European School of Internal Medicine
ESIM 2013
Clin Path Conference

Prof Ph JAEGER, MD, FRCP

Hon Chair of Nephrology

Royal Free & University College Medical School, London, UK

Invited Prof at the University of Geneva

Service of Nephrology, Department of Medical Specialties

University Hospitals of Geneva, CH

Multiple HYPOs

a transient bit of HYPER

a lot of fun to put all this together

\+ ----------

a typical case for internists

♀ *33 y.o.* *(1)*

-3 months: chaotic exit from her country

-2 months: progressive asthenia, muscle weakness (proximal muscles of lower limbs)

-1 week: can't walk anymore

-Day 0: Admission

°previously in good condition

°recent fatigue, loss of appetite, thirst +++, pollakiuria

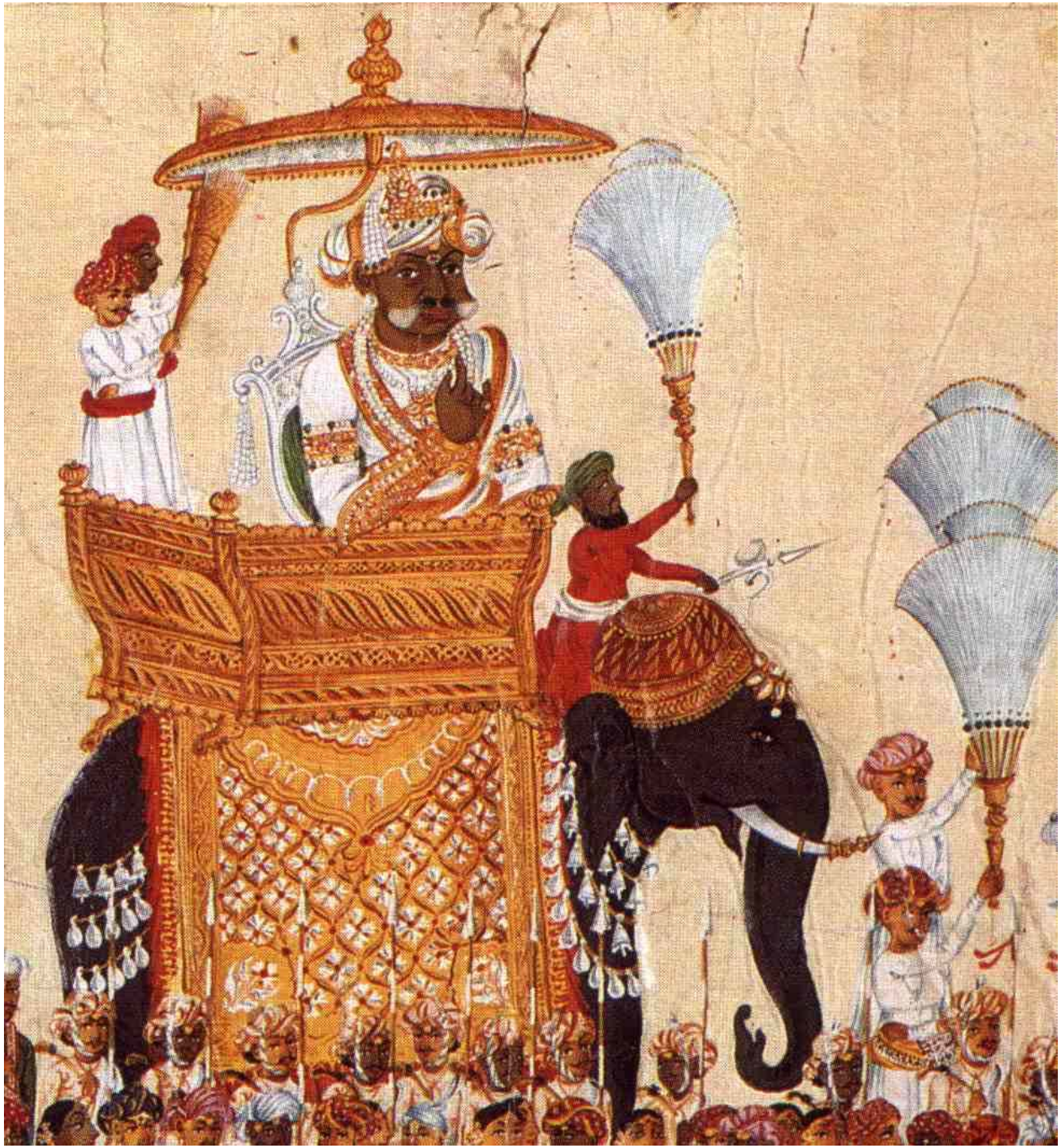
°family: diabetes (father + 2 aunts)
2 children (12, 10 y.o. in good cond.)

♀ *33 y.o.* *(2)*

Admission: Physical Examination

T 37°5, Pulse 104b/min, Resp 25/min
P 130/100 mm Hg
42.7 kg for 162 cm

Hand tremor, signs of marked nervosity
Teguments dry
Thyroid: not tender, firm,
Slightly + symmetrically enlarged
No Grave's ophtalmopathy
Thermophobia



Young woman
Family history of diabetes
Asthenia + Muscle weakness
Pollakiuria + Thirst

Tachypnea

DIABETES MELLITUS 1 ?

+ KETO-ACIDOSIS ?

Urine:

glucose neg
specific gravity 1005
U-pH 6.83

Serum:

glucose 5.2 mM
PO2 143 mmHg
PCO2 26.0 mmHg
HCO3 12.9 mM
BE -15.1 mM
pH 7.25
Na 138 mM
Cl 116 mM
Anion Gap 9 mM

Creatinine Clearance 58 ml/min

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glucose neg
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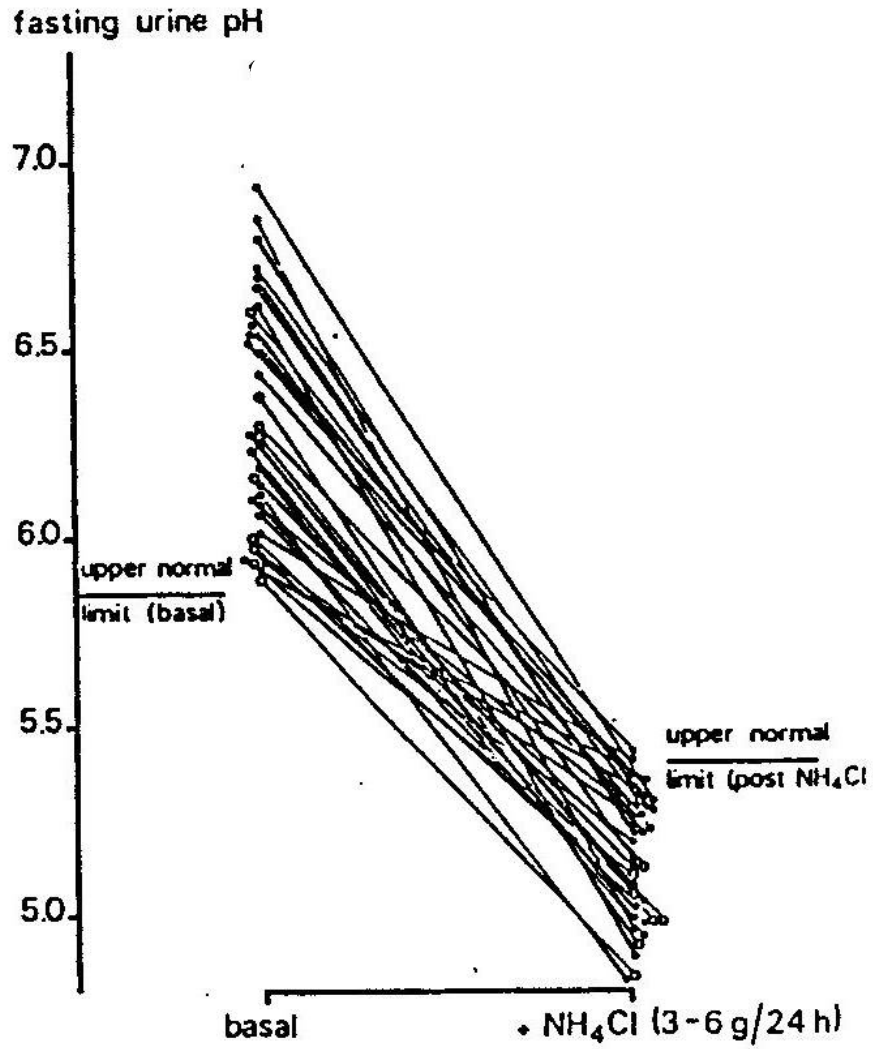
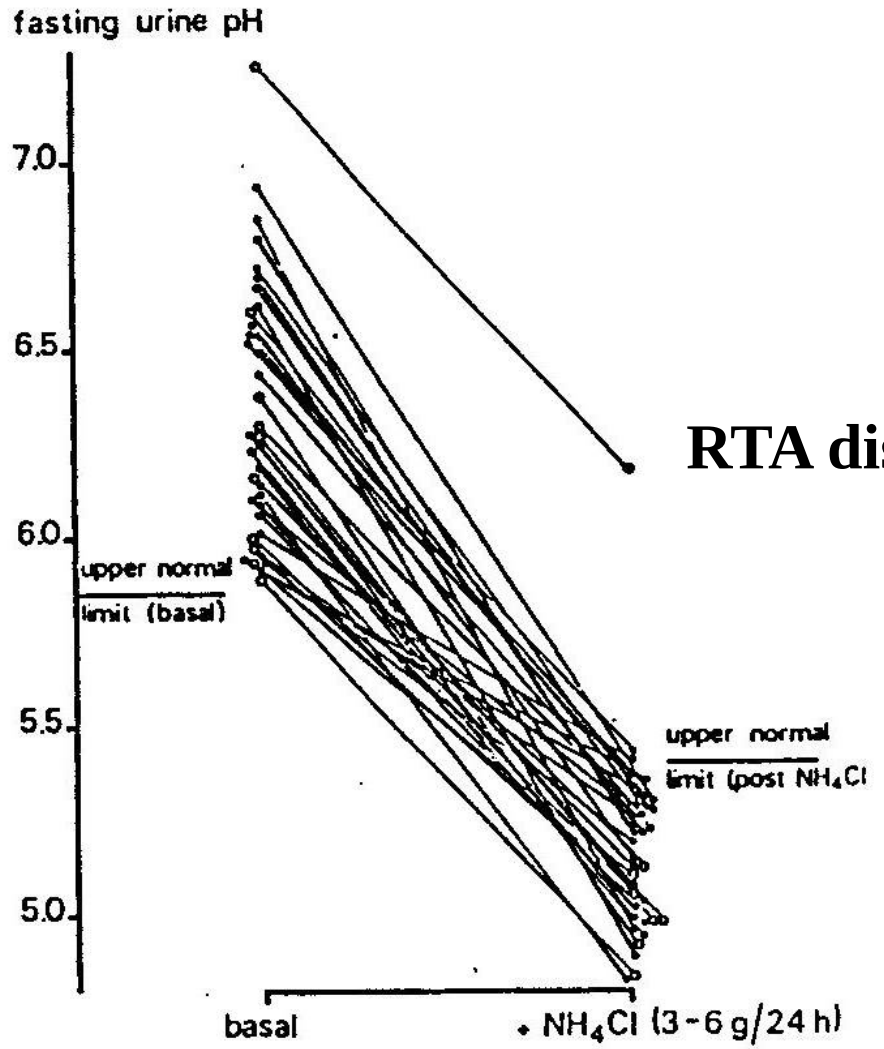

