Endocrinology Handbook

ICSM Endocrine Unit at
Hammersmith Hospital
Du Cane Road
London W12 ONN
UK

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Introduction

Diagnosis and appropriate treatment in clinical endocrinology rely heavily on the accurate use and interpretation of diagnostic tests. This handbook was devised as a means of guiding new junior staff (and refreshing the memories of their seniors!) when confronted by clinical problems and their investigation. This bible is meant to be brief and didactic with the inevitable costs as well as benefits of such an approach. It is envisaged that it will be reprinted at 6 monthly intervals incorporating corrections and additions, any suggestions and comments from readers are welcome.

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Authors

Andrew Hattersley	Maria Barnard	John Wilding	Stephen Gilbey	Peter Hammond
Michela Rossi	Duncan Bassett	Arshia Panahloo	Rachel Batterham	Maha Barakat
John Frank	Bernard Khoo	Jeannie Todd	Sarah Stanley	Elaine Murphy
Carel LeRoux	Waljit Dhillo	Karim Meeran	Niamh Martin	

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ICSM Endocrine Unit at Hammersmith Hospital
Du Cane Road
London
W12 ONN
UK

ANTERIOR PITUITARY

ANTERIOR PITUITARY FUNCTION

INSULIN TOLERANCE TEST (ITT)

INDICATION

Assessment of ACTH and cortisol reserve.
Assessment of growth hormone reserve in children with definite growth retardation and a subnormal growth hormone stimulation test (see exercise test).
Differentiation of Cushing's syndrome from depression.
GH response in adults.

CONTRAINDICATIONS

Ischaemic heart disease, Epilepsy,
Untreated hypothyroidism (impairs the GH and cortisol response).

PREPARATION

The patient should fast overnight (water permitted) and be recumbent during the test.
ECG must be normal and the patient's weight known.
In peri-pubertal children (bone age > 10 years) priming is needed

M: 100 mg testosterone i.m. 3 days before testing
F: 100 mcg ethinyloestradiol p.o. each for three days before the test.

Calculate Actrapid Insulin dose:

Normal pituitary function	0.15 U/kg
Hypopituitary	0.10 U/kg
Acromegaly, diabetes, Cushing's	0.2-0.3 U/kg

If the patient is hypoadrenal for any reason (or on hydrocortisone), the case must be discussed with senior medical staff before administration of insulin. Patients with a cortisol <100 are very unlikely to have a normal response and may therefore not need the test.
50mls 50% dextrose available for immediate administration (but only use if persistent hypoglycaemia).
Glucometer.
6 fluoride oxalate tubes (grey top Vacutainers)
6 serum (clotted) tubes (red top Vacutainers)

SIDE EFFECTS

Sweating, palpitations, loss of consciousness and rarely convulsions.

METHOD

1. Site indwelling cannula.
2. At 0 minutes, take baseline bloods and then inject insulin i.v.
3. Take samples for GH, cortisol and glucose at 0, 30, 60, 90, and 120 mins, flushing the cannula with saline between samples.

4. At 30 minutes check whole blood glucose with Glucometer and repeat the insulin dose if not hypoglycaemic (this will mean prolonging sampling by 30 min).
5. Adequate hypoglycaemia (≤2.2mmol/l) should be symptomatic. Record symptoms in the notes. Once this has been achieved, patients need not remain hypoglycaemic.
6. There must be at least 2 specimens following adequate hypoglycaemia. This does not mean that the patients need spend that long hypoglycaemic.
7. At all times a doctor or nurse must be in attendance. A doctor should be present to administer the insulin but can leave once glucose levels start to rise following hypoglycaemia. The lowest glucose level following IV insulin is usually at 20-30 minutes, with spontaneous resolution.
8. Reverse hypoglycaemia with simple oral treatment (biscuit or milk). If symptoms very severe or patient unrousable (rare) consider giving i.v. 50% dextrose (10-15 ml), or 1 mg i.m. glucagon (1 amp), and continue sampling.
9. Obtain specimen for glucose before reversal of symptoms.
10. Check whole blood glucose on glucometer every time a specimen is taken.
11. If a patient has a hypoadrenal crisis they should receive i.v. 0.9% saline and hydrocortisone 100 mg.
12. Once test completed, give supervised meal.
13. Patient should not drive for 2 hours after the test.

INTERPRETATION

- The test cannot be interpreted unless hypoglycaemia (≤2.2mmol/l) is achieved.
- Adequate cortisol response is defined as a rise of greater than 170 nmol/l to above 500 nmol/l. Patients with slightly impaired cortisol responses may only need steroid cover for major illnesses or stresses. They will need instruction about this and should carry a steroid card.
- In Cushing's syndrome there will be a rise of less than 170 nmol/l above the fluctuations of basal levels of cortisol.
- Adequate GH response is a rise to >20 mU/l. In adults this may be a sensitive indicator of hypopituitarism but its principal role is in children who may require GH treatment. In children a rise to greater than 39 mU/l (15ng/ml) is considered normal (2.59 mU/l = 1ng/ml). Appropriate priming is very important if they are peri-pubertal. Before treatment with growth hormone children should have two stimulatory tests.

SENSITIVITY AND SPECIFICITY

If there is adequate hypoglycaemia and the patient is not hypothyroid then cortisol response is a good test of ACTH/adrenal reserve. 5-15% of normals will show a suboptimal response as defined by these two criteria.

20% of patients with Cushing's syndrome will show a rise greater than 170nmol/l but a rise of less than this is rare in depression or alcoholic pseudo-Cushing's.

GH responses are reduced in 20% of normal children and some small children whose peak GH is 10-20mU/l may benefit from GH replacement.

REFERENCES

Plumpton et al., Br. J. Surg. 56, 21 (1969). Greenwood et al., J. Clin. Invest. 45, 429 (1965).

GLUCAGON TEST

INDICATION

Assessment of growth hormone and ACTH/cortisol reserve especially when insulin-induced hypoglycaemia is contra indicated.

CONTRAINDICATIONS

Phaeochromocytoma or insulinoma (may provoke an attack)

Starvation >48 hours or glycogen storage diseases (inability to mobilise glycogen may result in hypoglycaemia)

Severe hypocortisolaemia (0900h level <55 nmol/l)

Thyroxine deficiency may reduce GH and cortisol response.

