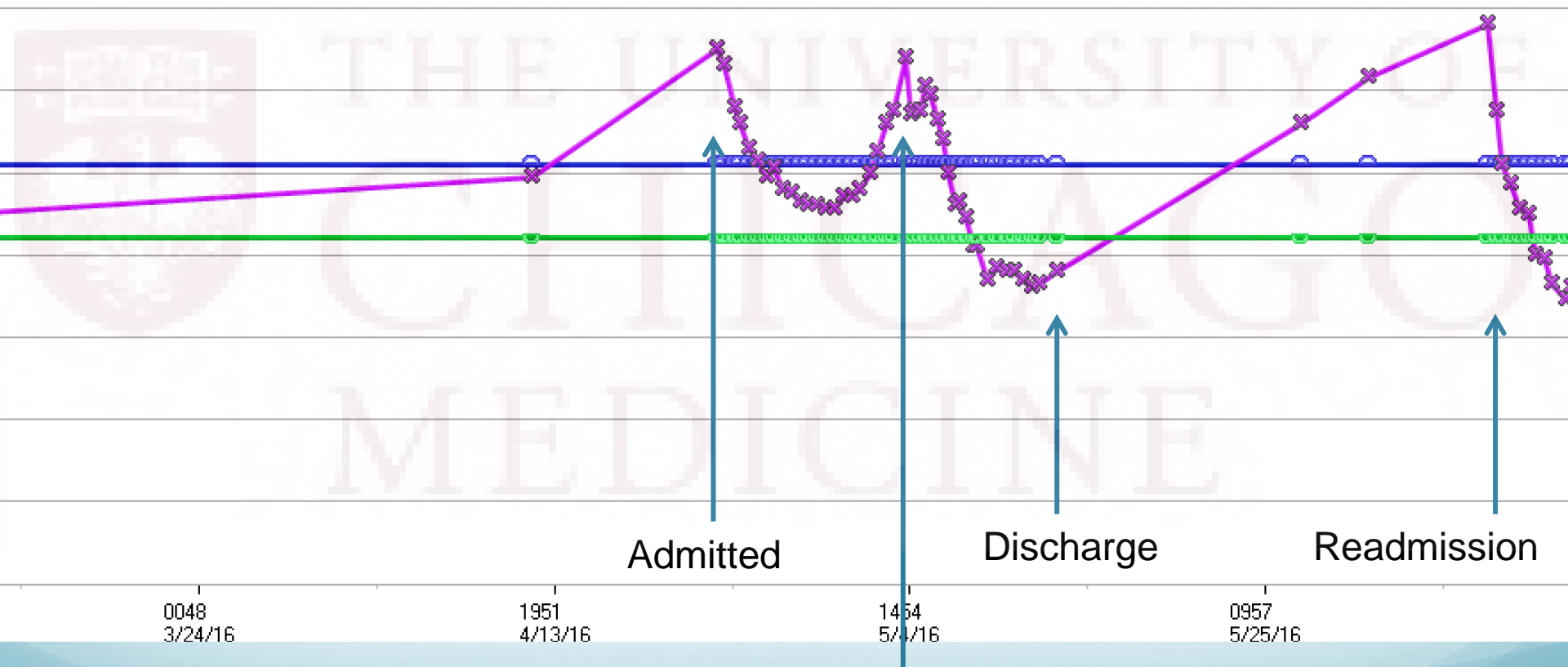


**FIG. 3.** The rate of  $1\alpha$ -hydroxylation of 25D to  $1,25-(\text{OH})_2\text{D}$  in the kidneys is tightly regulated. PTH, calcitonin, and prolactin stimulate hydroxylation, whereas  $1,25-(\text{OH})_2\text{D}$  itself, serum phosphate, and a low glomerular filtration rate (GFR) inhibit  $1\alpha$ -hydroxylase activity.  $\text{TNF}\alpha$  and possibly other cytokines may also inhibit hydroxylation.