fasting urine pH
7.0
6.5
6.0
5.5
5.0
upper normal limit (basal)
upper normal limit (post NH4Cl
basal
+ NH4Cl (3-6 g/24 h)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upper normal limit (basal)
upper normal limit (post NH4Cl
basal
NH4Cl (3-6 g/24 h)

RTA dist

U-pH 6.83
S-HCO3 12.9 mM

?

NH4Cl loading 0.1 g/kg/30 min
U-pH 6.88
S-HCO3 7.9 mM

RTA dist

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Pollakiuria + Thirst

Hypo-P ?

Young woman

Family history of diabetes

Asthenia + Muscle weakness

Pollakiuria + Thirst

S-P 1.0 mM

Young woman

Family history of diabetes

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Hypo-K ?

Young woman
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Pollakiuria + Thirst

Hypo-K

S-K 2.3 mM

Young woman
Family history of diabetes
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Hypo-K

S-K 2.3 mM
FE-K 29.3 %

Young woman
Family history of diabetes
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Hypo-K

S-K 2.3 mM
FE-K 29.3 %

Renal leak of K

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Family history of diabetes
Asthenia + Muscle weakness
Pollakiuria + Thirst

S-K 2.3 mM
FE-K 29.3 %

Hypo-K

Renal leak of K

Young woman
Family history of diabetes
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Hypokalemia

S-K 2.3 mM
FE-K 29.3 %

Renal leak of K

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Family history of diabetes
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Hypokalemia

S-K 2.3 mM
FE-K 29.3 %

Renal leak of K

ALKALOSIS	NL ACID-BASE STATUS	ACIDOSIS
diuretics	deficit in Mg	prox RTA
hyperaldosteronism		dist RTA

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NDI

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S-K 2.3 mM
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Creatinine Clearance 58 ml/min

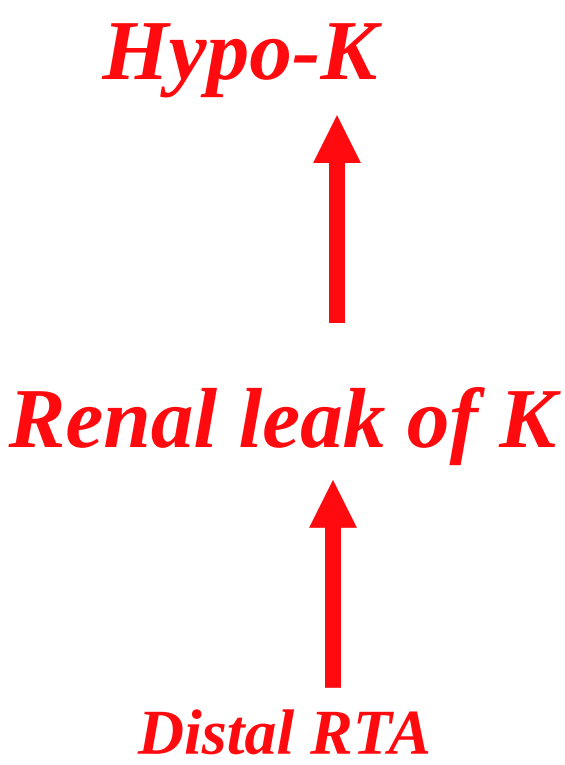
FE-K 29.3 %

Renal leak of K

Distal RTA

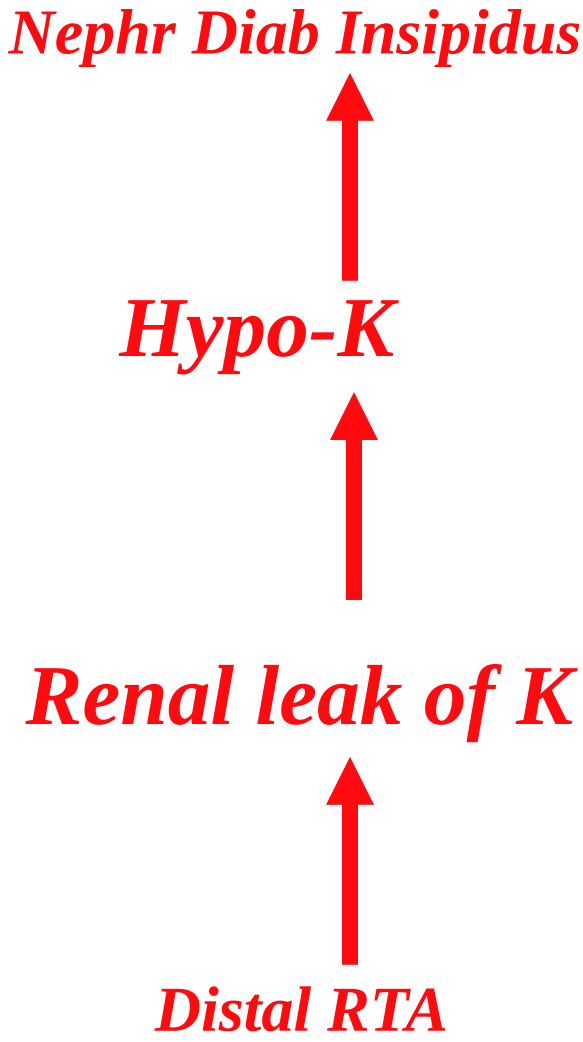
Asthenia + Muscle weakness (?)