SIDE EFFECTS

Nausea is common (30%) and patients may rarely vomit.

PREPARATION

Fasting from midnight. The patient does not need to be continually observed as hypoglycaemia is not provoked.

Calculate glucagon dose: adults: 1 mg, (1.5mg if > 90kg) children: 15 mcg/kg

6 fluoride bottles (grey top Vacutainers) and 6 plain tubes (red top Vacutainers)

METHOD

1. Insert an indwelling cannula.
2. Take basal samples for glucose, cortisol and GH.
3. Give the glucagon i.m. (the deltoid may be a suitable site).
4. Take further samples at 90, 120, 150 and 180 minutes.

INTERPRETATION

Adequate cortisol response is defined as a rise of greater than 170 nmol/l to above 550nmol/l. Adequate GH response is a rise to a value greater than 20 mU/l.

SENSITIVITY AND SPECIFICITY

This test is probably slightly less reliable test of somatotroph and corticotroph function than the ITT. It is an excellent alternative in patients who can not tolerate hypoglycaemia because of epilepsy, ischaemic heart disease or hypopituitarism. The false negative rate for cortisol response is 30% (but only 8% of normals will not show either a peak value of 550nmol or a rise of 170nmol/l). Only 4-8 % of normals will not show an adequate rise in GH: this is usually in patients over 50.

REFERENCES

Rao R.H. et al., Metabolism 36, 658-663 (1987).

ATH 12/89.

THYROTROPHIN RELEASING HORMONE (TRH) TEST

INDICATION

To assess TSH reserve. Differential diagnosis of pituitary and hypothalamic causes of TSH deficiency.

CONTRAINDICATIONS

As patients should be off thyroxine for 3 weeks prior to test so this test, it is rarely used in people on thyroxine.

PREPARATION

Overnight fast not necessary.
200 mcg TRH
i.v. cannulae 19 or 21 gauge.
3 x clotted tubes (red top Vacutainers): 6 ml per sample.

SIDE EFFECTS

Patients should be warned that they may have transient side effects after the injection such as a metallic taste in the mouth, flushing and mild nausea, and should be on a recliner or bed.

METHOD

1. Site indwelling cannula.
2. Take baseline bloods for TSH and thyroxine.
3. Inject TRH slowly i.v. over 2 minutes.
4. Flush butterfly with heparin/saline.
5. Take samples for TSH at t = 30 mins and 60 mins.

INTERPRETATION

The normal result is a TSH rise to >5 mU/l with the 30 min value exceeding the 60 min value.
If the 60 min sample exceeds the 30 min value then this usually indicates primary hypothalamic disease.
In hyperthyroidism, the TSH remains suppressed and in hypothyroidism there is an exaggerated response. With the current sensitive TSH assays basal levels are now adequate and dynamic testing is not usually needed to diagnose hyperthyroidism.

SENSITIVITY AND SPECIFICITY

An inadequate rise of TSH is not an indication for thyroxine replacement unless the serum thyroxine, free T4 or free T3 is reduced. The TSH is not only undetectable in pituitary disease and thyrotoxicosis but also in some cases of euthyroid ophthalmic Grave's disease and multinodular goitre.
A late rise in TSH may be seen rarely in thyroid and pituitary disease as well as hypothalamic disease.

REFERENCE

Hall et al., Lancet i: 759-63 (1972).
ATH 11/89

GONADOTROPHIN RELEASING HORMONE GnRH/LHRH TEST

INDICATION

1) To further investigate possible gonadotrophin deficiency.
2) To confirm precocious puberty.

PREPARATION

Overnight fast not necessary if done alone.

In women with a normal menstrual cycle the test should be performed in the follicular phase (day 3-7 of the cycle).

Larger dose or priming with LHRH if suspected of hypogonadism may be necessary.

(N.B. Do not prime with sex steroids if indication 2 above)

100 mcg LHRH (GnRH – Gonadorelin).

3 clotted tubes (red top Vacutainers – 7 ml)

METHOD

1. Site indwelling cannula.
2. Take baseline bloods: LH, FSH and testosterone (M) or oestradiol (F).
3. Inject GnRH intravenously.
4. Flush cannula with saline.
5. Take samples for LH and FSH at t = 30 and 60 mins.

INTERPRETATION

- The normal peaks can occur at either 30 or 60 minutes. LH should exceed 10 U/l and FSH should exceed 2 U/l. An inadequate response may be an early indication of hypopituitarism.
- Gonadotrophin deficiency is diagnosed on the basal levels rather than the dynamic response. In males this is based on low testosterone in the absence of raised basal gonadotrophins and in females low oestradiol without elevated basal gonadotrophins and no response to clomiphene.
- Pre-pubertal children should have no response of LH or FSH to LHRH. If sex steroids are present (i.e. the patient is undergoing precocious puberty), the pituitary will be “primed” and will therefore respond to LHRH. Priming with steroids MUST NOT occur before this test.

SENSITIVITY AND SPECIFICITY

This test has a low sensitivity and specificity for hypogonadotrophic hypogonadism. The response may be normal or even exaggerated (especially in patients with hypothalamic disease). Basal levels are better discriminants. Serial investigations in patients with pituitary disease especially irradiation may give early indication of the development of hypopituitarism.

REFERENCE

Mortimer et al., BMJ, 3: 267-271.

ATH 11/89, AP 1/98.

COMBINED PITUITARY FUNCTION TESTS (CPT)

INDICATION

Assessment of all components of anterior pituitary function used particularly in pituitary tumours or following tumour treatment.

CONTRAINDICATIONS

Ischaemic heart disease.

Epilepsy.

Untreated hypothyroidism (impairs the GH and cortisol response).

SIDE EFFECTS

Sweating, palpitations, loss of consciousness and rarely convulsions with hypoglycaemia.

Patients should be warned that with the TRH injection they may experience transient symptoms of: a metallic taste in the mouth, flushing and nausea.

PREPARATION

The patient should fast overnight and be recumbent during test.

ECG must be normal and the patient's weight known.

