The ins and outs of thyroxine therapy

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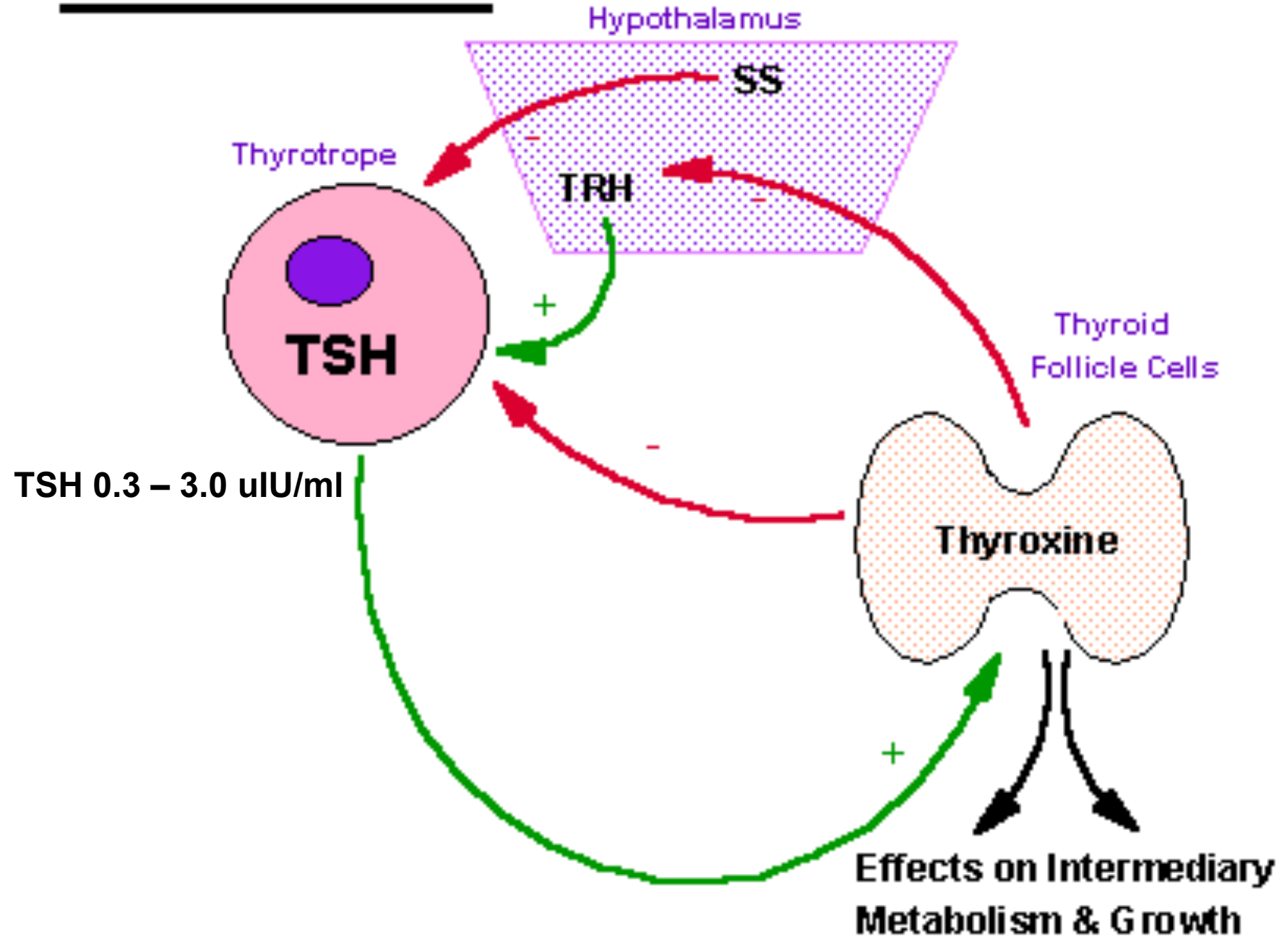
Objectives

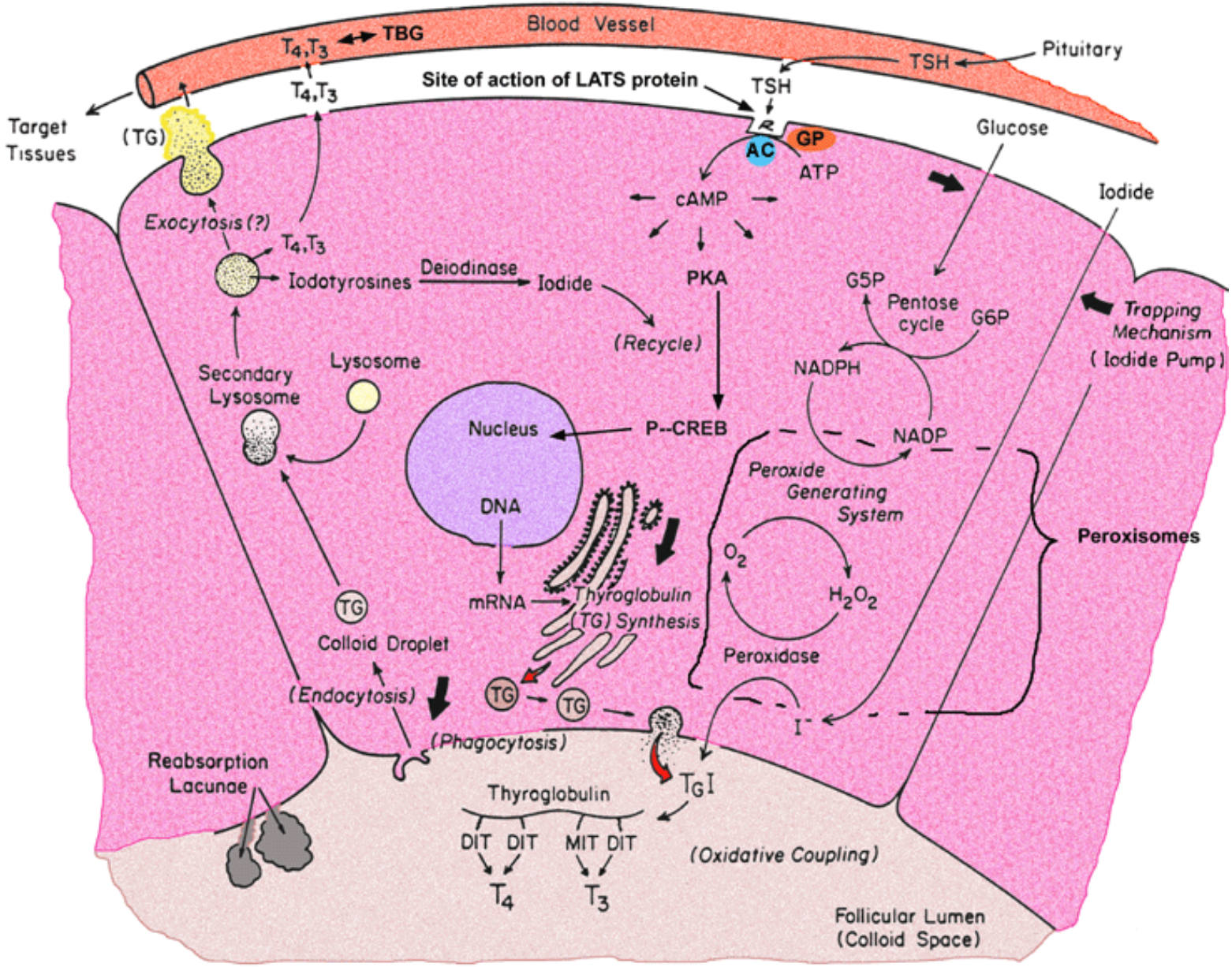
1. Review the use of thyroxine therapy in thyroid disease and non-thyroidal illness
2. Discuss approaches to correct replacement therapy in hypothyroidism including combination T4 +T3 treatment
3. Review the factors (biological and pharmacokinetic) that alter thyroxine requirements
4. Identify the adverse consequences of over-treatment