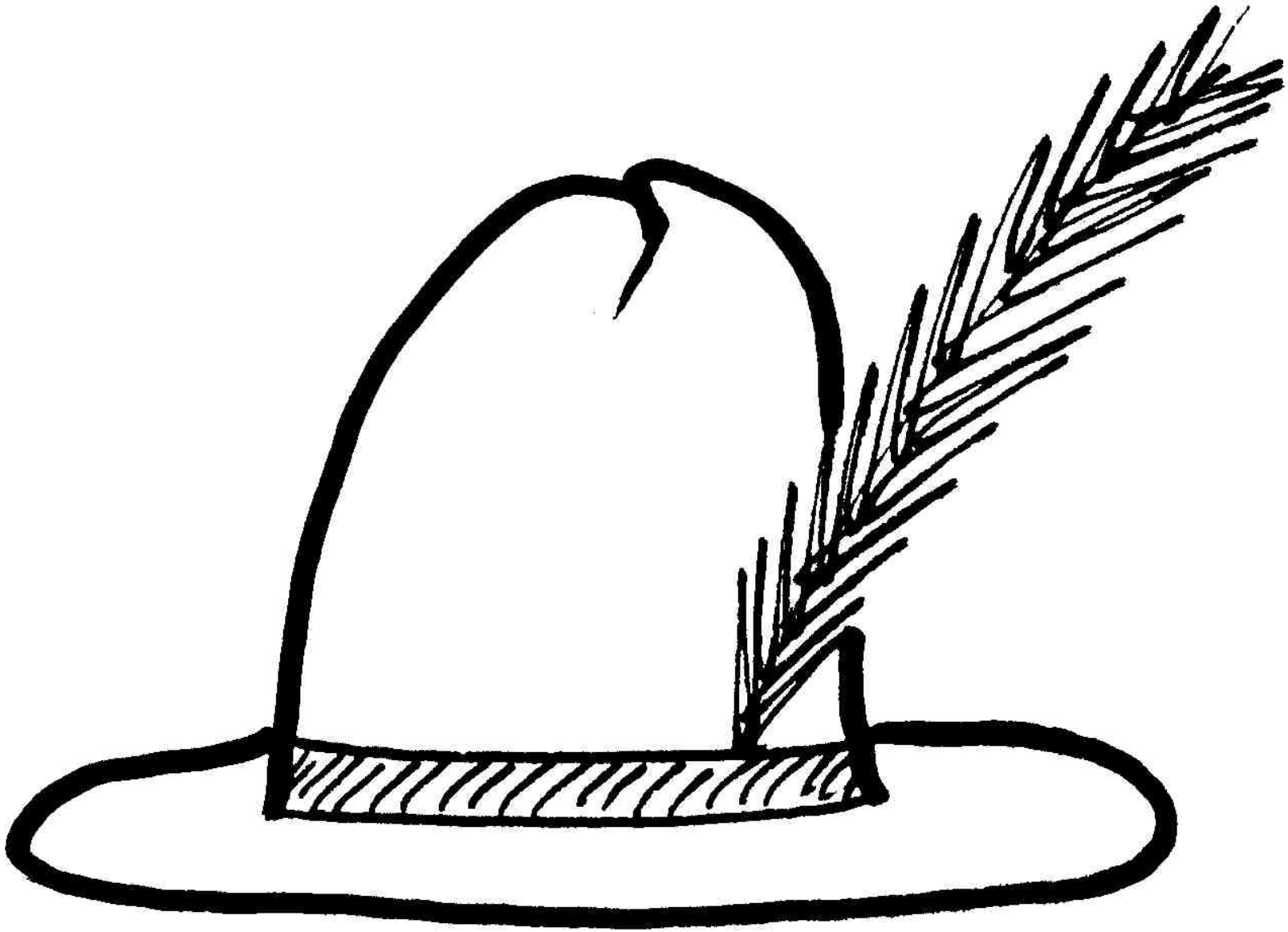
S-K 2.3 mM
FE-K 29.3 %

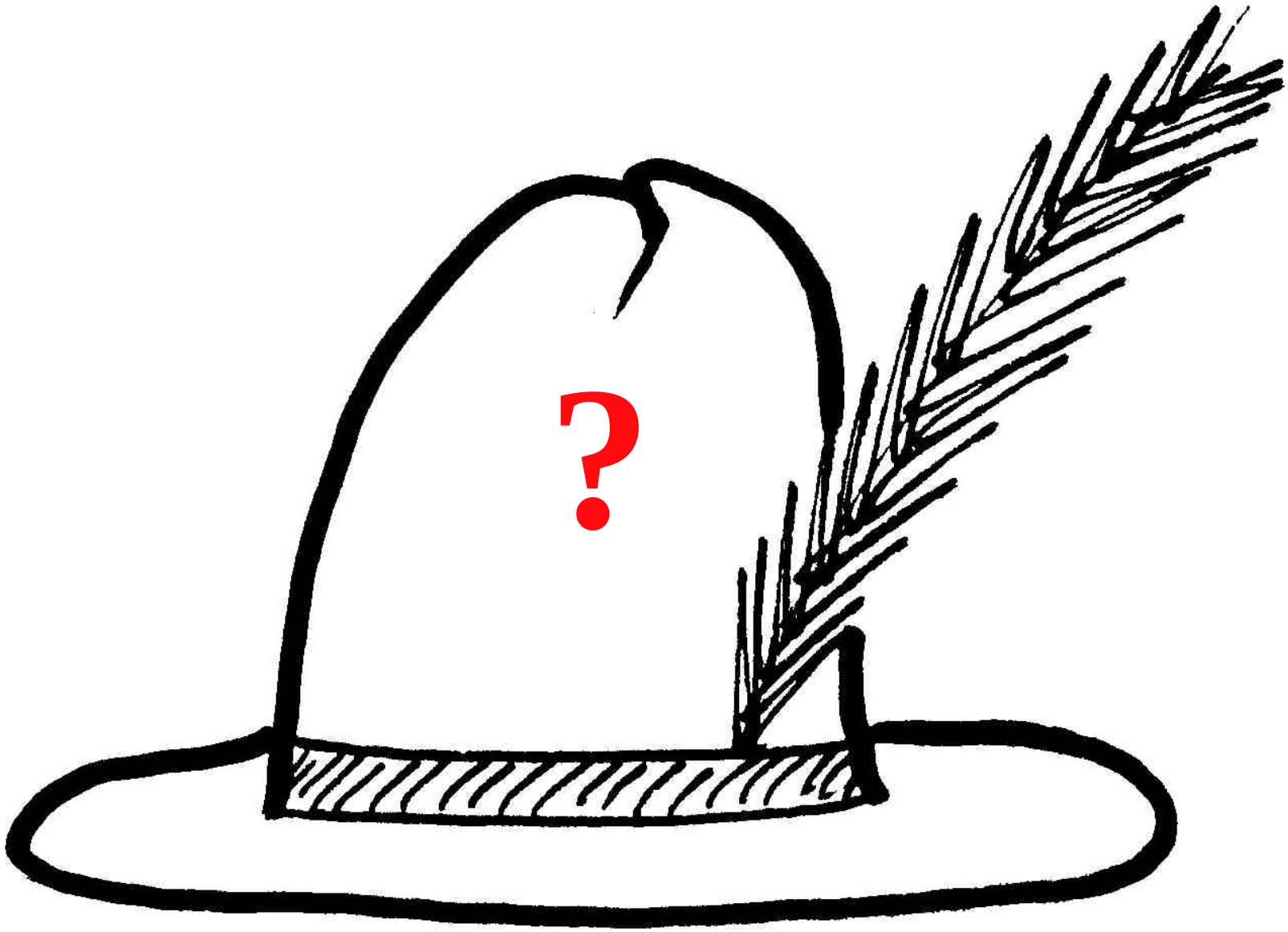


Asthenia + Muscle weakness
Pollakiuria + Thirst

S-K 2.3 mM
FE-K 29.3 %
U-spec grav 1005
Total S-Protein 93 g/l







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Thermophobia

Thyroxine nmol/l (n 68-160)	**203**
Triiodothyronine resin, % (25-35)	**30**
TSH, µU/ml (0.5-5)	**0.2**

I. Hyperthyroidism

AB antithyroglobulin	**1/75’000**
AB antithyroid microsomes	**1/75’000**
Scintigraphy: 131-I uptake	**< 1%**

Silent thyroiditis

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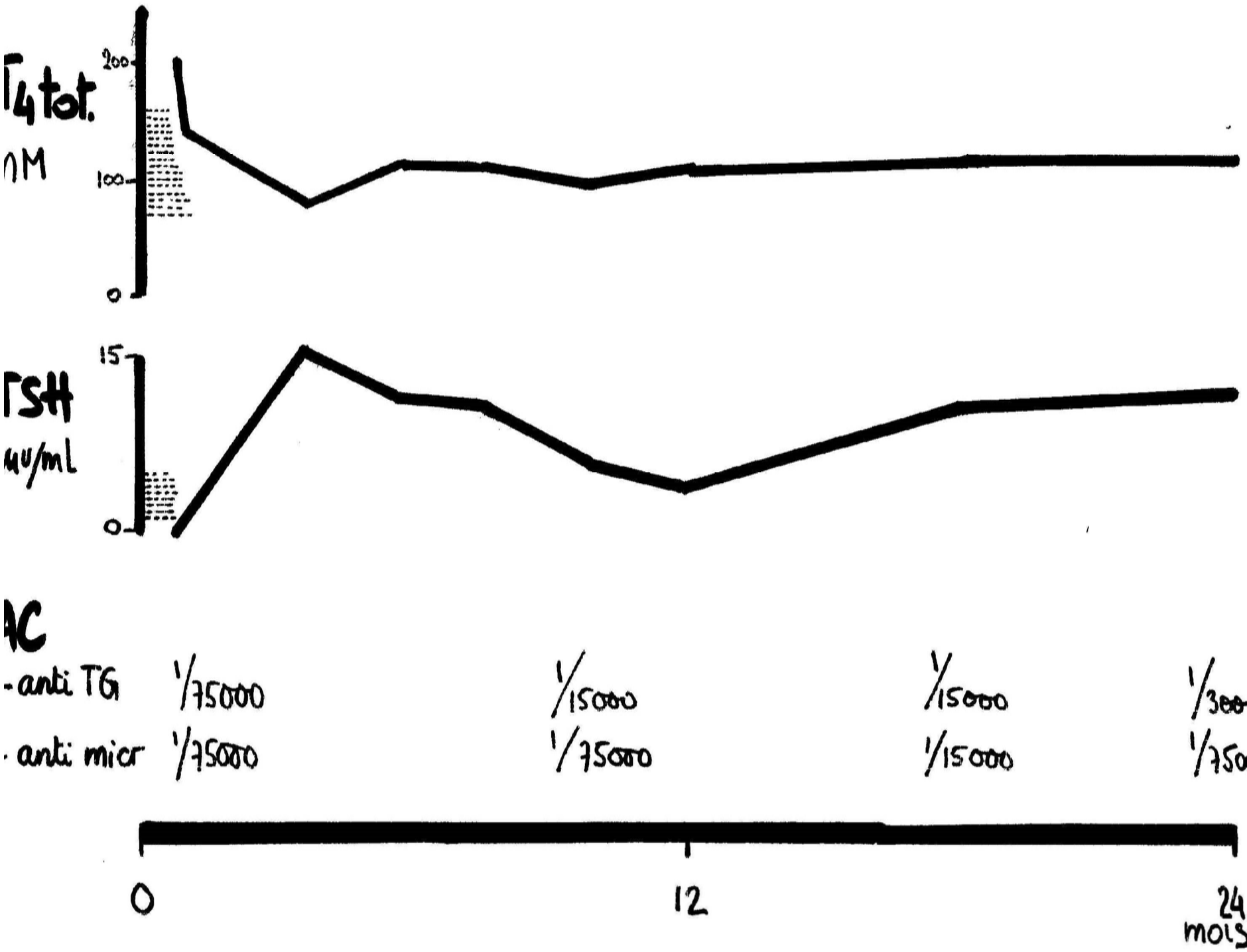
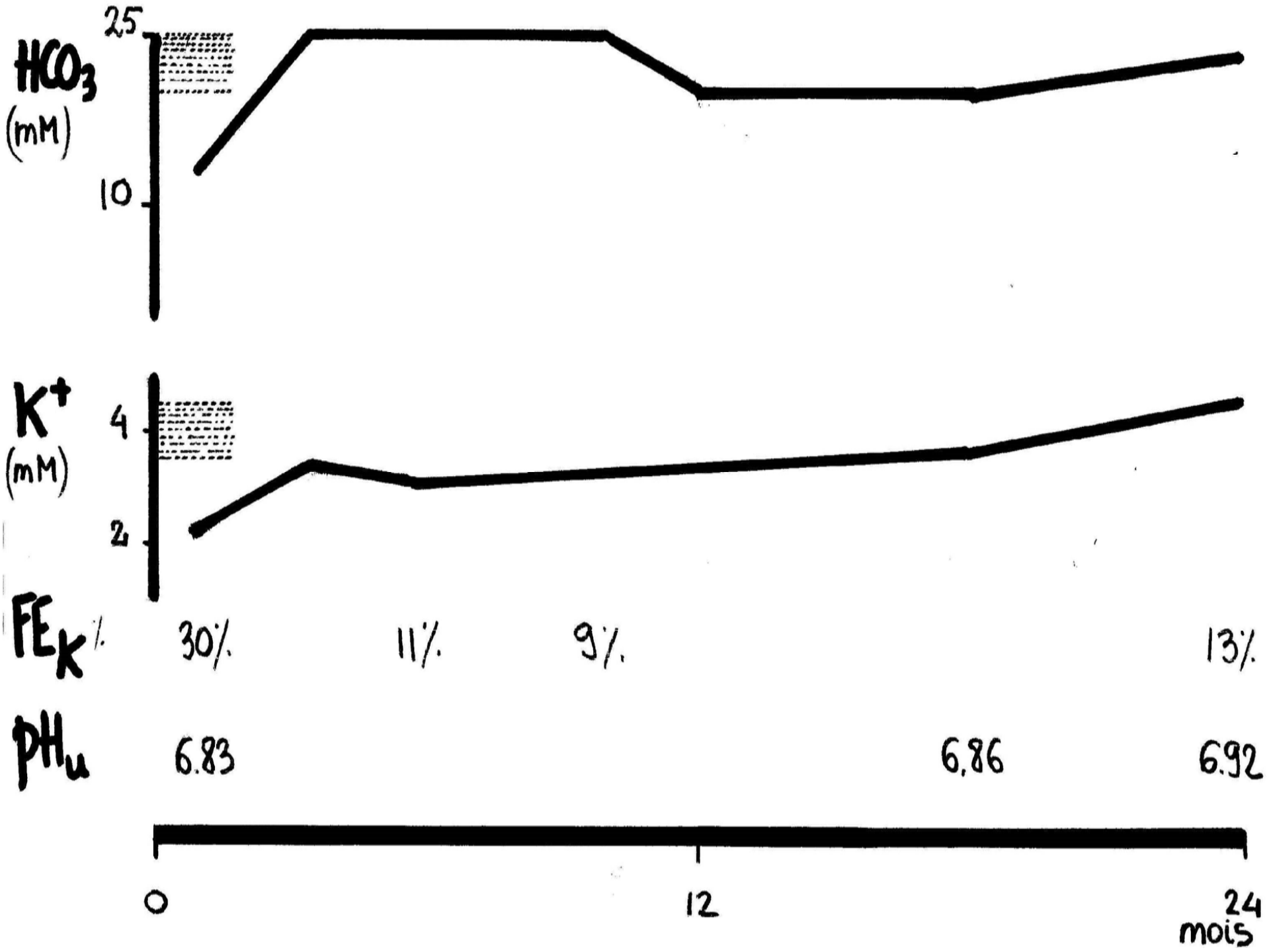