In peri-pubertal children (bone age >10 years) priming is needed

M: 100 mg testosterone i.m. 3 days before testing

F: 100 mcg ethinyloestradiol p.o. each for three days before the test.

Calculate Actrapid Insulin dose:

Normal pituitary function	0.15 U/kg
Hypopituitary	0.10 U/kg
Acromegaly, diabetes, Cushing's	0.2-0.3 U/kg

TRH (Roche) 200 micrograms as slow i.v. injection.

LH/FSH releasing hormone (GnRH) – 100 mcg as i.v. bolus.

50mls 50% dextrose available for immediate administration.

Cannula, 18-20g.

Glucometer.

6 fluoride tubes (grey top Vacutainers).

7 clotted tubes (red top Vacutainers) for samples.

500 ml bag 0.9% saline to flush cannula.

3 way tap to assist the taking of samples.

STANDARD METHOD

1. Site indwelling cannula.
2. Take baseline blood samples for testosterone/oestradiol, prolactin, thyroxine, LH, FSH, TSH, GH, cortisol (14 ml clotted) and glucose (2 ml fluoride).
3. Then at T = 0 inject insulin and GnRH i.v. as boluses followed by the TRH over 2 minutes.
4. Take samples for LH, FSH, TSH, prolactin, GH, cortisol (7 ml clotted) and glucose (2 ml fluoride) at 30, 60 minutes and GH, cortisol, glucose at 90 and 120 minutes.
5. Flush the cannula with saline between samples.

6. At 30 minutes check blood glucose with Glucometer and repeat the insulin dose if not hypoglycaemic. Adequate hypoglycaemia (2.2mmol/l) should be symptomatic. Record symptoms in the notes.
7. Hypoglycaemia should be reversed by giving i.v. 50% dextrose, or i.m. glucagon (1 amp) and continue sampling. Take further samples for GH, cortisol and glucose at 90 and 120 minutes. There must be at least 2 specimens following adequate hypoglycaemia.
8. At all times a doctor or nurse must be in attendance.
9. If the patient has a hypoadrenal crisis with hypotension then they should be given i.v. 0.9% saline and hydrocortisone.
10. Once test completed, give supervised meal.
11. Patient should not drive for 2 hours after the test.

"SPLIT" COMBINED PITUITARY FUNCTION TEST

This test is no longer used, but the details are kept for historical reasons and for those sitting the part 1 MRCP (!) In patients with prolactinomas, and in some acromegalics with near-normal GH levels, it is useful to monitor the responses to TRH and GnRH alone. This test is only useful after treatment if it is known there was an abnormal test result prior to treatment. In these patients, the test is "split" as follows:

Time	Glucose	TSH	T4	PRL	GH	LH	FSH	Testo/E2	Cortisol
0		Take	Take	Take	Take*	Take	Take	Take	
Give GnRH 100 mcg IV bolus and TRH 200 mcg IV over 2 mins									
30		Take		Take	Take*	Take	Take		
60	Take	Take		Take	Take	Take	Take		Take
Give insulin IV bolus as calculated above.									
90	Take				Take†				Take
120	Take				Take†				Take
150	Take				Take†				Take
180	Take				Take†				Take

*only if an acromegalic with low GH

†not needed if acromegalic with low GH

INTERPRETATION

The interpretation of the different components of the standard CPT is listed under the insulin tolerance test, the TRH test and the GnRH test.

In the "split" protocol it is possible to observe the isolated response of GH and Prolactin to TRH. In normals the prolactin will rise by 100% of its basal value while in patients with prolactinomas there is frequently a subnormal response. In normals there is a reduction in GH with TRH but there is a rise in 80% of acromegalics. It is only worth using the "split" protocol on a patient following treatment if they were tested by this protocol pre-treatment. The loss of the paradoxical rise to TRH in acromegaly is a good indicator of successful treatment.

ATH 12/89

VISUAL FIELD TESTING (GOLDMANN or HUMPHRIES PERIMETRY)

INDICATION

Before and after pituitary surgery and before and during pregnancy in patients with macroprolactinomas.

METHOD

At Charing Cross this is done by the Orthoptists. Contact Caroline Calcutt (x1497 or 1132). At Hammersmith they are done on Monday mornings or all day on Tuesday, but still phone her on 1132 to book . If you are doing it yourself, follow the instructions below.

1. There is an automated Visual field (Allergan Humphrey) testing machine in the eye room of clinic A (room A11). It is computer controlled and fairly user friendly.
2. Switch machine on. It will perform a self test taking about 5 minutes. Once this is complete the computer will ask you several patient details, such as which eye you are testing. These can be easily fed in using the screen touch sensitive pen.
3. Cover one eye with the eye patch present on top of the machine. Place the patient's chin on the rest at the centre of the hemisphere and the head against the upper band. You will need to manually adjust the position of the chin rest (using the rotating control) until the patient, when looking straight ahead, can see a yellow dot.
4. The patient must be given the hand held pushbutton and told to fix on the yellow dot. He must press the button whenever he sees a flash of light anywhere in the sphere. The patient may need his glasses to allow him to see the object.
5. When the patient is ready, simply select "AUTOMATIC DIAGNOSTIC TEST" from the menu. The machine will automatically find the blind spot and proceed to check the entire visual field by flashing lights at random. It will also check that the patient continues to fixate on the yellow dot by occasionally checking his blind spot.
6. When complete, a printout of the field can be obtained. Repeat the procedure for the other eye.

INTERPRETATION

Formal perimetry is highly accurate and reproducible. Field loss is always significant; it can occur as the result of the pituitary tumour or from the treatment of the tumour. If an increasing field loss is noted it is vital that the patient has a CT scan on that admission.

KM 7/94 (updated 7/01)

SUSPECTED CUSHING'S DISEASE

Order 2 vials of CRH for any patient with suspected Cushing's. Patients need a CRH test after their LDDST and also for their IPSS. Book three admissions at the start (one for midnight cortisol, LDDST and CRH test, the second for HDDST and the third for IPSS), and book the IPSS with James Jackson. Overnight dexamethasone suppression testing and isolated CRH testing are not used in our department, but the methods are at the end of the section for completeness.

