What I wish I had known twenty years ago!

John Wass

Professor Endocrinology, Oxford University, UK

ABCD Autumn Meeting in London on 6th November 2015

Chateau Margaux 1961

Price in 1965 - £29 - for one bottle

Price in 2015 - £984 - for one bottle

UK Statistics

- Most publication productive nation in the world

  14% most cited articles

  8% world publication (0.88% of world population)

  70 Nobel prizes

  4 Universities in the top twenty

- UK is unique in the charity sector for Research Funding

- The opportunities for research in the UK have never been better

Areas of Research

- Genetics
- Clinical Trials
- Translational Science
- Health Care Improvement Science
- Medical Education
- Various Aspects of Audit
- Clinically Focused Research

NIHR

3.4 Billion per year

98% of hospitals doing research

Support for research infrastructure and research posts

Academic medicine strategy

Four objectives:

- Help to make the NHS a better home for research by providing greater support to research-active and research-interested membership.
- Ensure that the RCP has a strong voice in relation to health research.
- Improve the RCP's profile in the field and develop good relationships with relevant stakeholders.
- Develop opportunities and mechanisms to ensure that the membership is engaged with the RCP's academic medicine work.

Conclusions

- The UK is a world leader in medical research
- The opportunities to do significant translational medical research in the UK are second to none
- The academic programmes & mentoring schemes for aspiring young medical scientists are very well developed in the UK
- Ask for career guidance and help –worthwhile academics will always give enthusiastic support

Survey of Tier 3 Services
October 2015

791 surveyed
- ABCD
- DUK
- Society for Endocrinology

169 responses (21%)

76 CCG territories covered

60% have tier 3 services (increased from 35% in 2013)

Two thirds based in secondary care

Obesity – need for engagement

Bariatric Surgery rates falling

(comparing badly with France and Sweden)

Thyroid Patients on Thyroxine

"Tired"

Check:-

- Vitamin D
- Vitamin B12
- Endomysial Antibodies
- Parietal Antibodies
- Calcium

Depression

Vitamin D Deficiency

Is common – 87% of hip fracture patients in Oxford

insufficient > 25nmol/L

deficient < 25nmol/L

Cause – usually unknown

Give plenachol (cholecalciferol) as below:

vitamin D < 25 – 40,000 units daily for six days

Vitamin D > 25 – 20,000 units daily for six days

Then 40,000 units monthly

Hypothyroidism

Epidemiology (Whickham survey)

High TSH (>5.0mU/L)

7.5% female

2.5% males

> 65 yrs

1.7% overt

13.7% subclinical *hypothyroidism*

Oxford Handbook of Endocrinology,

Eds, John Wass and Katharine Owen 2014

Hypothyrodism

Synthetic levothyroxine - on an empty stomach

- 1.6-1.8 mcg/kg/day

Young - commence 50-100 mcg *Increase 25mcg*

Elderly - commence 25 – 50mcg *every 4 weeks*

TSH checked after 4-6 weeks at each increment

aim TSH < 2.5 mU/L

For preference use the same brand

Garber et al, 2012, Thyroid 22, 1-32

Persistent elevation of TSH on Thyroxine

Mostly poor compliance

Interference with absorption of thyroxine

Coeliac disease

Drugs ↓ absorption of thyroxine *Calcium salts*

Ferrous sulphate

Aluminium hydroxide

Cholestyramine

↑ clearance of thryoxine *Omeprazole*

Rifampicin

Phenytoin

Phenobarbitone

Atrophic gastritis with h pylori (↓ T4 by 30%) *Carbamazepine*

Imatinib

A Thyroxine Absorption Test Followed by Weekly Thyroxine Administration:

A Method to Assess Non-Adherence to Treatment

JN Walker, S Pallai, V Ibbotson, A. Vincent, N Karavitaki, AP Weetman, JAH Wass , A Allahabadia

Eur J Endocrinol. 2013 May 10;168(6):913-7

Supervised 7 x 1.6 mcg/kg weekly - with monthly TSH monitoring

"Allergy" to Thyroxine

Tablets contain:

- Lactose
- Starch
- Stearates
- Citrate
- Acacia

Use liquid thyroxine

Subclinical hypothyrodism

Raised TSH – normal thyroid hormone levels

Note past radioactive iodine

+ve thyroid antibodies (5% per year → overt)

8 x risk of hypothyroidism

with elevated TSH 38 x increased risk

Thyroid antibodies increase the miscarriage rate

? Replace if attempting pregnancy

Vanderpump MP 2010, Clin End, 72, 436-40

Subclinical hypothyrodism

Give thyroxine if TSH > 10 mU/L

If TSH 4-10 mU/L + symptoms consider trial of thyroxine

In patients attempting pregnancy - treat mild TSH elevation

Biondi B 2008 End. Rev 29, 76-131

Pearce S et al 2013 2, 215-228

Hypothyroidism
Combine T4 & T3?