T4 tot.
nM
200
100
0
TSH
µU/ml
15
0
AC
- anti TG 1/75000 1/15000 1/15000 1/3000
- anti micr 1/75000 1/75000 1/15000 1/75000
0
12
24
mois


HCO3 (mM)
25
10
K+ (mM)
4
2
FEK %
30%
11%
9%
13%
pHu
6.83
6.86
6.92
0
12
24
mois

20 years later…

Hypothyroidism

Incomplete RTA (distal)

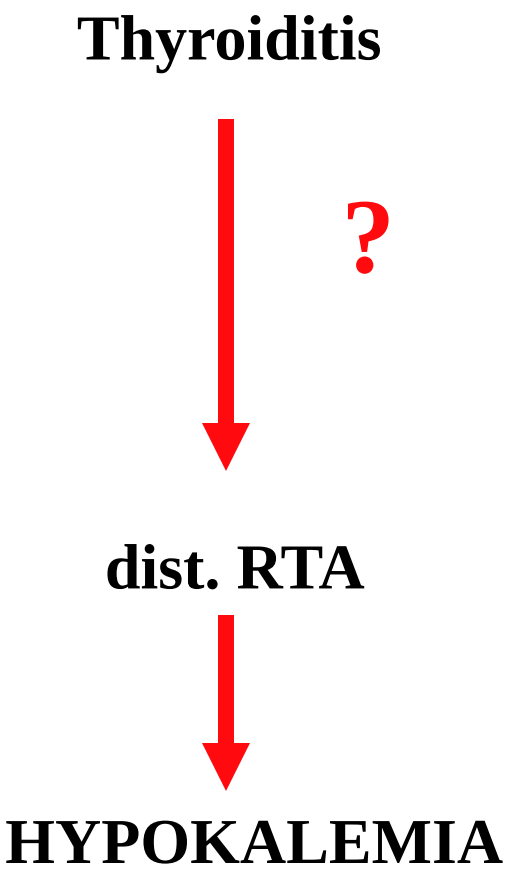
Renal stone disease

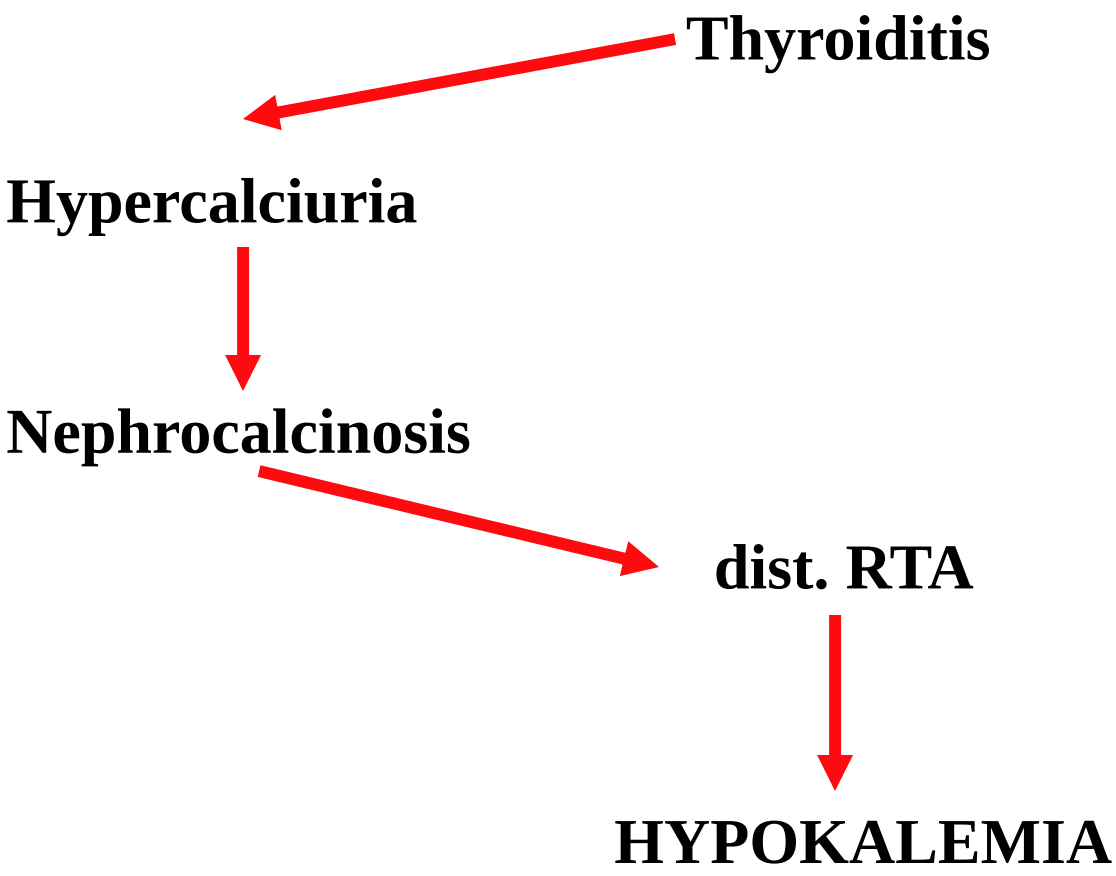
Suspicion of nephrocalcinosis