Control of TSH

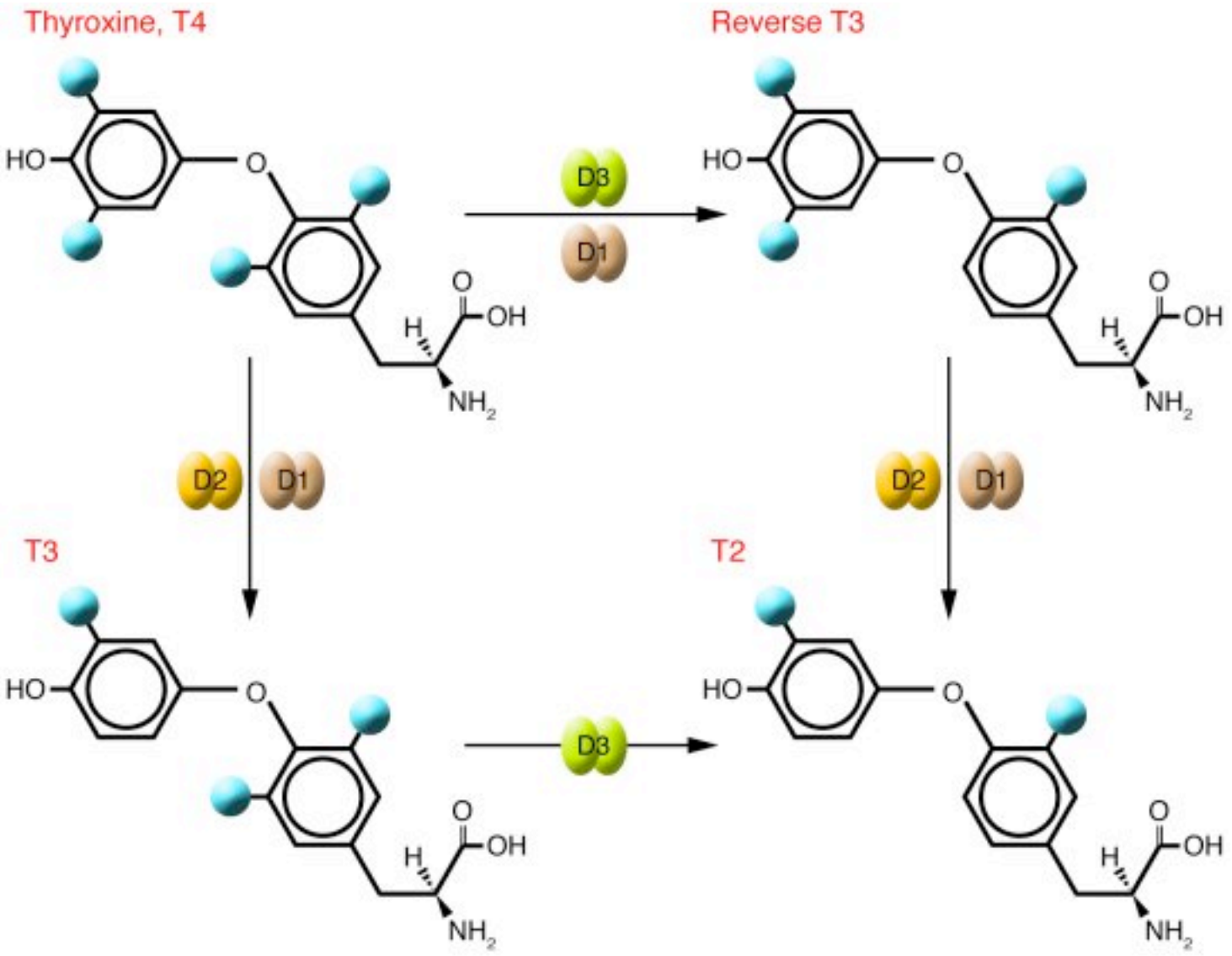


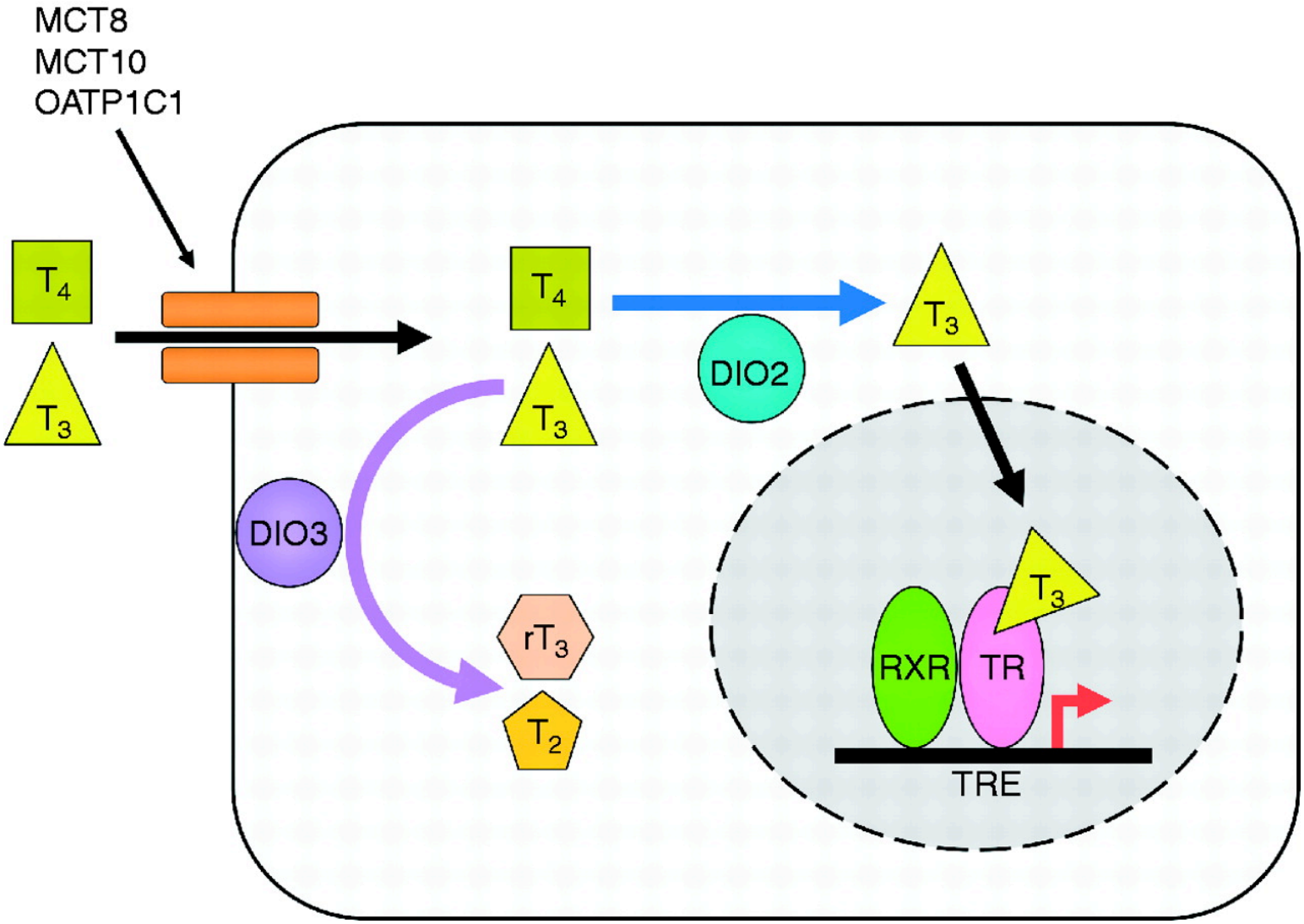
TSH 0.3 – 3.0 uIU/ml

Thyroid Hormone Synthesis by Thyroid Follicle Epithelial Cells



(Modified from Hadley, *Endocrinology, 4th Ed,* Prentice Hall: Upper Saddle River, NJ, 1996.)


Thyroxine, T4
Reverse T3
T3
T2
HO
O
H
OH
O
NH2
D3
D1
D2
D1
D2
D1
D3


MCT8
MCT10
OATP1C1
T4
T3
T4
T3
DIO2
T3
DIO3
rT3
T2
T3
RXR
TR
TRE

Mrs. T

- A 53 y.o. client asks for a consultation
- She has been started on thyroxine therapy (100 mcg OD) by her GP but she does not know why
- She thinks he may have discovered a mass in her neck
- Dispensing lisinopril and atorvastatin for past 2 years, lanzaprazole for GERD
- She also takes Centrum Silver and calcium carbonate 500 mg OD
- Worried+++

Which of the following could be the cause for prescribing thyroxine?