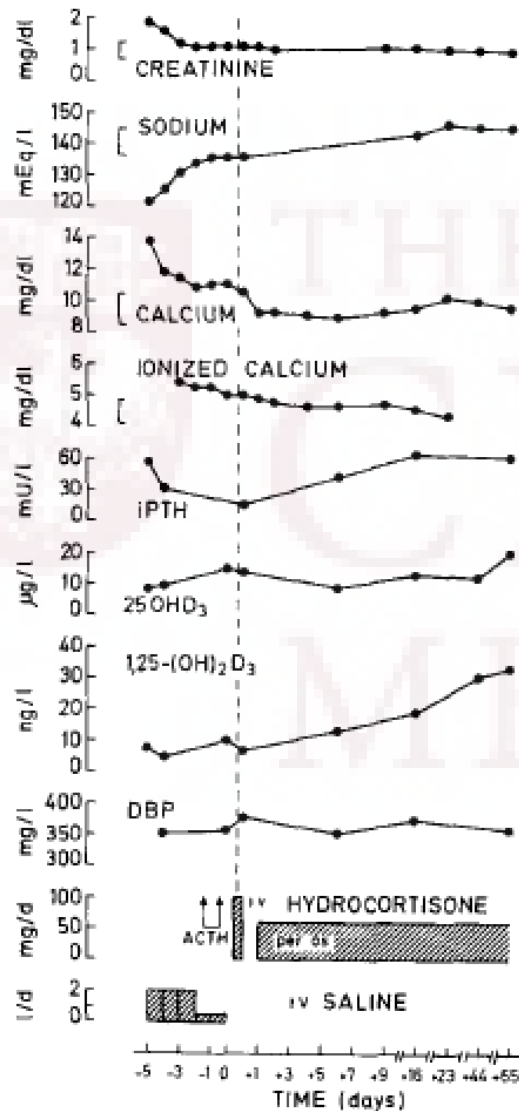
# Clinical Course Continued

- Presented back to UCMC with Calcium 13.6, Creatinine 3.0
- ID suspects she was not compliant with fluconazole and HAART
- LP showed high opening pressure concerning for recurrent cryptococcal meningitis. Cryptococcal Antigen later returned positive.
- Re-started on Amphotericin as well as IV fluids
- Calcium quickly downtrended