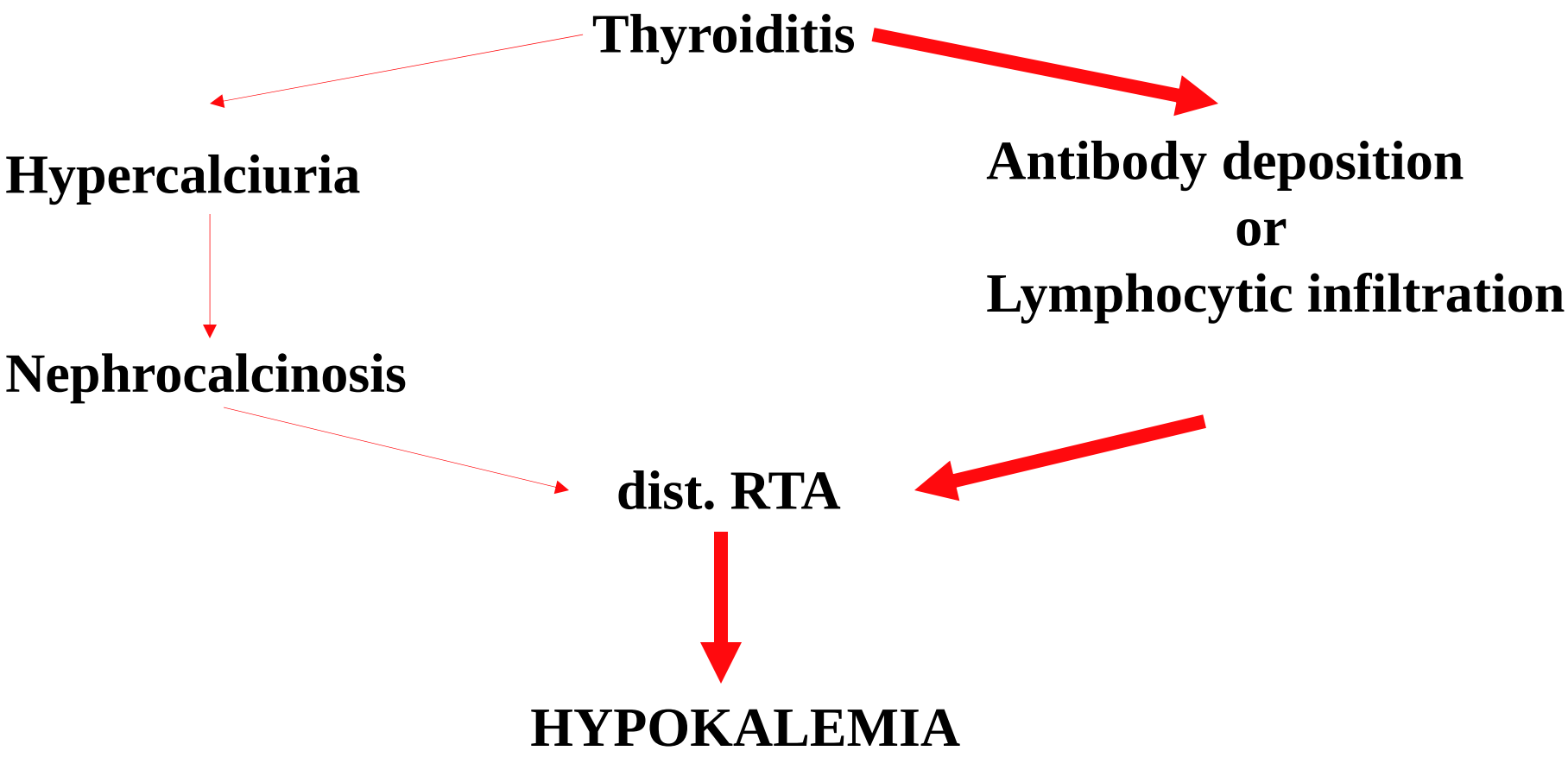
Thyroiditis

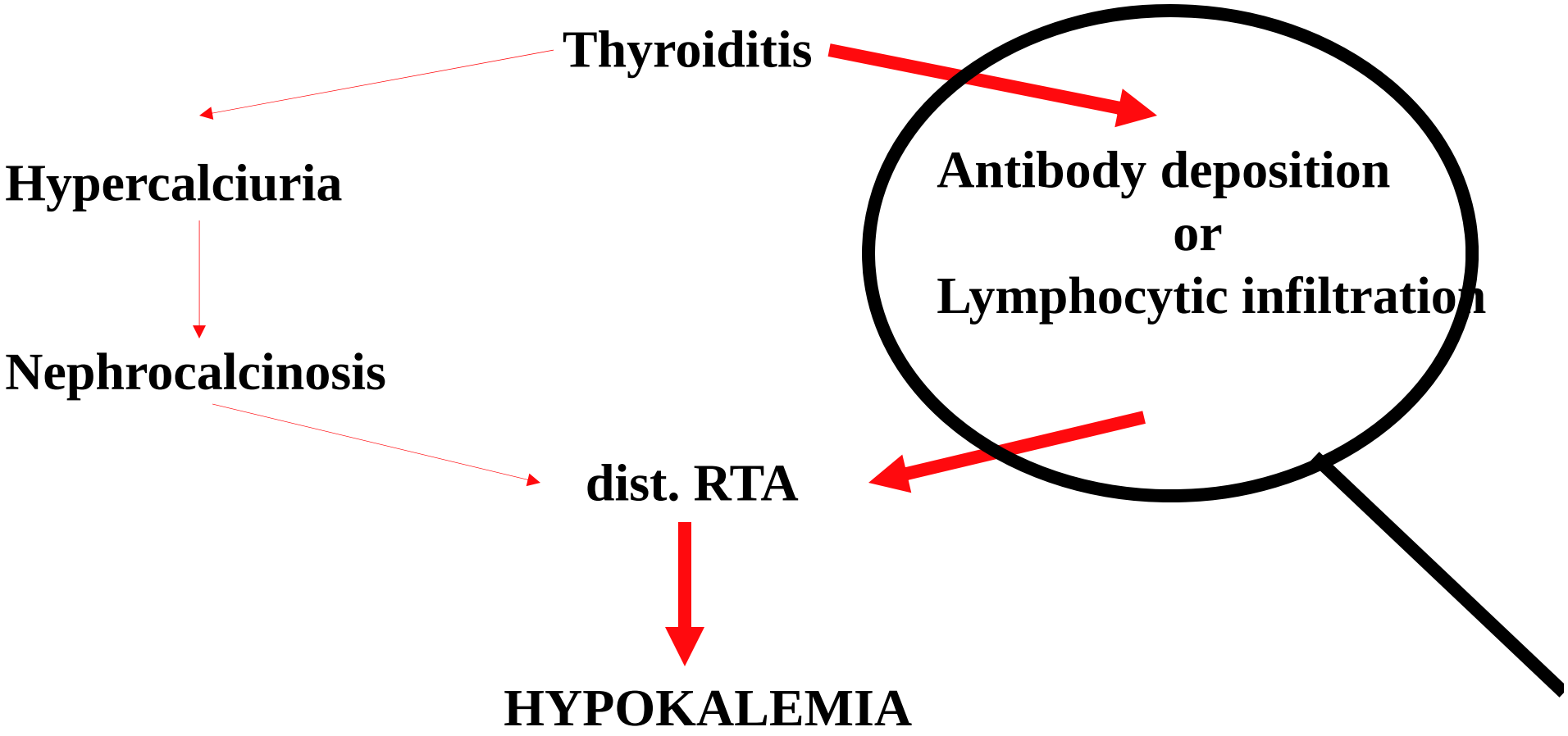
dist. RTA

HYPOKALEMIA

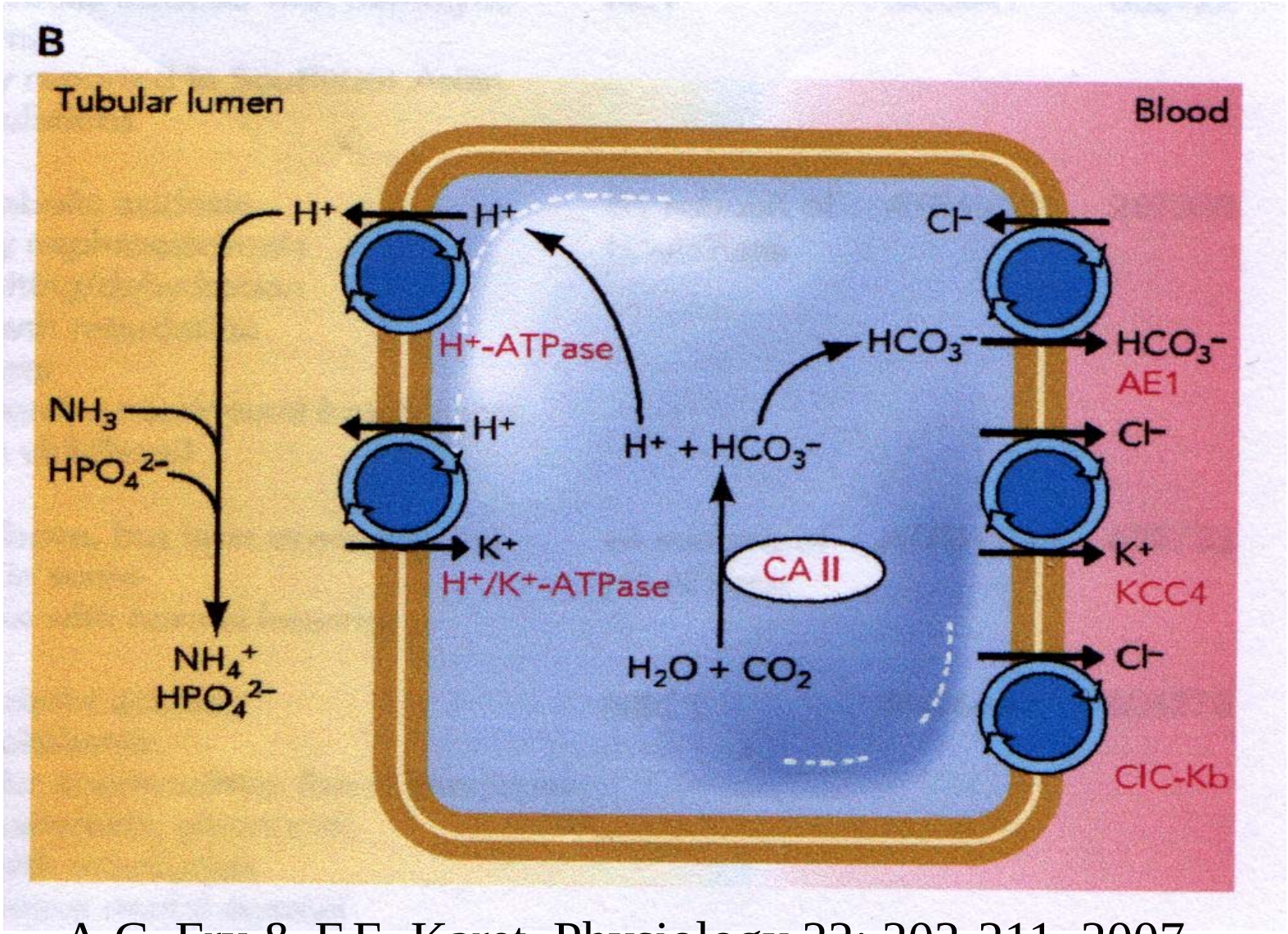

Thyroiditis
?
dist. RTA
HYPOKALEMIA


Thyroiditis
Hypercalciuria
Nephrocalcinosis
dist. RTA
HYPOKALEMIA


Thyroiditis
Hypercalciuria
Antibody deposition
or
Lymphocytic infiltration
Nephrocalcinosis
dist. RTA
HYPOKALEMIA