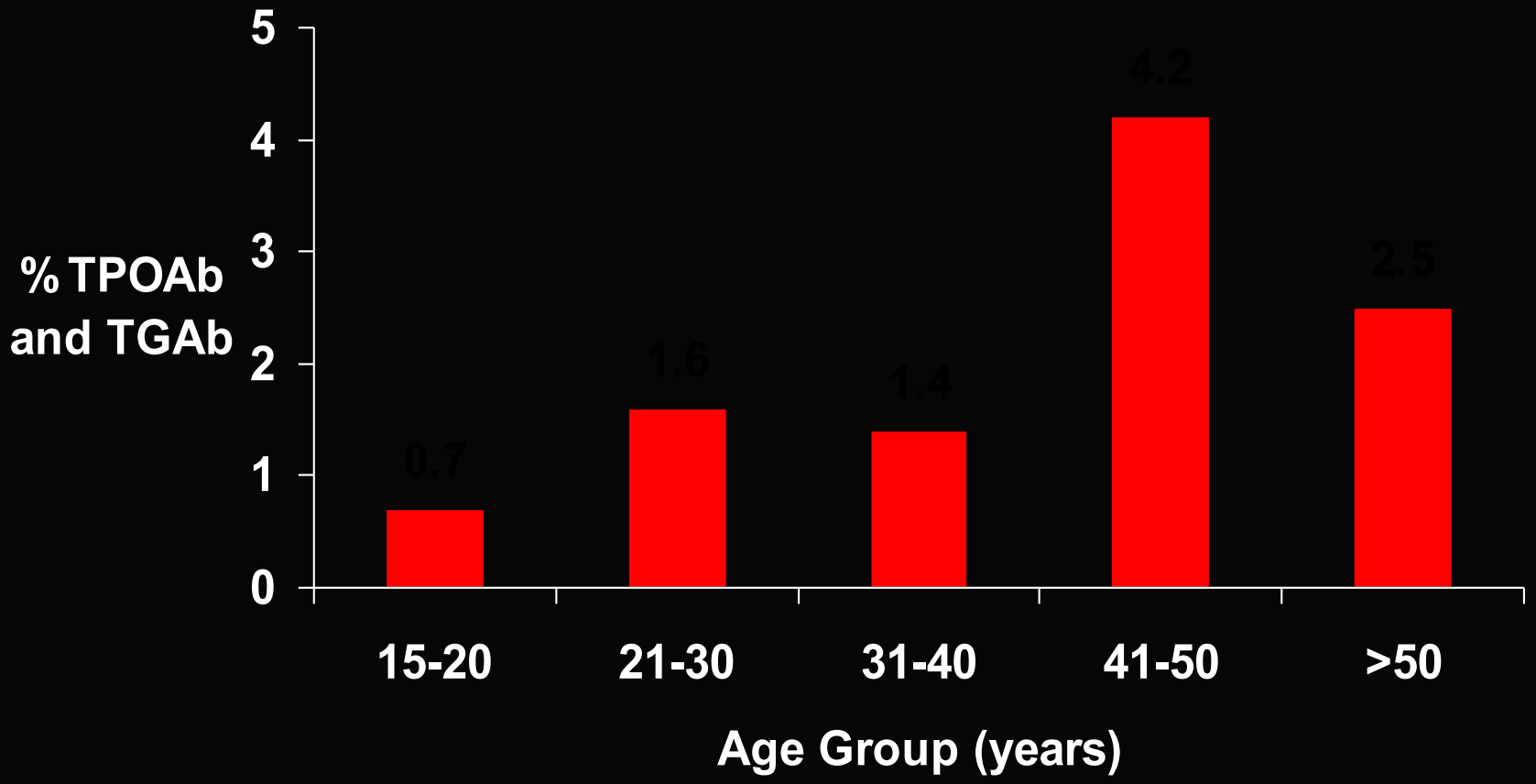
A. Euthyroid goitre
B. Thyroid nodule
C. Graves' disease
D. Thyroid carcinoma
E. Hashimoto's thyroiditis
F. Painless thyroiditis
G. Iodine deficiency

A. Not really
B. Not really
C. Hell, no!
D. Yes, Level A
E. Yes, Level A
F. Possibly
G. No

How common?

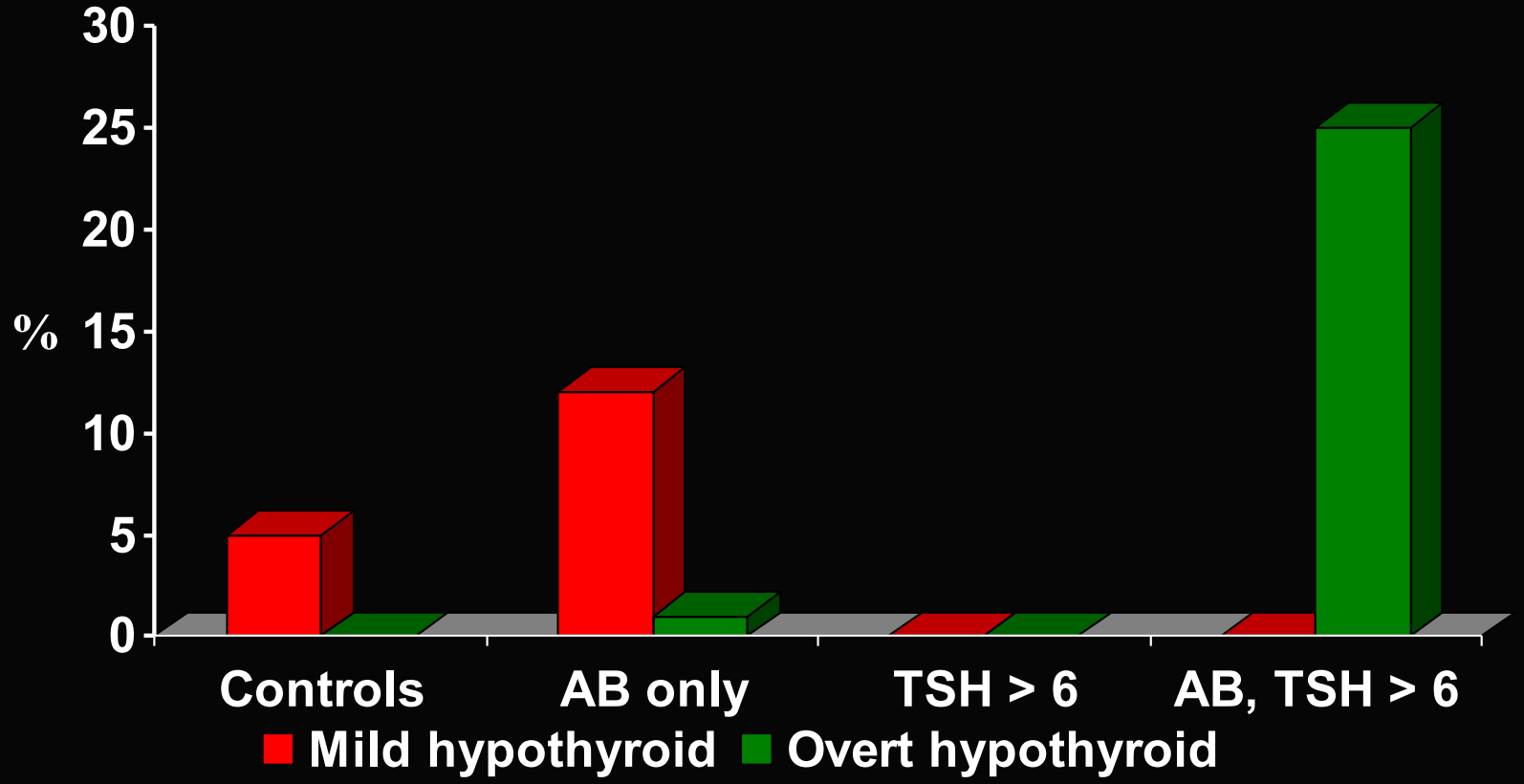
- Whickham survey (1977):
  - mean age of onset 57 yrs
  - Prevalence = 2%
  - women 10 x more common
- Colorado Thyroid Disease Prevalence Study (1999)
  - ↑ TSH in 9.5%
  - ↓ TSH in 2.2%
- NHANES (2003)
  - 5% undiagnosed thyroid disease
  - 4.6% hypothyroidism (0.3% overt/ 4.3% mild)
  - Blacks - 1.5% hypothyroid, 0.7% hyperthyroid