5% treated hypothyroid patients - symptomatic

Causes – other endocrine/non endocrine disease –

Coeliac disease
Vitamin D deficiency
B12 deficiency
Depression

Treatment – ensure TSH < 2.5 mU/L

latrogenic hyperthyrodism – arrhythmias
fractures

Conversion of T4 → T3 may not be normal in 10%

Trial of T3 5mcg thrice daily + reduce T4

Nygaard B 2009 Eur J Endocrinol 2009; 161, 895-902

Pituitary Hypothyroidism

Monitor fT4 in hypopituitary hypothyroidism

→ (upper normal)

Pregnancy & Hypothyroidism

Risks

Spontaneous miscarriage rate increased x 2

preeclampsia – 21% if sub optimally treated

Foetus dependant on maternal thyroxine until 12 weeks

Risk of impaired foetal intellectual & cognitive development

Increased perinatal death

Lazarus J 2011 Br. Med. Bull, 97 137-48

Pregnancy & hypothyroidism

Management

Diagnosed in pregnancy - start 100mcg & measure T4 and TSH in 4 weeks

If on T4 – increase dose by 25-50 mcg

- optimise (TSH <2.5 mU/L) prior pregnancy

On confirmation of pregnancy

- aim TSH < 2.5 mU/L plus fT4 upper end of normal
- monitor thyroid function monthly in first trimester
- no contemporaneous iron

Case History

C.C. Aged 23

Weight loss 65 to 45kg

Holiday in Borneo – pigmented

Vomiting Na 126 x 2

Not investigated

Died – undiagnosed Addison's

Addison's disease

Primary — Prevalence 93 – 140/million
Incidence 4.7 – 6.2/million in Caucasians

Secondary — Hypothalamo-pituitary disease
Exogenous steroids – oral
inhaler
joint
Congenital adrenal hyperplasia
Post treatment of Cushing's

Charmandari et al Lancet 2014 383 2152-2167

Features of Addison's

Anorexia & weight loss	100%
Tiredness, weakness	100%
Skin pigmentation	94%
Postural hypotension	88-94%
Abdominal pain	
Arthralgia	
PUO	13%
Salt craving	16%

Secondary vs. Primary

No mineralocorticoid deficiency

No pigmentation

Drugs and Adrenal Insufficiency

Ketoconazole Fluconazole	*Inhibit cortisol synthesis*
Phenytoin Rifampin	*Increase cortisol metabolism*

Investigation

Na ↓ (90%) (normocytic)

K ↑(65%)

Cortisol ↓

ACTH ↑

Synacthen

Anaemia

Eosinophilia

Mild-hypercalcaemia

Adrenal suppression

Depot synacthen

Treatment of Acute Adrenal Suppression

BMJ 2012: 345 e6333

BMJ

BMJ 2012;345:e6333 doi: 10.1136/bmj.e6333 (Published 9 October 2012)

EDITORIALS

How to avoid precipitating an acute adrenal crisis

Most importantly, heed patients' requests for hydrocortisone

John A H Wass *professor of endocrinology*[1], Wiebke Arlt *professor of medicine*[2]

Emergency Management - Life threatening!

Fluids – several litres first 24 hours

Hydrocortisone 100mg i.v.

+ 100mg i.m then 6 hourly

or

200mg i.v. by continuous infusion/24 hours

Not mineralocorticoid because xs glucocorticoid steroids

Patients will die if inadequately treated

Intercurrent illness

Surgery

↑ dose

Intercurrent illness

Addison's Disease Self Help Group

http://www.addisons.org.uk/

Patients on Steroids

Prednisolone more than 5mg/day
more than 1 month

NB. Inhaled steroids
dermatological steroids
joint injected steroids

All suppress the synacthen test

Hydrocortisone

Minor - endoscopy 100mg i.m. before

Moderate - hernia repair - 100mg i.m. 6 hourly/24 hours

Major - open heart surgery - 100mg i.m 6 hourly/72 hours

Then resume normal medication

Major illness

Hydrocortisone 100mg i.m. 6 hourly until illness resolved

Pregnancy and Addison's Disease

Normal pregnancy

- CBG ↑
- Free cortisol increases last trimester
- Renin ↑

In Addison's

- ↑ HC by 25-50% last trimester
- Adjust mineralocorticoids by BP and K+

During labour

- Parenteral steroids

Yuen et al Endocrine 2013 44, 283-292

Treatment of Primary Adrenal Insufficiency

Glucocorticoids

Mineralocorticoids

- Fludro 100-150 daily
- Monitor renin

DHEA

- 25-50 mg daily

- May improve mood and wellbeing

Future
NHS Five Year Forward View

- Patients – better informed consumers
- IT – GP and hospital records linked
- GP – better integration of care
- More home care
- Apps
- Pharmacogenetics
- Patients knowing their genome
- Better prevention
- More (fewer) expert centres for rarer diseases