Thyroiditis
Hypercalciuria
Nephrocalcinosis
Antibody deposition
or
Lymphocytic infiltration
dist. RTA
HYPOKALEMIA

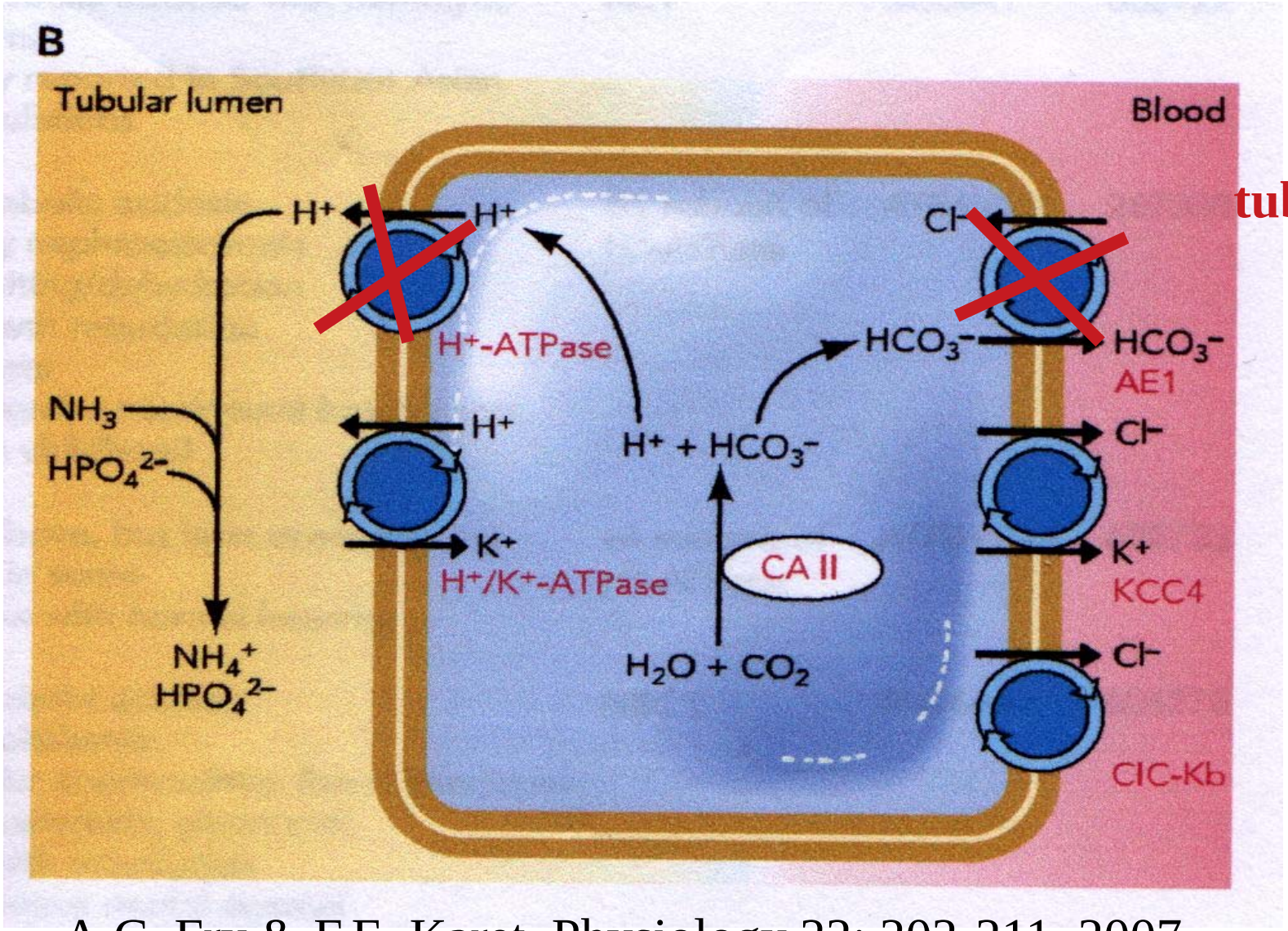
Distal Renal Tubular Acidification



A.C. Fry & F.E. Karet, Physiology 22: 202-211, 2007

Distal Renal Tubular Acidification

Secondary dist RTA

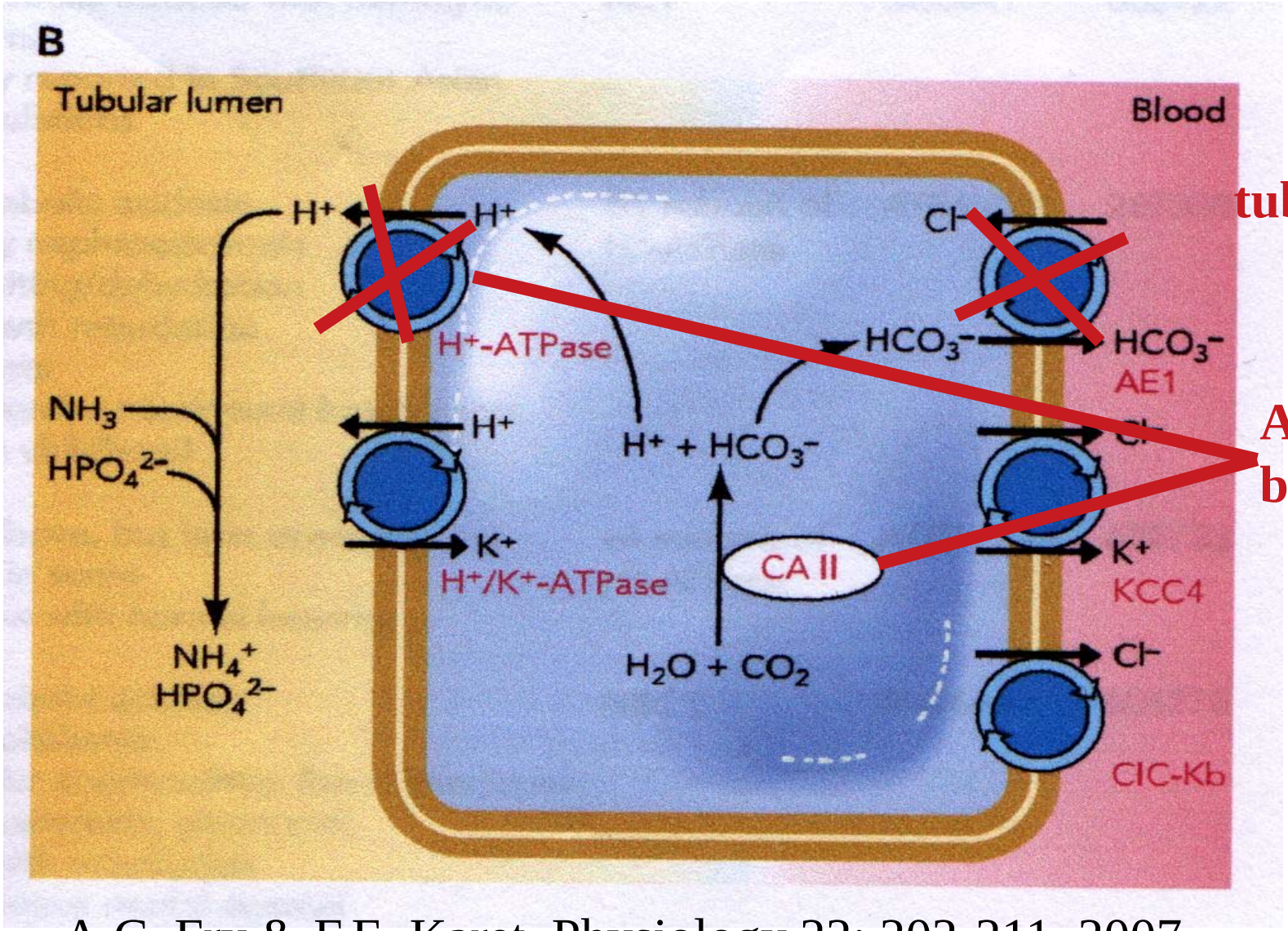


tubulitis

A.C. Fry & F.E. Karet, Physiology 22: 202-211, 2007

Distal Renal Tubular Acidification

Secondary dist RTA



A.C. Fry & F.E. Karet, Physiology 22: 202-211, 2007

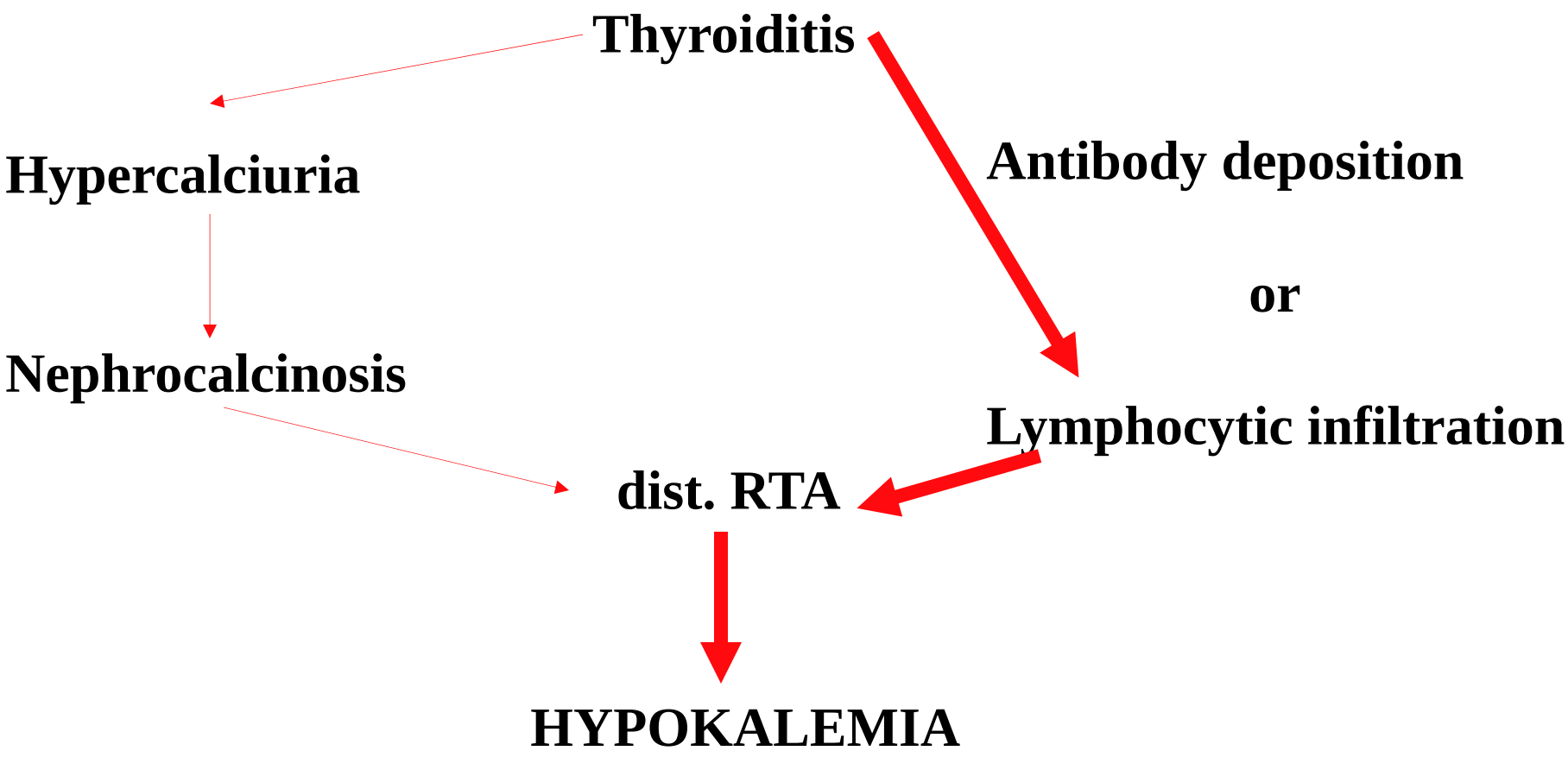
Renal Biopsy

- **No evidence for Nephrocalcinosis**

- **Light Microscopy:**
  - **Interstitial infiltration with lymphocytes (predominantly close to the glomeruli)**

- **Electron Microscopy:**
  - **Nl glomeruli and TBM tubular epithelium**

- **Immunofluorescence:**
  - **No immunoreactive material along TBM (anti-IgA, -IgG, -IgM, -C3, -thyroglobulin, no thyroglobulin-containing immun complexes)**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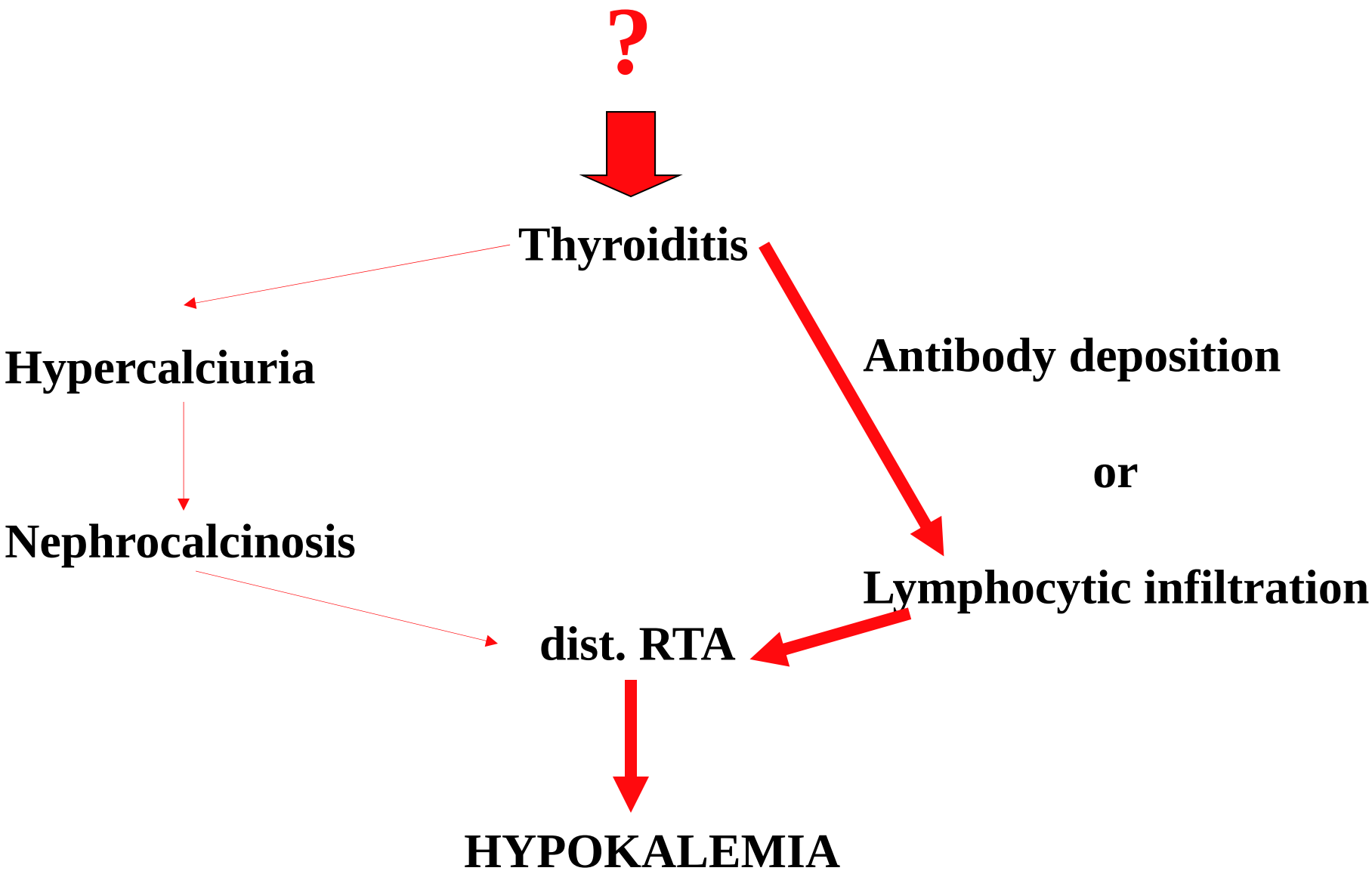
?
Thyroiditis
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dist. RTA
HYPOKALEMIA

Young woman

Family history of diabetes

Asthenia + Muscle weakness

Pollakiuria + Thirst

S-P 1.0 mM

S-K 2.3mM

Stressful life events and Graves' disease

BRITA WINSA HANS-OLOV ADAMI REINHOLD BERGSTRÖM
ANDERS GAMSTEDT PER ANDERS DAHLBERG ULF ADAMSON
ROLF JANSSON ANDERS KARLSSON