Age group distribution of thyroid antibodies in 693 Jamaicans



Smikle M et al. West Indian Med J 1994

Percentage of subjects who develop mild or overt hypothyroidism over a 4-yr period



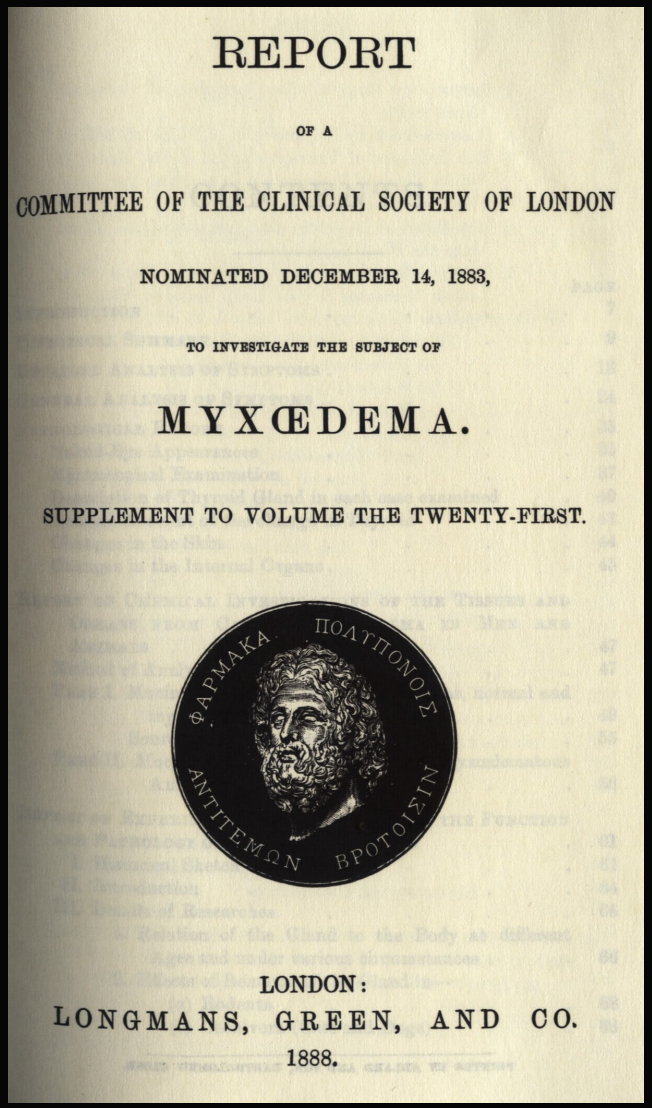
BMJ 1981;282: 258-62

When should you screen for thyroid disease?

- ✓ Goitre
- ✓ Unexplained weight change
- ✓ Depression, psychosis?
- ✓ Postpartum women
- ✓ Elderly (> 60 yrs vs. age 35 yrs q 5 yrs)
- ✓ Down's syndrome
- ✓ Atrial fibrillation
- ✓ Unexplained osteoporosis
- ✓ Lithium, amiodarone
- ✓ Hyperemesis gravidarum

Hypothyroidism

"Of the intellectual changes, slowness in apprehension, thought and action is most constant…. Irritability is a marked feature….. In some cases placidity alternates with occasional outbursts of fretfulness or irritability…. Sleep is noted as good but in many cases there is excessive somnolence…. Delusions and hallucinations (and insanity) occur in nearly half the cases….insanity takes the form of acute or chronic mania, dementia or melancholia, with a marked predominance of suspicion and self-accusation…."



REPORT

OF A

COMMITTEE OF THE CLINICAL SOCIETY OF LONDON

NOMINATED DECEMBER 14, 1883,

TO INVESTIGATE THE SUBJECT OF

MYXŒDEMA.

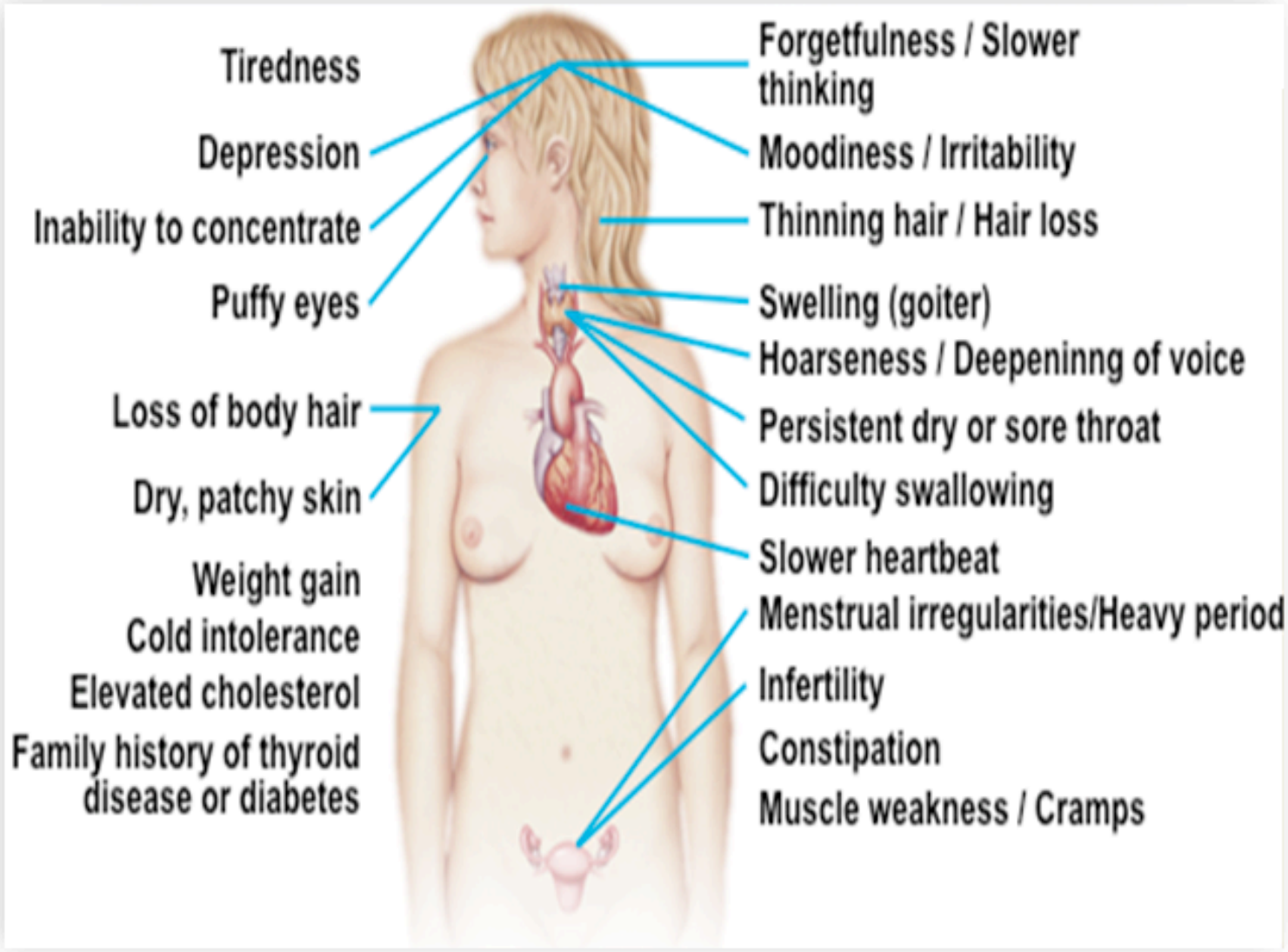
SUPPLEMENT TO VOLUME THE TWENTY-FIRST.

LONDON:
LONGMANS, GREEN, AND CO.
1888.