LOW DOSE DEXAMETHASONE SUPPRESSION TEST + CRH

INDICATION

Screening test for Cushing's syndrome, especially if the result of the overnight suppression test contradicts other investigations. In women with a high testosterone this test may be used to differentiate PCO and partial hydroxylase deficiencies (CAH) from autonomous androgen secreting tumours.

CONTRAINDICATIONS

Patients on enzyme inducing drugs e.g. anti-convulsants may rapidly metabolise dexamethasone.
Oestrogens (e.g. pregnancy, HRT or COC) may induce cortisol binding protein and artificially increase total cortisol levels.
Care in diabetes mellitus and patients who are psychologically unstable.

PREPARATION

This is usually an inpatient test with no particular patient preparation. Occasionally the test can be done as an outpatient if you believe the patient is likely to have their tablets on time. They need a 9am cortisol at the start and end of the test. The final (9^{th}) dose is given with the patient nil by mouth, and the CRH given 2 hours later.
Stop all oral oestrogen therapy 6 weeks prior to test. Patients on sex steroid implants might generate results that are difficult to interpret. Measuring SHBG and CBG might be helpful in this circumstance. A sample for gut hormones (in a green topped (heparinised) bottle with trasylol (200 mcl)) should be sent with each of the cortisol samples.

METHOD

1. The patient takes 0.5 mg dexamethasone p.o. at *strict* 6 hour intervals (i.e. 0900h, 1500h, 2100h and 0300h) for 48 hours.
2. The cortisol (red top), ACTH (purple top) and gut hormones (green top with trasylol) are measured at 0900h (before the first dose) on the first day ("T=0") of the test and 24 ("T=24") and 48 hours later (6 hours after the last dose) ("T=48"). Samples are taken in red top Vacutainers (serum) for cortisol and purple top tubes on ice for ACTH. The red topped sample can be used to measure SHBG and CBG if needed.
3. A total of eight doses of dexamethasone should be written up (9am, then 3pm, 9pm, 3am, 9am, 3pm, 9pm, 3am). The ninth dose should be written up AFTER the blood sample at 9am has been collected on day 2. If the test starts on a Sunday morning (day 0), the CRH test will be done on Tuesday (day 2). It is important that no food is taken that morning, as variability in absorption of

dexamethasone for those 2 hours may result.

4. Blood taken on day 1 at 9am (“T=24”)(immediately before that dose) and day 2 at 9am (“T=48”) and a **FURTHER** dose (dose 9) of dexamethasone is given at 9am. A CRH test should follow **exactly** 2 hours after that dose of dexamethasone (11am on Tuesday if the test starts on Sunday (common at Charing Cross) and 11am on Wednesday if the test starts on Monday (more common at Hammersmith)) (“T=50”). This timing after the last dose of dexamethasone seems to be critical, as it will affect the 11.15 sample (“T=50+15”). The patient must FAST from midnight before the CRH test, as food will affect dexamethasone absorption in the 2 hours before the CRH test. Thus blood is taken at 11am (called “T=50” as it is 50 hours into the test) and again 15 minutes after CRH (at 11.15 (“T=50+15”))
5. A high dose dex suppression test **can** then be commenced (at 11.30 am) to finish at 9am on Friday, or on Thursday morning to finish on Saturday morning.

INTERPRETATION

If the 0900h cortisol (“T=48”) value is less than 50nmol/l the patient has shown suppression. Failure to suppress is seen in the autonomous secretion of cortisol found in Cushing's syndrome. In virilisation from PCO or partial hydroxylation deficiencies there will be suppression of testosterone. This is not seen in ovarian or adrenal tumours.

The 11.15am (“T=50+15”) plasma cortisol following the CRH test that follows the LDDST (2h after the last dose of dexamethasone and then 15 minutes after the CRH) should be <38 nM. A cortisol > 38nM at this timepoint is indicative of Cushing’s syndrome.

There is as yet no data as to the value of the “T=50” sample (just before CRH administration).

SENSITIVITY AND SPECIFICITY

Suppression in patients with Cushing's syndrome is rare (2-5%). Some reported cases metabolise dexamethasone slowly and so achieve higher circulating levels than expected. This test is more specific than the overnight suppression test with a lower false positive rate. Failure of suppression in patients is rarely seen in patients with systemic illness, endogenous depression, or on enzyme inducing drugs e.g. phenytoin or rifampicin.

In virilisation some cases of PCO do not show suppression so imaging and venous sampling is required to exclude ovarian or adrenal tumours.

For the CRH test after dexamethasone, a cortisol >38nM at T=50+15 minutes is 100 sensitive and 100 % specific. (Yanovski).

REFERENCES

Crappo A., Metabolism 28, 955-979 (1979). Yanovski (1993) : JAMA: 269(17): 2232-2238
Newell Price: Endocrine reviews: 19(5): 647-672.

ATH 11/89, KM 07/02, KM 01/03

HIGH DOSE DEXAMETHASONE SUPPRESSION TEST

INDICATION

Patients with definite Cushing's syndrome of unknown aetiology.

CONTRAINDICATIONS

Patients on enzyme inducing drugs e.g. anti-convulsants may rapidly metabolise dexamethasone. Oestrogens (e.g. pregnancy, HRT or COC) may induce cortisol binding protein and artefactually increase total cortisol levels. Take care in patients with severe depression or hypomania.

PREPARATION

Stop all oral oestrogen therapy 6 weeks prior to test. Again implants can cause problems.
This is an inpatient test and should only be performed after at least 2 baseline values for 24 hour urinary free cortisol and 0900h cortisol and ACTH levels (see below).

METHOD

1. This test often follows the LDDST. The final sample from the LDDST (2+48) can often be used as the basal sample for this test. Basal 0900h cortisol (red top Vacutainer) and ACTH (purple tops Vacutainers on ice) are measured ("8+0").
2. During the test the patient takes 2 mg dexamethasone p.o. at *strict* 6 hour intervals (i.e. 0900h, 1500h, 2100h and 0300h) for 48 hours.
3. The cortisol and ACTH are measured at 0900h on the first day of the test and 48 hours later ("8+48"). In some patients the dexamethasone may be continued for 72 hours in which case an additional 0900h serum cortisol and ACTH are taken ("8+72").