The role of stressful life events in the onset of Graves' disease (toxic diffuse goitre) is controversial. However, the numerous early clinical reports that supported such an association were not adequately controlled and specificity of the diagnosis could be questioned. Later studies have not shown a causal relation, but these studies were small, did not have proper controls, or epidemiological methods were inappropriate. To assess possible associations between life events, heredity, social support, and Graves' disease, we have done a population-based case-control study in a defined area with about 1 million inhabitants.

Over 2 years, 208 (95%) of 219 eligible patients with newly-diagnosed Graves' disease and 372 (80%) of all selected matched controls answered an identical mailed questionnaire about marital status, occupation, drinking and smoking habits, physical activity, familial occurrence of thyroid disease, life events, social support, and personality. Compared with controls, patients claimed to have had more negative life events in the 12 months preceding the diagnosis, and negative life-event scores were also significantly higher (odds ratio 6·3, 95% confidence interval 2·7–14·7, for the category with the highest negative score). Individuals who had relatives with thyroid disease (especially first-degree and second-degree relatives) were more likely to have Graves' disease (3·6, 2·2–5·9). Slightly more patients than controls were divorced (1·8, 1·0–3·3) and reported a less frequent intake of alcohol (0·4, 0·2–0·8). When results were adjusted for possible confounding factors in multivariate analyses, risk estimates were almost unchanged.