Aetiology of hypothyroidism

- Autoimmune thyroiditis:
  - Hashimoto's thyroiditis (goitrous hypothyroidism)
  - Atrophic thyroiditis
- Radioactive iodine therapy (postablative hypothyroidism)
- Surgical hypothyroidism
- Thyroiditis: subacute, painless, postpartum
- Dyshormonogenesis
- Iodine excess or deficiency
- Goitrogens e.g. lithium, thionamides
- Congenital hypothyroidism
- Infiltrative diseases
- Secondary hypothyroidism

Hypothyroidism



Elderly

- **Dementia**
- **Anaemia**
- **Depression**
- **CHF**

Children

- **Slow growth**
- **Weakness**

Cutaneous manifestations of hypothyroidism

- Puffy facies with blepharoptosis
- Dry rough skin
- Eczema craquele
- Nonpitting edema (pitting can also occur)
- Periorbital swelling
- Pallor due to vasoconstriction, anaemia and I/S fluid
- Carotenemia
- Coarse brittle hair, madarosis
- Brittle, thickened, slow-growing, striated nails

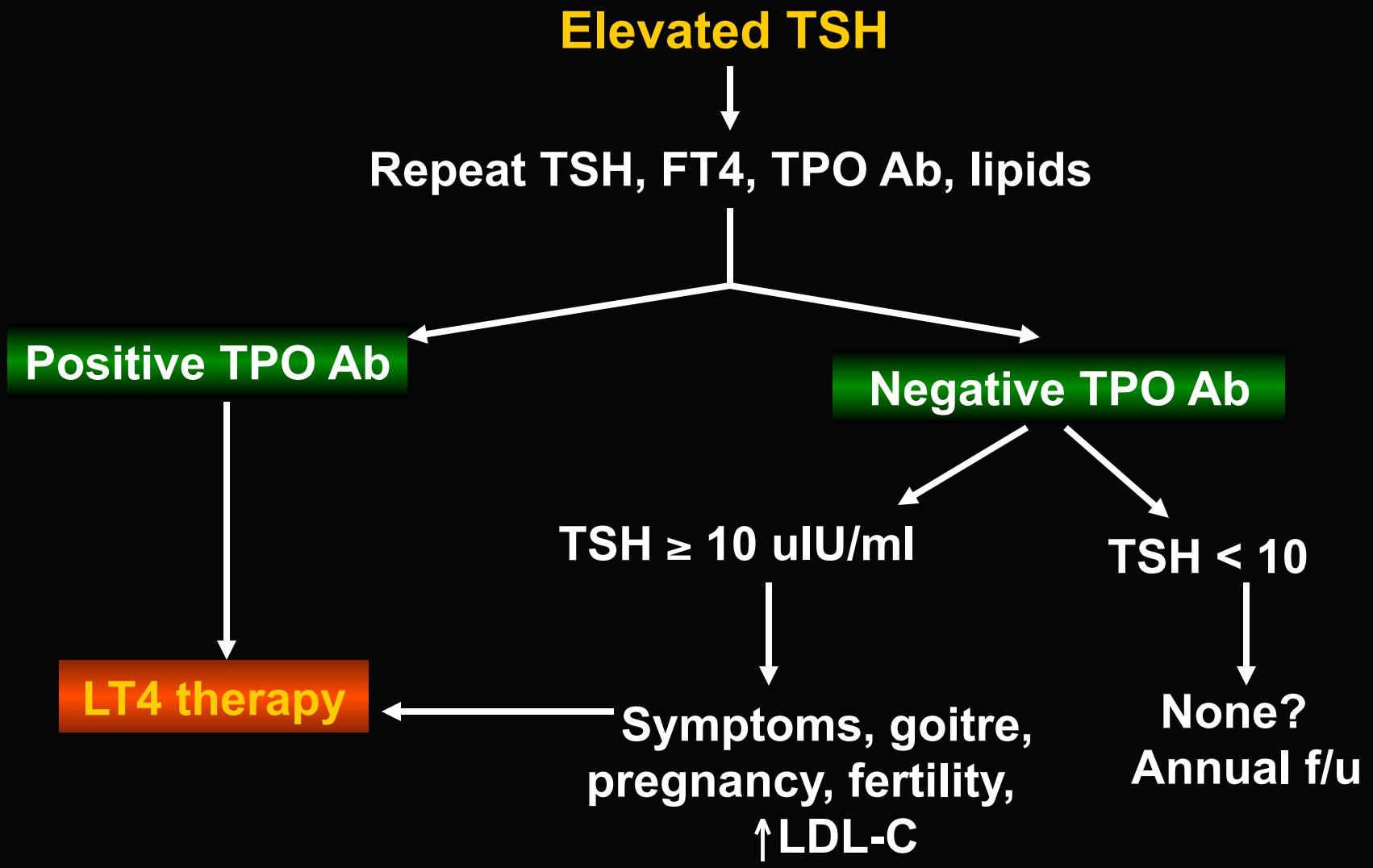
Making the diagnosis

- Need a free T4, TSH
- Total T3, free T3 and T3-uptake are not necessary and confuses everybody
- Thyroid nuclear scan is a waste of money and time!
- Thyroid peroxidase antibodies are optional
- Thyroid sonogram defines anatomy if the physical exam is not helpful

38 yr old poet

- Routine visit
- PMH: 2 c-sections
- FH: HTN
- Executive panel: TC 6.8 mmol/l, LDL-C 4.9 mmol/l
- TSH 8 uIU/ml (NR 0.35 - 5.00)

Mild hypothyroidism



Cooper D. NEJM 2001

Treating hypothyroidism

- Primary hypothyroidism: start 25-50 mcg OD for 2-4 weeks then increase by 25-50 mcg every month until TSH is 0.3 – 3.0 uIU/ml
- Surgical hypothyroidism: 1.6 mcg/kg/d
- Adding T3 to T4: *no consistent data*

Pharmacokinetics

- Peak 2-4 hours
- Half life 7 days – cumulative dose is more important
- Absorption:
  - 21% duodenum
  - 45% upper jejuneum
  - 34% in lower and ileum
- Absorption increased by fasting, decreased by some foods especially fibre

62 year old GP's wife..

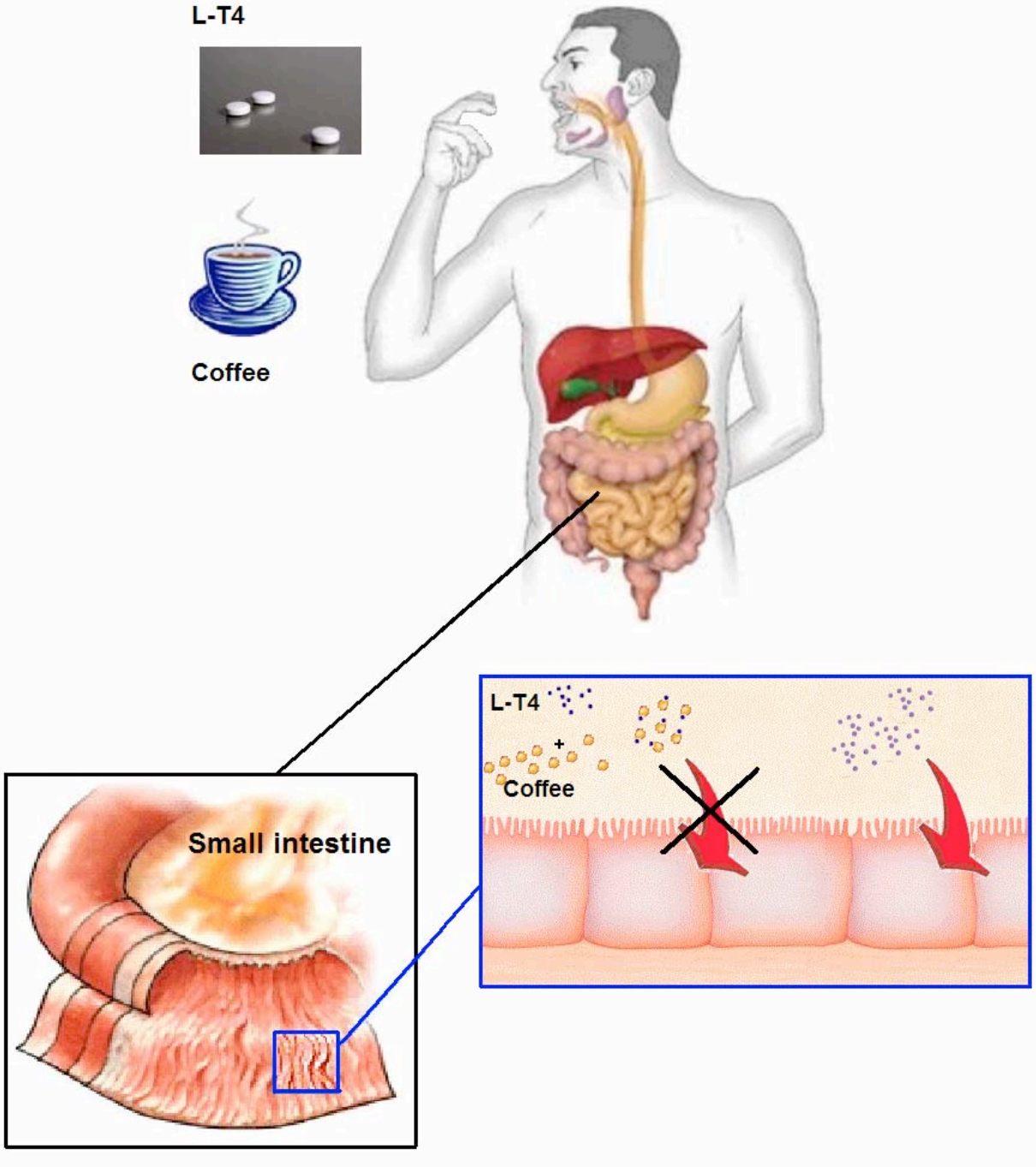
- Hashimoto's thyroiditis
- On 100 mcg OD
- She tells you that her doctor is not satisfied with her control as her tests are frequently off
- You note that she infrequently fills her prescription and she admits to non-compliance
- What options are there?