INTERPRETATION

If the 0900h cortisol is less than 50% (some say 90%) of the basal value after 48 hours of dexamethasone this is classified as showing suppression. Suppression with high dose dexamethasone is usually seen in Cushing's disease but not in ectopic ACTH production or adrenal tumours.

SENSITIVITY AND SPECIFICITY

The high dose dexamethasone test is useful but not totally reliable in the differential diagnosis of Cushing's syndrome as it is neither very sensitive nor specific. Suppression occurs in 75% of patients with Cushing's disease, 10-25% of patients with ectopic ACTH and 0-6% of patients with adrenal tumours. Patients with ectopic ACTH who show suppression tend to have occult and relatively benign tumours with lower levels of ACTH and cortisol. These patients are very hard to differentiate from Cushing's disease.
The 0900h cortisol after 48 hours is considered to be the best parameter to use to discriminate between Cushing's disease and ectopic ACTH. The criterion of 50% suppression at 48 hours should not be applied too rigidly as many cases of Cushing's disease will suppress by 40 or 45% or suppress after 72 hours. In difficult cases it is advisable to repeat the test as no patients with an adrenal tumour have been shown to have reproducible suppression and cases of Cushing's syndrome may show cyclical variation.

REFERENCES

Crappo A., Metabolism 28, 955-979 (1979).

BILATERAL SIMULTANEOUS INFERIOR PETROSAL SINUS SAMPLING (IPSS) WITH CRF

INDICATION

Patients with Cushing's syndrome and high ACTH levels in whom there is not a clinically definite pituitary source. The aim of this test is to differentiate pituitary from a non-pituitary source of ACTH and to lateralise a corticotroph adenoma.

CONTRAINDICATIONS

(Discuss with interventional radiology x34943)

Allergy to contrast dye.
Ischaemic Heart Disease.
Orthopnoea.
Bleeding tendencies (severe).

PREPARATION

Metyrapone and ketoconazole need to be stopped 1 week before IPSS.
Order synthetic **human (or ovine) CRF** in advance from Pharmacy (allow 5 days). DDAVP (10 micrograms IV) is a poor but possible alternative if CRH is not available. Document (in the notes) what type of CRH is being used.
Warn endocrinology lab (34681) 48 hours in advance.
Consent patient (risks of bleeding from cannula sites, CVA, dye allergy, pulmonary embolus). This should be performed by the radiologists.
The day before the procedure, check FBC, U + E, INR, G + S.
Fast for at least 4 hours.
2 people to attend to assist sample processing.
18 red Vacutainers.
18 EDTA Vacutainers, labelled before the study.
Syringes for sampling and flushing cannulae.
Ice.
Arrangements to transfer for immediate centrifugation.

SIDE EFFECTS

CRF can cause flushing and hypotension but this is rare with 100 mcg.
No complications of IPS sampling have been reported in over 50 patients reported in the literature, but we have had one patient who had a pulmonary embolus following the procedure and one who became asystolic during the procedure, but recovered when the procedure was abandoned.

METHOD

1. One catheter is placed in each inferior petrosal sinus (IPS) and their position confirmed on screening. A third catheter is placed peripherally (P) in the arm.
2. Two baseline samples are taken at approximately -5 and 0 minutes. Ask the radiologist for 10 ml from each site: one purple for ACTH and one red Vacutainer at each site. At T = 0 the CRF is injected intravenously as a bolus over 1 minute peripherally. For adults the dose is 100 mcg or

60mcg per square meter body surface in children.

3. Simultaneous samples from the 3 sampling sites are taken at T = 2, 5, and 10 minutes. At the same time as one of the sets of basal samples an arterial sample may be taken from the femoral artery if a pulmonary source of ACTH is possible, and peripheral samples may be taken at T = 60 and 90 minutes (see below). Only samples taken for ACTH should be stored in ice and spun within 15 minutes.
4. ACTH is measured in all samples. Cortisol is measured in the basal samples from all sites and in all the peripheral samples. Prolactin is measured in both IPS series.

INTERPRETATION

- A basal IPS:P ratio ≥ 2.0 indicates a pituitary source with 95% sensitivity and 100% specificity. A CRH stimulated ratio ≥ 3.0 increases the sensitivity to 100%, the 2 and 5 minute samples usually being sufficient. Pituitary ACTHomas are usually paramedian or lateral and there is suppression of the normal corticotrophs on the contralateral side (Crooke cell changes).
- If in addition the basal or stimulated ACTH level for one IPS sample is 1.5 times as high as the simultaneous contralateral side, this localises the pituitary tumour to the ipsilateral side with a sensitivity of 99% and a specificity of 82%. It has also been reported that prolactin and GH are often raised on the side of the tumour and that this is augmented by CRF.
- In IPS sampling the principal difficulty arises from the positioning of the sampling catheter. Jugular venous samples do not consistently show lateralisation. The measurement of prolactin can be used as a marker of proximity to the pituitary.
- Using the peripheral samples it is possible to look at the response to CRF of venous levels of Cortisol. The interpretation of this response is difficult but in general patients with Cushing's disease tend to have an exaggerated response (>850 nmol/l) and ectopic ACTH sources have a reduced response. The interpretation of the CRF test at present is uncertain as the reported series use different end points, varying doses of CRF and small numbers of patients. Until there is more local experience (see above) of this test it should not be used to differentiate sources of ACTH.
- It appears that in ectopic ACTH production a cortisol response greater than normal has not been described. It is not a sensitive test as approximately 25% of Cushing's disease do not respond to CRF with cortisol responses greater than normals.

REFERENCES

IPS sampling: Clinical Endocrinology 25, 687-96 (1986).
CRF test: A. Grossman et al., Clinical Endocrinology 29, 167-178 (1988).
Petrosal sinus sampling: NEJM 325, 897-905 (1991).

ATH; PJH 8/92.; KM 07/02

TREATMENT OF PATIENTS WITH CONFIRMED CUSHING'S SYNDROME.