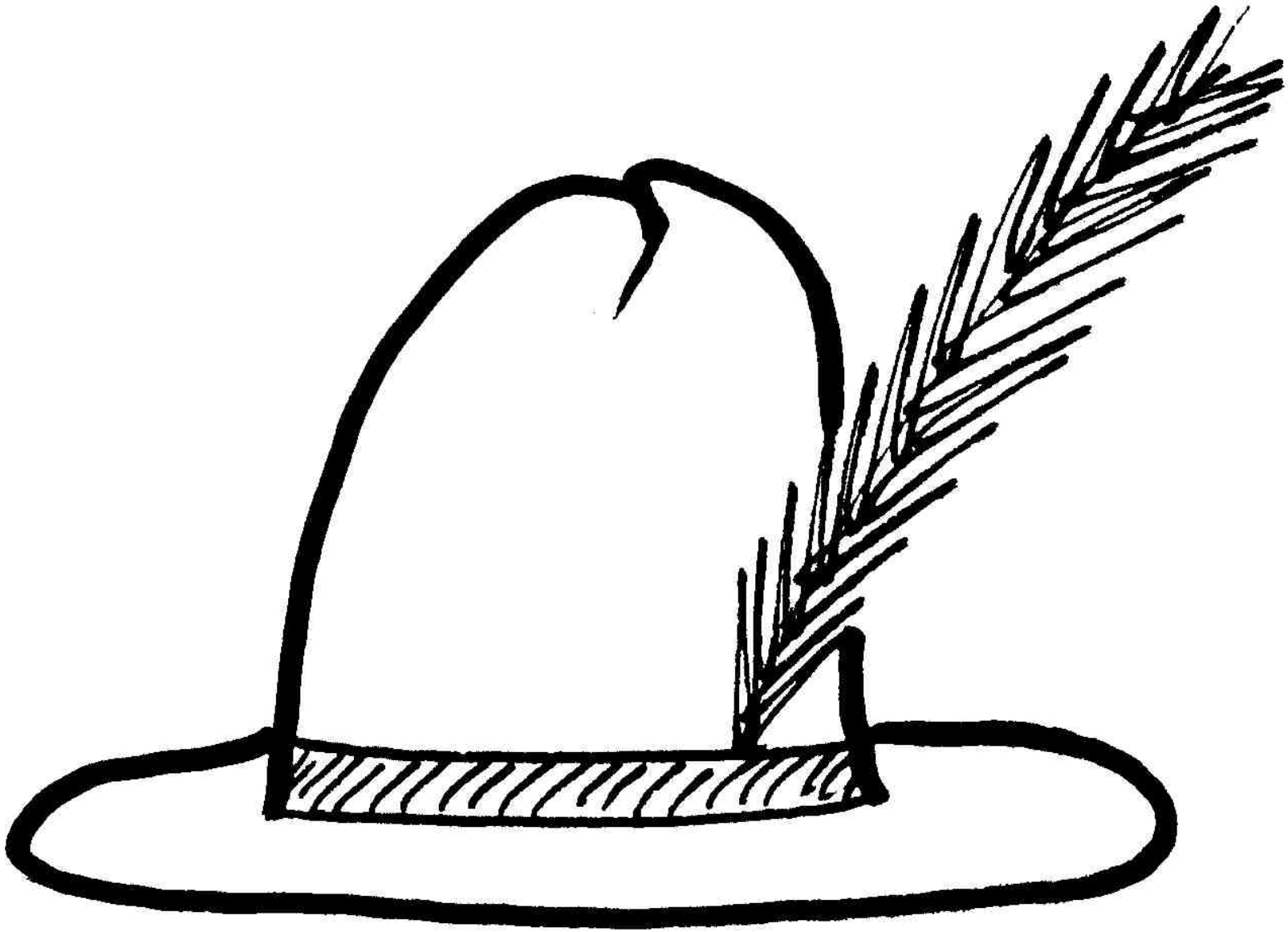
These findings indicate that negative life events and hereditary factors may be risk factors for Graves' disease.

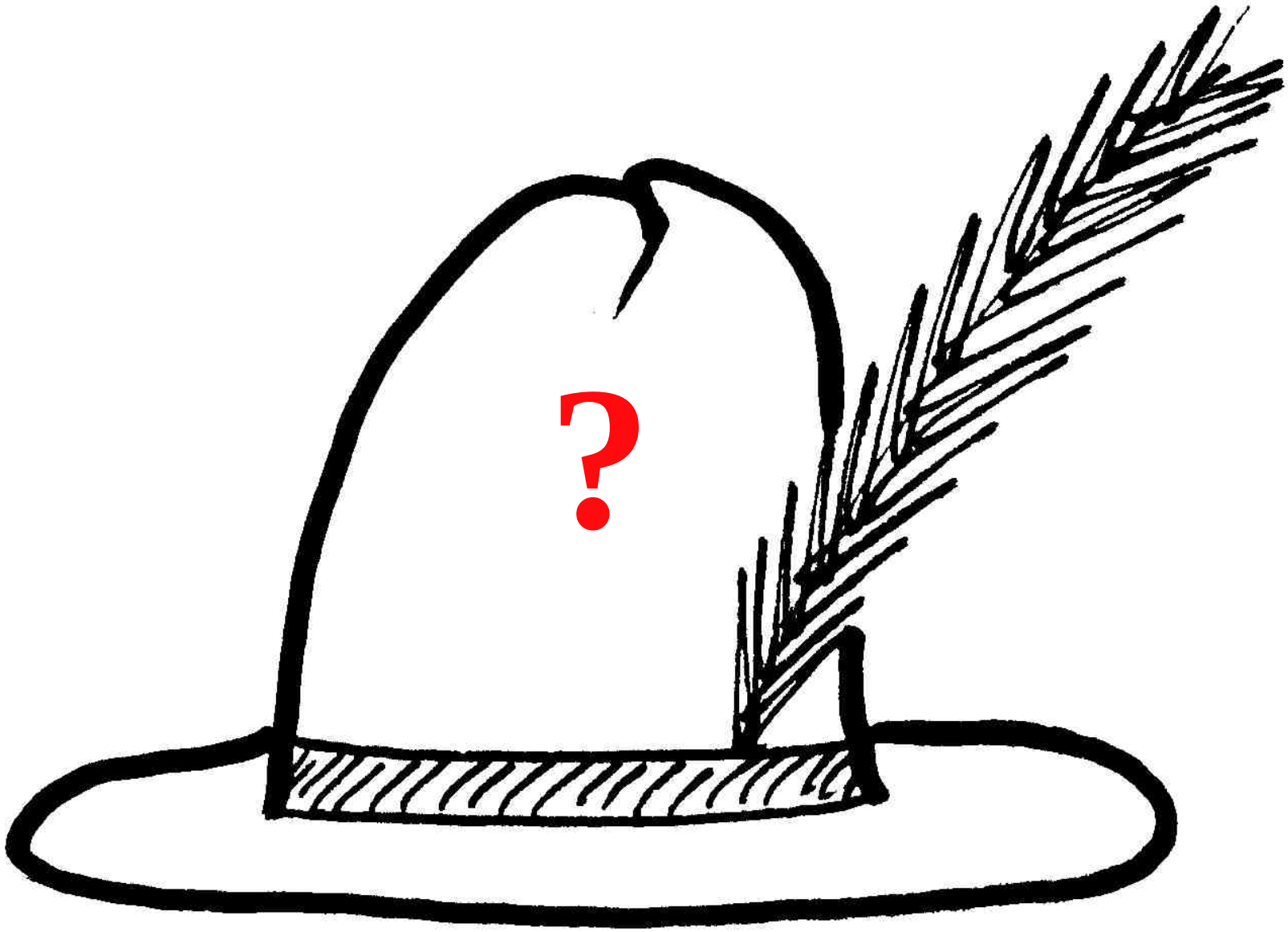
Lancet 1991; **338**: 1475–79.

Introduction

The cause of Graves' disease (diffuse toxic goitre) is largely unknown. Hereditary factors linked to the HLA

ADDRESSES: **Departments of Internal Medicine** (B. Winsa, MD, Prof A. Karlsson, MD) **and Statistics** (Prof R. Bergström, PhD), **and Cancer Epidemiology Unit** (Prof H. O. Adami, MD), **Uppsala University, Uppsala; and Departments of Internal Medicine, Örebro Hospital** (A. Gamstedt, MD), **Västerås Hospital** (R. Jansson, MD), **and Danderyd Hospital** (U. Adamson, MD, P. A. Dahlberg, MD), **Sweden**. Correspondence to Dr Brita Winsa, Department of Internal Medicine, University Hospital, 751 85, Uppsala, Sweden.





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S-P 1.0 mM

Young woman

Family history of diabetes

Asthenia + Muscle weakness

Pollakiuria + Thirst

Thyrotoxic periodic paralysis: ***profound muscular weakness***

Young woman

Family history of diabetes

Asthenia + Muscle weakness

Pollakiuria + Thirst

Thyrotoxic periodic paralysis: ***profound muscular weakness***

(associated with hypo-K, evident only when patient hyperthyroid)

In summary….

Multiple HYPOfunctions

hypo-K

hypo-HCO3

hypo-tubular acidification

hypo-citraturia

Multiple HYPOfunctions

hypo-K

hypo-HCO3

hypo-tubular acidification

hypo-citraturia

hypo-thyroidism

+ a transient bit of HYPERfunction

hyper-thyroidism

Multiple HYPOfunctions

hypo-K

hypo-HCO3

hypo-tubular acidification

hypo-citraturia

hypo-thyroidism

+ a transient bit of HYPERfunction

hyper-thyroidism

+ a lot of fun to teeze out all this together

= ----------

a typical case for internists