Weekly or biweekly dosing
Bedtime dosing

There are different doses – please minimize cutting of tablets

Any interfering substances?

- Iron
- Calcium
- MVI
- Coffee
- Food? 1 hour delay gives maximum absorption(30-70%; TSH 2.9 vs. 1.9 uIU/ml)


L-T4
Coffee
Small intestine
L-T4
+
Coffee

Are there any dietary precautions?

A. Increase fish or seafood	X
B. No soy products	X
C. No goitrogens (Brassica family e.g. cabbage, cauliflower, broccoli, Brussels sprouts, kale)	X
D. Iodine supplements e.g. kelp	X
E. High salt diet	X
F. Selenium supplements	X

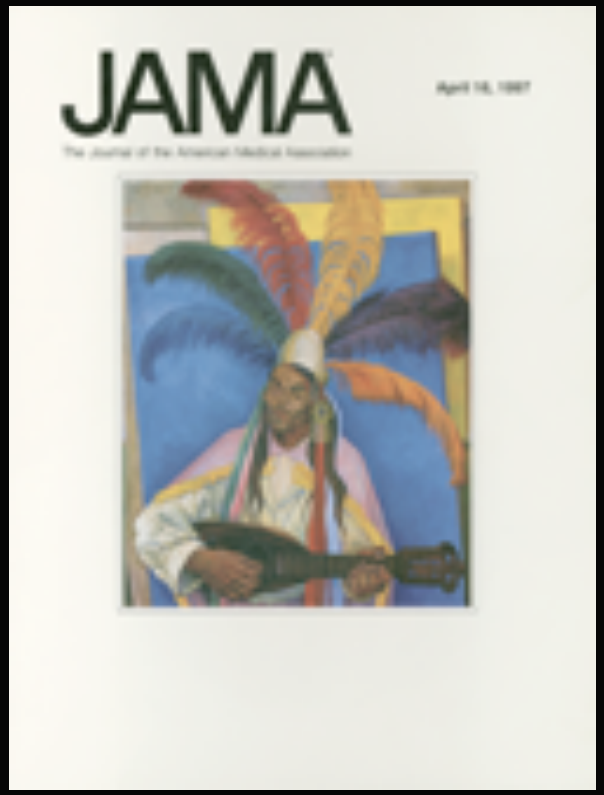
58 year old business man

- Thyroid cancer treated 18 months ago with surgery, radioactive iodine ablation and thyroxine suppression
- On Synthroid 125 mcg OD, comes for a refill, but there is none in your stocks.

Do you?:

A. Dispense another brand
B. Tell him to come back in 2 days
C. Send him to the pharmacy down the road

Brand vs. generic?



Thyroid storm
JAMA. 1997;277: 1238-1243

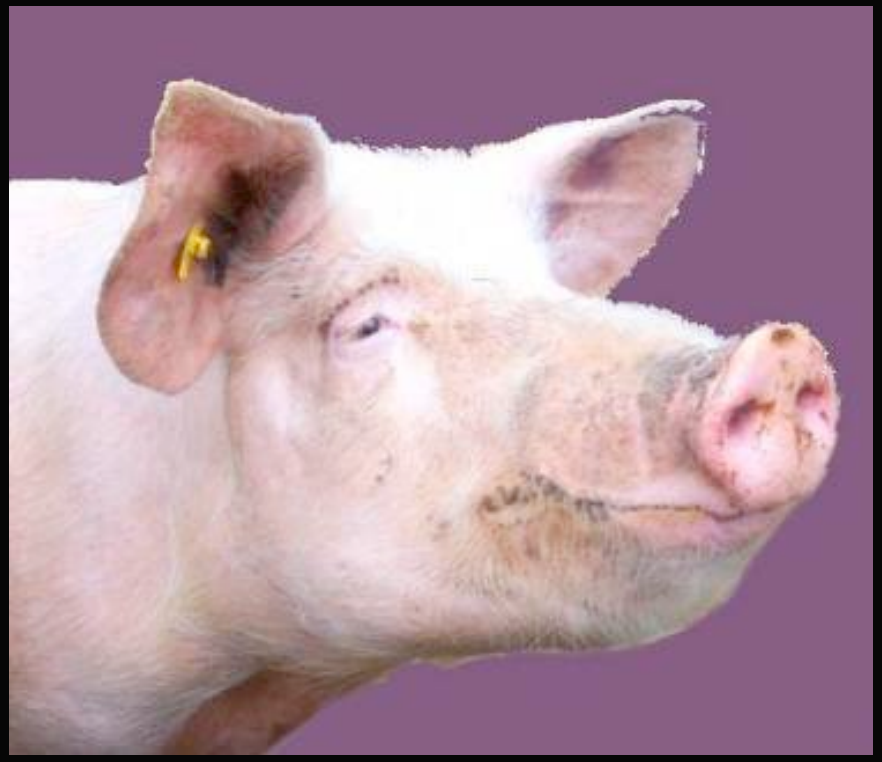
Special care:

1. Pregnancy
2. Children
3. Elderly
4. Comorbidities
5. Thyroid cancer

39 y.o. housewife….

- Has been on branded thyroxine for 8 months
- Still complains of lassitude, no energy, mental fogginess, difficult to concentrate
- Persists after several dose changes and doctor insists her dose is fine
- Heard on internet that she is on the wrong hormone
- “What do you think about Armour thyroid?

What about desiccated thyroid?



1 grain = 60 mg = 100 mcg LT4

Determinants of LT4 requirements

Factor	Dosing requirement
Aetiology of hypothyroidism	↑ in thyroidectomy patients
Age	↓ with age, monitor TSH
Sex	↓ in men
Pregnancy	30-50% ↑
Renal failure	↓
Food, herbs, supplements	↑
Lean mass	Better to assess dose