If the IPSS confirms pituitary Cushing's, the patient should be booked for pituitary surgery at Charing Cross in about 6 weeks. As soon as the diagnosis is confirmed, medical treatment with ketoconazole (200mg bd) should be commenced. Monitor cortisol and LFTs weekly. If cortisol > 250 nM, double ketoconazole to 400 mg bd. A week later, add metyrapone 250 mg tds, if cortisol >250 nM. Aim for

cortisol of 150-300 nM in the weeks before surgery.

PERIPHERAL VENOUS SAMPLING FOR SOURCES OF ECTOPIC ACTH

This is no longer performed at Hammersmith in view of its low sensitivity.

OVERNIGHT DEXAMETHASONE SUPPRESSION TEST

INDICATION

Initial screening test for Cushing's syndrome in a patient with a low clinical suspicion of Cushing's. If you have a high index of suspicion of Cushing's, omit this test and go directly to the LDDST + CRH.

CONTRAINDICATIONS

Patients on enzyme inducing drugs e.g. anti-convulsants may rapidly metabolise dexamethasone.
Oestrogens (e.g. pregnancy, HRT or COC) may induce cortisol binding protein and artefactually increase total cortisol levels.
Urine collection for 24 hr urinary free cortisol must not occur during this test.

PREPARATION

Outpatient test with no particular patient preparation.

METHOD

1. The patient takes 1 mg dexamethasone p.o. at 2300h and the 0900h cortisol is measured the next morning (7 ml clotted blood, in red top Vacutainer).
2. If the patient is collecting a 24hr urine sample for urinary free cortisol this should be completed before taking the dexamethasone.

INTERPRETATION

If the 0900h cortisol value is less than 35 nmol/l the patient has shown suppression. Failure to suppress is seen in the autonomous secretion of cortisol found in Cushing's syndrome. With this cut off, there will be a high false positive rate.

SENSITIVITY AND SPECIFICITY

Suppression in patients with Cushing's syndrome is rare with this test (2%). The reported cases metabolise dexamethasone slowly and so achieve higher circulating levels than expected. If there is strong clinical or biochemical evidence for Cushing's syndrome this test should be repeated or a formal low dose dexamethasone test performed.
Normal subjects rarely (2%) fail to suppress with overnight dexamethasone unless they are depressed (10-50%), obese (10%) or systemically unwell (10-20%). The formal low dose dexamethasone test is more specific.
This is a good screening test especially if combined with urinary free cortisol.

CRH TESTING (without dexamethasone).

Samples for ACTH should be collected in purple topped EDTA tubes and stored on ice in transit and taken rapidly to the lab to be centrifuged. This test will thus need regular transport to the lab. Samples for cortisol are red topped and can clot.

PREPARATION

Fast from midnight.
Label eight (8) tubes for ACTH (purple top) and eight (8) tubes for cortisol (red top).
Admit Monday 8.30 am. Cannulate and take basal Cortisol and ACTH at 8.30am.
Patient to remain recumbent until 9am (and fasted).

METHOD.

(Two further baseline samples at –15 mins (8.45 am) and 0 mins (9am) for ACTH and Cortisol).
Administer 100 micrograms human CRF at t=0.
Then sample at 15, 30, 45, 60, 90 and 120 mins (final sample 11am: for ACTH and cortisol at all timepoints.).

INTERPRETATION.

A rise in **cortisol** from basal to peak of >20% suggests a pituitary source.
A rise in **ACTH** from basal to peak of > 50% suggests a pituitary source.
Ref: Kaye and Crappo (1990). Ann Intern Med. 112: 434-444

A rise by 35% in **ACTH** at +15 and +30 minutes (mean) in comparison to the basal (-1 and –5 minutes) values suggests a pituitary source. Ref: Nieman etal (1993). JCEM 77: 1308-1312.

Please note that ovine (oCRF) was used in most studies. Human (hCRH) appears less potent, so smaller rises may be acceptable, suggesting Cushing's disease.

CORTISOL DAY CURVE (Cushing's syndrome only)

INDICATION

Assessment of control of Cushing's disease on therapy or after discontinuation of treatment.

CONTRAINDICATIONS

None

SIDE EFFECTS

None

PREPARATION

Stop all oestrogen therapy 6 weeks prior to test.
Non-fasting: breakfast and normal dose of tablets are taken at the usual time.
18-20g cannula.
6 red top Vacutainers.
Syringes.

METHOD

0900h	}	
1200h	}	Take blood
1500h	}	for cortisol
1800h	}	measurement
(2400h)	}	

INTERPRETATION

Normal response is a mean serum cortisol between 150 and 300 nmol/l, and should be maintained while patients are awaiting an adrenalectomy.
Higher levels indicate a need for increased therapy.

Random concentrations of cortisol can also be used on a day to day basis to determine effectiveness of cortisol suppression on medical treatment (with Ketoconazole (up to 400 mg bd), Metyrapone (up to 750 mg tds) or etomidate (3mg per hour by IV infusion).

REFERENCE

Trainer et al., Clin. Endo. 39, 441-443 (1993).

VERSION HISTORY

KM 07/01

PROLACTINOMAS AND NON FUNCTIONING PITUITARY ADENOMAS

Prolactinomas generally have a very high prolactin. Non functioning adenomas (NFA's) also might have a high prolactin.

Drug history and pregnancy test.
Non functioning pituitary adenomas have the capacity to cause "disconnection hyperprolactinaemia", where the mass physically blocks the transfer of dopamine to the lactotrophs. Such patients (with NFAs) may present with amenorrhea and even galactorrhoea. Levels of prolactin of up to 4000 mU/l can occur with macroadenomas. Non functioning microadenomas (present in 10% of the population) do not cause hyperprolactinaemia.

Prolactinomas generate levels of about 2000 mU/l even when extremely small (2mm for example). Large (macro) prolactinomas typically have very high levels (10,000 mU/l to 1,000,000mU/l).
Very high levels are subject occasionally to the hook effect, whereby the assay reports a normal prolactin in the presence of extremely high concentrations of prolactin unless the laboratory dilutes the sample.
Another assay problem to be aware of is MACROPROLACTIN. This confusing term refers to the falsly elevated report that one can get from an antibody reaction with prolactin. It is more accurately called "big prolactin". The patients have normal biologically active prolactin, but have reports of elevated levels.