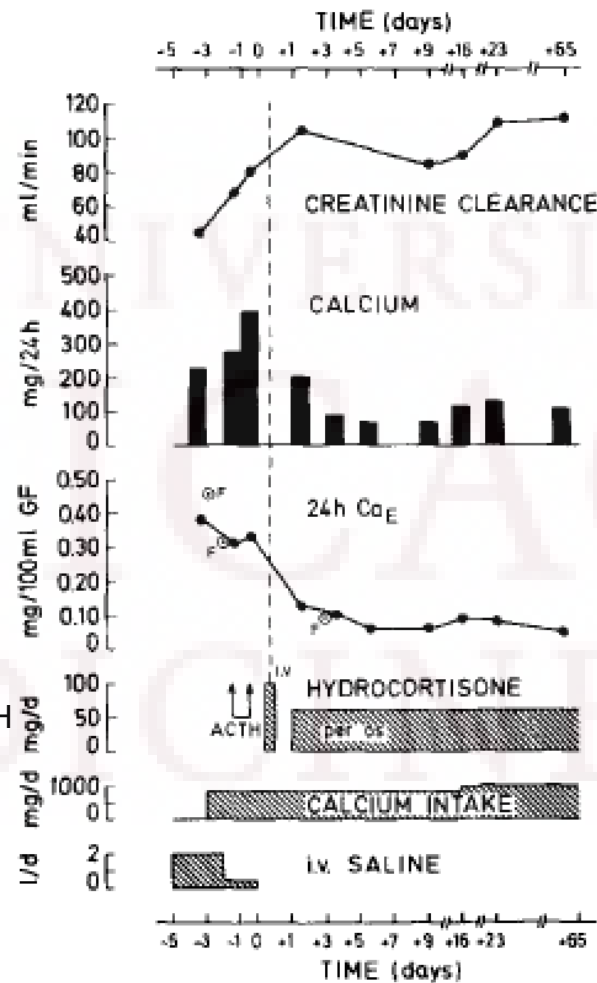


First day of  
Hydrocortisone

# Hypercalcemia and AI



Low 1,25-OH  
Vitamin D

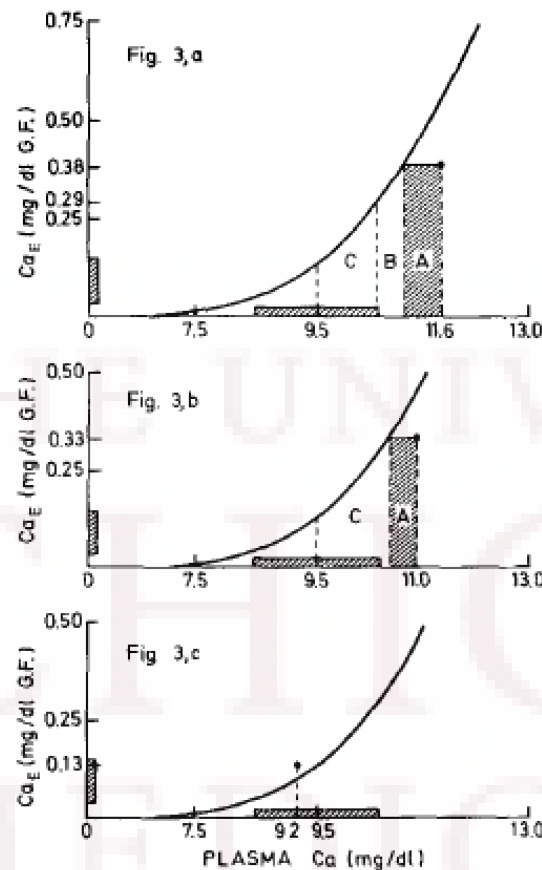


Elevated urine  
calcium but not as  
high as one might  
expect – tubular  
reabsorption of Ca

Oral calcium did not increase  
serum Ca

Fig. 2. Changes in creatinine clearance, 24 h urinary calcium output, and calcium excretion in mg/100 ml glomerular filtrate (Ca<sub>E</sub>). F indicates 2 h "fasting" Ca<sub>E</sub> values.

Fig. 1. Sequential changes in serum creatinine, sodium, total and ionized calcium, parathyroid hormone (iPTH), 25-hydroxy-



**Fig. 3.** The relation between 24 h  $Ca_E$  and plasma calcium. The solid line represents the relationship in normal subjects [Nordin et al. (11)]. The components of hypercalcemia are indicated by A (increased tubular calcium reabsorption), B (decreased glomerular filtration rate), and C (increased calcium input into the extracellular space). **a** Day -4 to -3, while the patient was volume depleted; **b** day -1 to 0, when volume depletion had been corrected by saline infusions; and **c** day +1 to +2 during hydrocortisone treatment (20 mg orally t.i.d.).

## *Case report*

### Hypercalcaemia in Addison's disease: calciotropic hormone profile and bone histology

- Low PTH, 1,25-OH Vitamin D levels
- Bone biopsies done in two patients with hypercalcemia related to Addison's disease – no signs of cell mediated bone resorption at trabecular surfaces; bone activity seemed to be suppressed
- Etiology presumed to be bone resorption but mechanism unclear

# Proposed etiology

- What is the etiology?
  - Volume Contraction
  - Adrenal insufficiency [?non-compliant with Hydrocortisone?]
  - ?25→1,25-OH Vitamin D mediated by cryptococcal meningitis that she was not being compliant with?
- Thoughts?

# References

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