Drugs interfering with administration

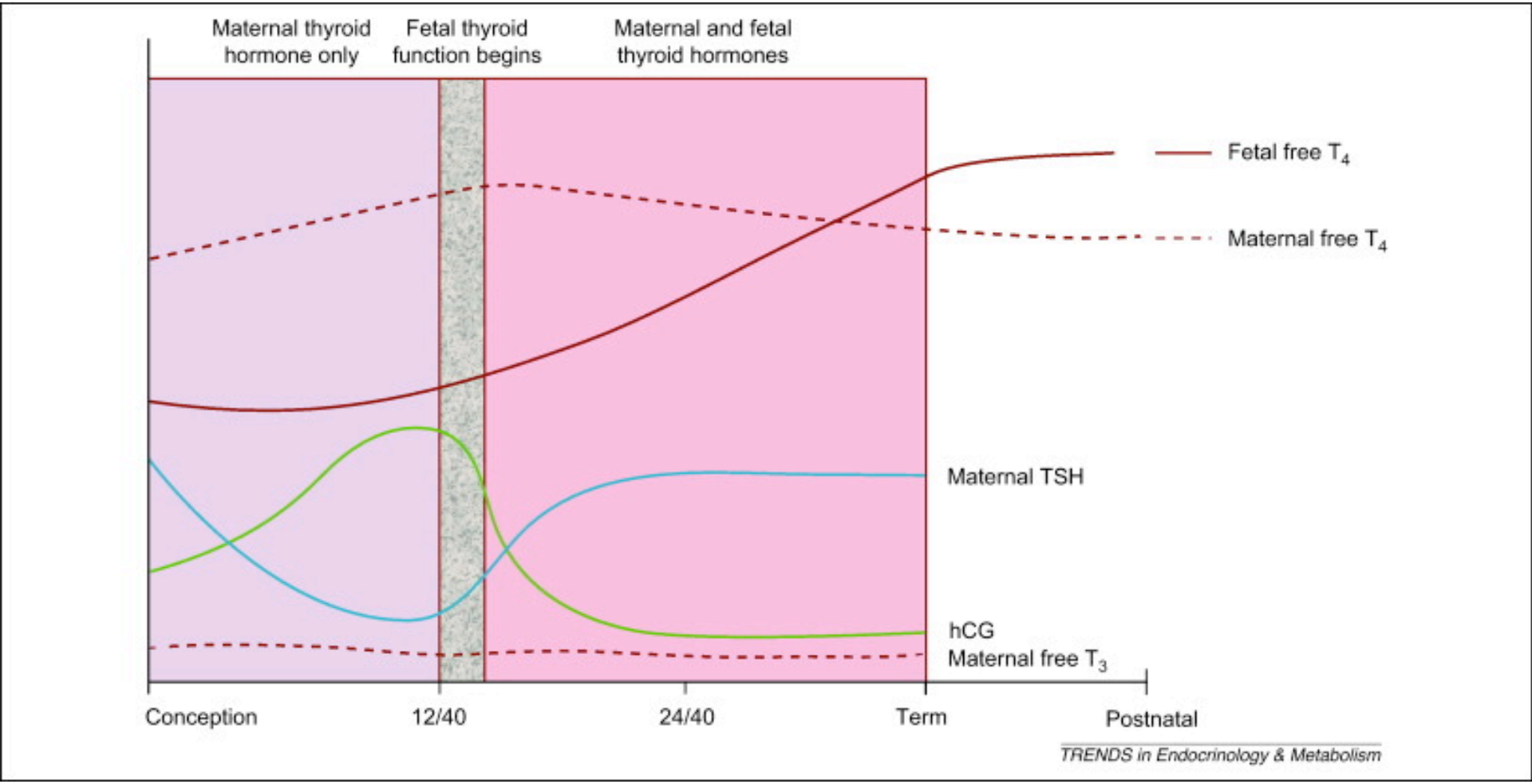
- *Thyroid synthesis*: lithium, amiodarone
- *Absorption:* antacids, PPI, H2RB,laxatives, anion-exchange resins
- *Metabolism:* phenobarbitone, phenytoin, carbamazepine, sertraline
- *TSH secretion:* glucocorticoids, bromocriptine
- *Deiodinase activity:* amiodarone, beta-blockers, glucocorticoids

33 year old HR exec has been on LT4 75 mcg/d for Hashimoto's. She is now pregnant. Her GP is on vacation for 3 wks. She is in a panic and asks your advice. She said her last TSH was normal – maybe 1.0.

What would you do?

A. Find another GP stat!
B. Stay on the same dose
C. Can harm the baby, reduce dose
D. Increase the dose
E. Give 250 mcg iodine daily

Pregnancy-induced thyroid function changes



Trends Endocrinol Metab 2011; 22:164–170

- T_4 dose usually needs to be incremented by 4 to 6 wk gestation and may require a 30% or more increase in dosage. USPSTF recommendation level: A; evidence, good (1| ⊕⊕⊕⊕).

Noncompliant hypothyroid patients

- Unexpectedly high dose requirements
- Normal FT4 with elevated serum TSH
- Erratic and nonsensical serial TFTs

Potential indications for referral

- Confusing laboratory results
- Anyone diagnosed with the Barnes test!
- Unanticipated response to T4 therapy
- Associated heart disease
- Possible central/ secondary hypothyroidism