Protocol for distinguishing prolactinomas from NFAs:

Day 0: take blood for prolactin, then ask patient to take 250ug of cabergoline
Day 3: take blood for prolactin
Day 7: take blood for prolactin

Distinguishing prolactinomas from NFAs can be tricky. A marked fall in prolatin following a single dose of bromocriptine or cabergoline suggests a NFA, whereas prolactinomas have a more gradual fall.

Treatment of NFAs does not respond (in terms of size) to dopamine agonists whereas prolactinomas shrink. Dopamine agonists might still be useful to suppress the prolactin to prevent amenorrhoea and galactorrhoea in NFA patients.

Pregnancy and the pituitary.
The normal pituitary lactotrophs expand during pregnancy and can push up a NFA towards the optic chiasm, so regular field testing is essential in macroadenomas. Prolactinomas (micro and macro) often grow during pregnancy. Dopamine agonists can be continued, and in difficult cases up to 1.5 mg cabergoline daily has been used with good effect. This is NOT licenced. Bromocriptine has been around since 1974, and is thus often favoured in pregnancy although cabergoline seems to have fewer side effects. Pituitary expansion continues during breast feeding, and thus full discussion of risks and benefits of breast feeding need to be discussed with the patient.

PITUITARY TUMOURS

OPERATIVE MANAGEMENT OF PITUITARY TUMOURS (CXH)

PRE-ADMISSION

Patient should have had:

- Full endocrine assessment.
- Neurosurgical assessment.
- Neuro-ophthalmological assessment including Humphrey fields in previous 6/12
- Baseline investigations:
  CT/MRI brain
  Free T4, TSH, prolactin, oestradiol (females), testosterone (males), FSH, LH, profile.
  ECG and CXR if age >60 years.
  IGF-1, GH, with oral GTT if clinically indicated
- If prolactinoma confirmed, treat with dopamine agonist drug (eg. Cabergoline), then repeat CT/MRI scan (1-3 months after prolactin normalised or at minimum plateau). Surgery indicated if tumour non-responsive.
- Check TFTs. If patient is hypothyroid need short synacthen test to exclude associated steroid dependency. Replace with T3 20 mcg tds for 4 days pre-op if surgery urgent, or thyroxine if surgery not imminent.
- Cushing's disease: start patient on drugs, titrating to random cortisol 150–300 nmol/l:
  Ketoconazole: 200 mg bd – needs weekly LFTs initially, can cause hepatitis
  Metyrapone: 250 mg bd to 750 mg tds – side effects are lethargy, peripheral oedema, hirsutism
  Etomidate: up to 3mg per hour by IV infusion.

PRE-OPERATIVE MANAGMENT

- Confirm neurosurgical operating date (day 0) with consultant neurosurgeon, Mr. Nigel Mendoza (Day 0, Usually a Thursday). If surgery is on Wednesday, call this day –1, so that the protocol below is not affected. (Thursday remains day "0"). If surgery is on Friday, treat this as "day 1" and proceed directly to dexamethasone over the weekend.
- Admit 1-2 days pre-op. (Surgical decision).
- For trans-cranial surgery: dexamethasone 4 mg qds, start 1 day pre-op.
- For trans-sphenoidal surgery:
  Hydrocortisone 100 mg i.m. qds starting with pre-medication. (An IV infusion of 4.2 mg per hour (100 mg over 24 hours) is an alternative).

POST-OPERATIVE MANAGEMENT OF HYDROCORTISONE

- Write up (a drug chart with this information is available on http://meeran.info with the link "CRH chart):
  Day 1: Three doses of hydrocortisone 50 mg i.m. on day 1 (9am, 3pm, 9pm (usually Friday). (Or continue the IV infusion of 4.2 mg per hour = 100 mg over 24 hours).
  Day 2 + 3 (Sat + Sun) dexamethasone 0.5 mg 6 hourly starting at 9am. This serves both as replacement steroid and a low dose dexamethsone suppression test. (8 doses, last at 3am on

Monday morning).

Day 4 (Mon) NIL BY MOUTH until 11.15 am (food may affect dexamethasone absorption). An urgent morning (9am) cortisol sample needs to be sent to lab **and then a ninth dose** of 0.5 mg dexamethasone administered with the patient NIL BY MOUTH.

Blood should be taken at 11am for cortisol and CRH 100 mcg administered intravenously immediately. A further sample for cortisol should be taken **exactly** 15 minutes later.

After the test, the patients should not have any further steroid that day (0.5 mg dexamethsone will cover them for the day).

Day 5: The following morning, (usually Tuesday) an urgent 9am cortisol should be sent.

After the test, start HC 10mg + 5mg + 5mg and discharge on this dose.

- Interpretation of cortisol result from day 5 (not Cushing's disease – usually non functioning):
  If cortisol >350 nmol/l, then can be sent home without hydrocortisone.
  If 300-350 nmol/l, then use clinical grounds and pre-op assessment.
  If < 300 nmol/l, then continue hydrocortisone.
- Interpretation of cortisol result (if Cushing's disease):
  If cortisol is detectable, use the results of the dexamethsone suppression test to determine whether further pituitary surgery is urgently indicated.

  If surgery is on a Monday or Tuesday, dexamethasone should be started on Wednesday, so that the CRH test will be on Friday.

POST OPERATIVE MANAGEMENT OF DIABETES INSIPIDUS

- Fluid balance charts should be kept. A spot urine osmolality is checked every 4 hours.
- If urine output >1l per 4 hrs consider desmopressin (adult dose 0.5-1.0 mcg s.c. q6h). Prior to administration check paired plasma and urine osmolality.
- DI is confirmed by the presence of a high plasma osmolality (>295) in the presence of an inappropriately low urine osmolality (U:P ratio <2:1). (urine SG < 1.005).
- If the plasma osmolality is low the patient may be over-drinking due to a dry mouth. A low urine osmolality is appropriate.