Inappropriate use of LT4

- Wilson's syndrome

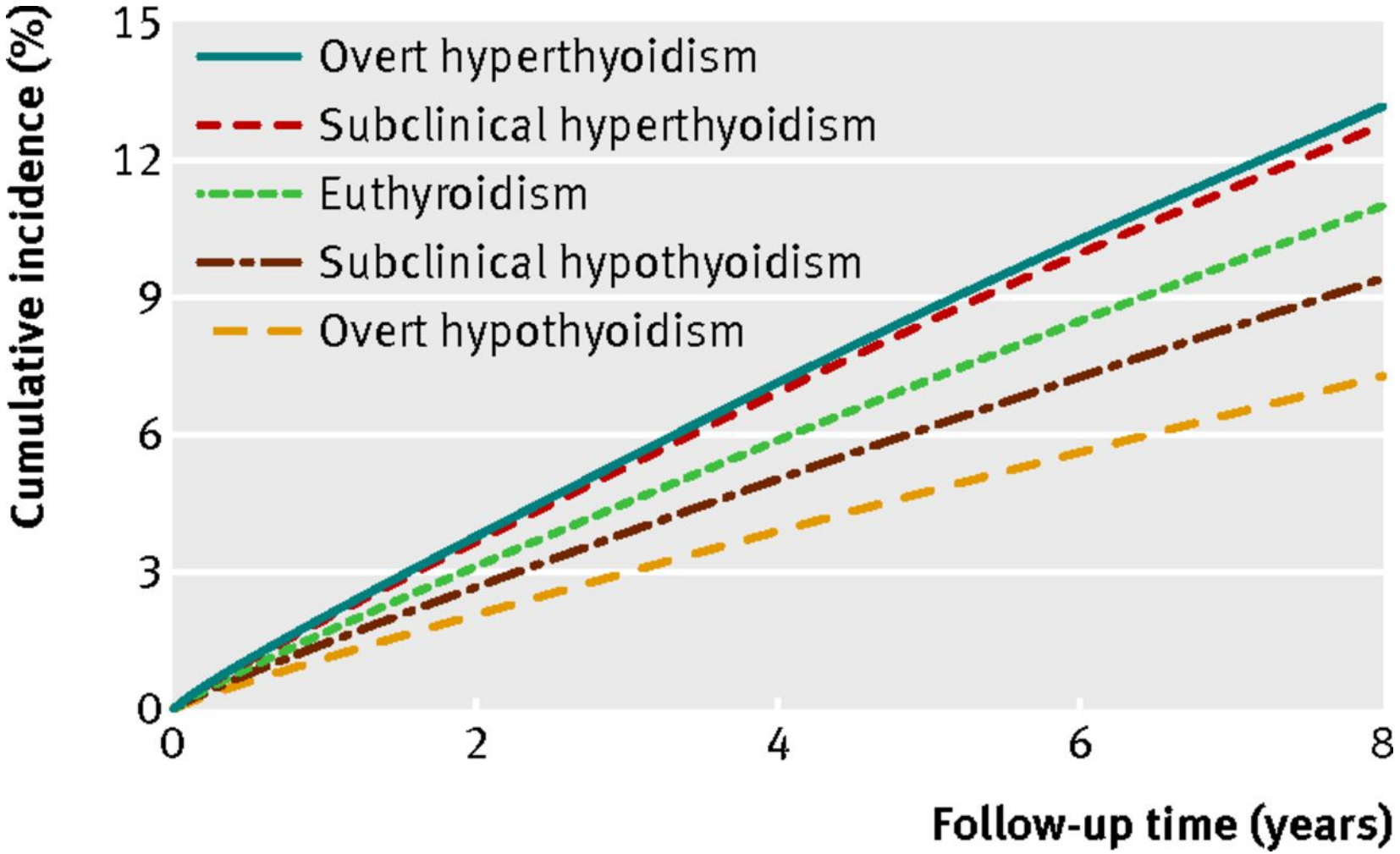
- Obesity

- Fatigue after surgery

78 year old Mrs. P

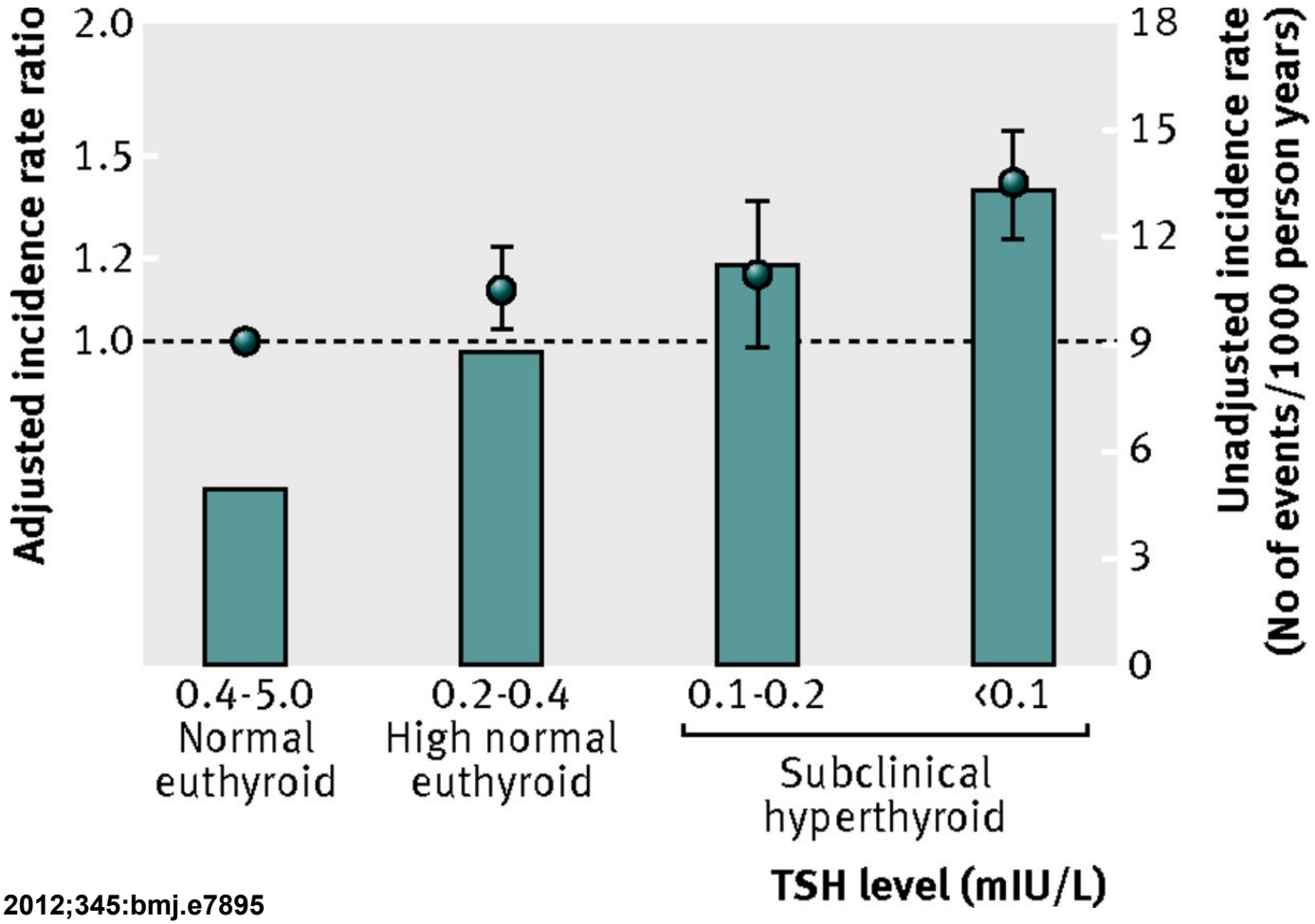
- Wife of supreme court judge
- Benign solitary nodule in 1987
- Placed on Eltroxin 100 mcg/d
- Mild hypertension on diuretic
- Petite, otherwise feels well
- TSH 0.07 uIU/ml (0.3-3.0)]
- After d/c, “more calm, less irritable, sleeps better”

Cumulative incidence of atrial fibrillation in relation to baseline thyroid dysfunction (age >65 years)



Selmer C et al. BMJ 2012;345:bmj.e7895

Adjusted incidence rate ratios (box and whiskers) and unadjusted incidence rates (bars) for atrial fibrillation by level of TSH in euthyroid and subclinical hyperthyroid patients



Selmer C et al. BMJ 2012;345:bmj.e7895

Effects on bone

- TSH-suppressive doses associated with bone loss in some but not all studies.
- A recent extensive meta-analysis concluded the same but only in postmenopausal women
- No or a minimal excess of bone fractures, however, has been observed in patients on LT4 even if TSH is suppressed

J Clin Endocrinol Metab 1996; 81: 4278-4289

Summary

1. Review the use of thyroxine therapy in thyroid disease and non-thyroidal illness
2. Discuss approaches to correct replacement therapy in hypothyroidism including combination T4 +T3 treatment
3. Review the factors (biological and pharmacokinetic) that alter thyroxine requirements
4. Identify the adverse consequences of over-treatment

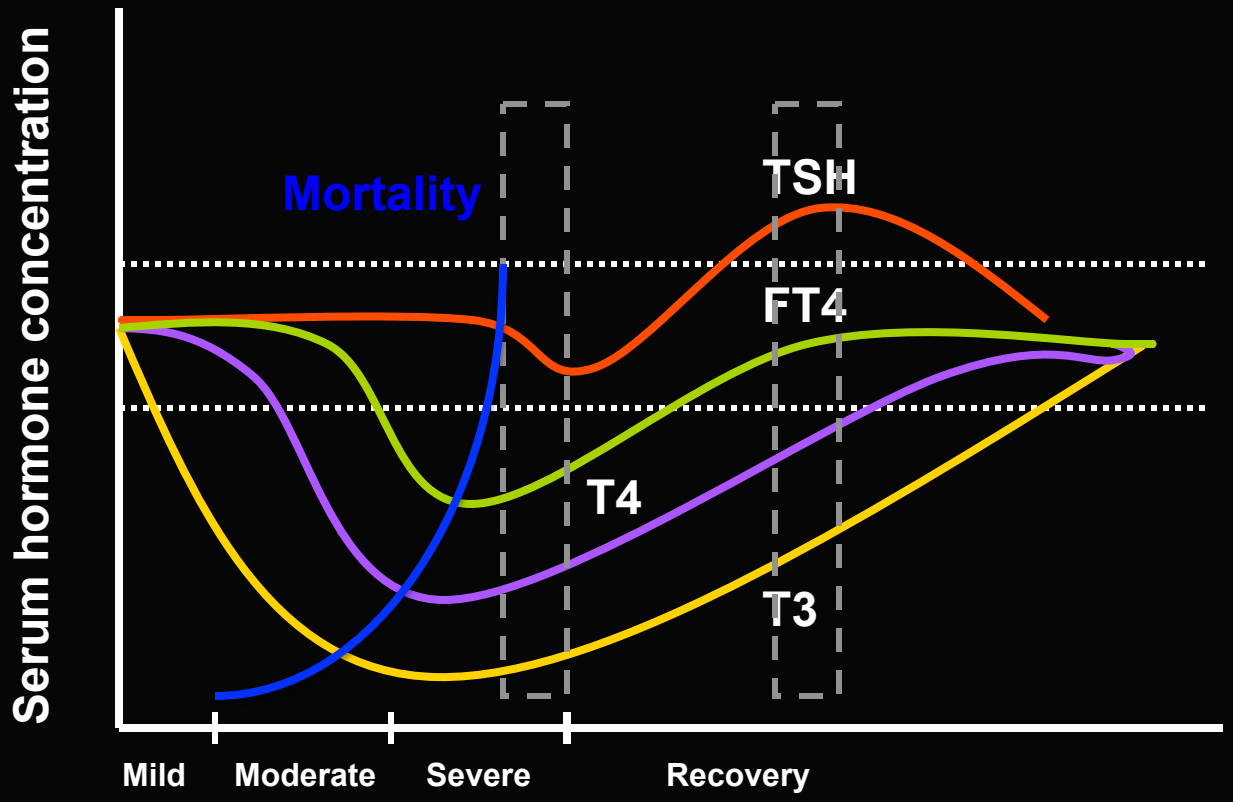
65 year old woman spends 3 wk in ICU with sepsis and renal failure

- transferred to the ward as significantly improved
- has continuing fatigue
- TSH 23 mIU/ml (0.5-5.0)

Should we treat her?

A. Start thyroxine
B. Repeat TSH in 2 weeks
C. Obtain more tests e.g FT4, thyroid scan

Continuum of thyroid function tests in non-thyroidal illness (euthyroid sick syndrome)



BMJ 2000;320:1332