ON DISCHARGE

- Discharge drugs HC 10mg + 5mg + 5mg
- Advise patient regarding increasing dose with illness etc.
- Arrange electrolytes (esp Na) to be measured the following Monday (10 days postop) as there is a risk of hyponatraemia, especially if the patient had Cushing's disease.
- Steroid card and contact details of MEDIC ALERT (see index).
- Pituitary stimulation tests and ITT (±OGTT for acromegaly) to be performed 3-4 weeks post-op following cessation of steroids from the night before test. Hydrocortisone to be resumed after test until results known.
- Endocrine follow up should be 6 weeks post-op.

- Joint pituitary endocrine clinic 3 months post-op (list F27), when Nigel Mendoza should organise an MRI. (Discuss with Laura – ward clerk).
- Radiotherapy referral if appropriate.
- If patients have had Cushing's disease, and do not need hydrocortisone replacement, dexamethasone suppression tests should be performed regularly (at least 2-3 yearly). (risk of recurrence).
- Patients on hydrocortisone should be offered an ITT 2 years after surgery as there is a chance of recovery of corticotrophs (or recurrence).

AP 01/98, KM 07/01

HYDROCORTISONE DAY CURVE (HCDC)

INDICATION

To establish the correct dose and distribution of hydrocortisone replacement therapy throughout the day.

CONTRAINDICATIONS

None

SIDE EFFECTS

None

PREPARATION

Stop all oestrogen therapy 6 weeks prior to test.
No need to fast.
Take normal morning hydrocortisone and patient should note down actual time taken.
18-20g cannula.
Red top Vacutainers.
Syringes.

METHOD

Take blood at the following times:

- Blood sample on arrival, noting time of sample and time and dose of hydrocortisone.
- Pre lunchtime (2^{nd}) dose
- 1 hour post lunchtime (2^{nd}) dose
- pre evening (3^{rd}) dose
- post evening (3^{rd}) dose or at 6pm.

INTERPRETATION

Aim for adequate cortisol levels throughout the day (peak <900 nmol/l, trough >100 nmol/l).
As a very rough guide, the values below are what we commonly find. Minor departures do not necessarily need dose adjustment, especially if the patient is well.
morning peak cortisol 500 – 800 nM
lunchtime peak cortisol 400 – 500 nM
post evening dose 300 – 400
Once adequate levels are achieved, this rarely needs to be repeated, unless there is a significant change in other medication (eg. Starting HRT).

VERSION HISTORY

KM 7/00.

GROWTH HORMONE

A Word on UNITS

2.59 mU=1 mcg. This is controversial, and some authorities use 2mU as 1mcg and others use 3mU as 1mcg. This is because mU were originally defined using a bioassay, and hence their value varies between laboratories. In this document, please use 2.59 mU as 1 mcg. This is important both because administration of GH is now changing to mcg of GH. Thus a “safe” level of GH in acromegaly is <5mU/l or <1.9 ng/ml.

Human Growth Hormone (HGH) Prescribing for Adult onset Growth Hormone Deficiency (AOGHD)

The prescription of HGH follows NICE guidelines, (issued August 2003). HGH is recommended if the patient fulfils the following 3 criteria.

1. Confirmed severe GH deficiency, peak GH of less than 9 mU/L on ITT, or a cross-validated GH threshold in an equivalent test (e.g. Glucagon Stress Test).
2. Perceived Quality of Life impairment, measured using the Quality of Life assessment of Growth Hormone Deficiency in Adults (QoL-AGHDA) questionnaire, score has to be 11 or greater (total of 25 questions).
3. The patient must be on full replacement for any other pituitary hormone deficiencies

Once on a maintenance dose, the patient continues for a 6-month trial period of GH replacement, followed by a repeat AGHDA. If the patient’s score improves by 7 or more (that is a decrease of at least 7), they qualify to continue long term GH replacement. If not then it is recommended to stop.

N.B.
In young adults (<25 yrs, linear growth completed but not reached peak bone mass) with confirmed severe GH deficiency, GH is recommended until peak bone mass is achieved and then reassess as above with AGHDA

Treatment is self administered by a daily subcutaneous injection. Start at a low dose (0.1mg-0.2 mg daily) and titrate up (by 0.1 mg) at monthly intervals, by monitoring IGF-1, and response to adverse effects, until a maintenance dose is achieved, ideally within 3 months. The current median maintenance dose is 0.4 mg daily. We aim for an IGF-1 level in the middle of the reference range (age and sex matched). Women may require a higher dose than men and the dose requirement may decrease with age.

The IGF-1 may be within normal range pre GH replacement, and some centres aim for the median or upper half of the normal range on treatment.

Side Effects may include headache, arthralgia, myalgia, fluid retention, mild hypertension, carpal tunnel syndrome, visual problems, nausea and vomiting, paraesthesia, antibody formation, reactions at the injection site, rarely benign intracranial hypertension (reverses off treatment).

Contraindications for GH
Evidence of tumour activity
Critically ill patients
Known hypersensitivity to GH or any of the excipients
Pregnancy and lactation
Preproliferative or proliferative Diabetic retinopathy

Practicalities re prescribing GH.
You need to
1.Provide the prescription, GH is available from the hospital pharmacy (and not usually the GP as it is a red listed drug)
2.Fax a patient information form to the drug company (who supply syringe etc, and fund first part of treatment)
3.Fax a referral form to the drug company nurse who arranges a home visit to the patient to educate re administering injection

Monitoring of treatment in OPD
Blood pressure, weight, waist/hip circumference
IGF-1, glucose
Lipids annually
BMD at 2-3 yrs if osteopenia/osteoporosis present pre treatment
MRI pituitary pre treatment and 3-6 months after GH commenced.

EH 07/05

EXERCISE TEST

INDICATION

Used in a child with definite growth retardation preferably as assessed by reduced growth velocity and a random serum growth hormone (GH) of <15 mU/l. It is a physiological screening test used before formal testing of GH secretion (e.g. insulin tolerance test, arginine stimulation test).

METHOD

1. If child has difficult veins, cannulate before the test (butterfly is sufficient).
2. Take blood sample for GH (into a red top Vacutainer) at T = 0.
3. Take child to the outpatients staircase and note the time
4. Child should then run up and down the first flight of stairs, as hard and as fast as possible, for at least 10 mins and until the child becomes breathless and moderately fatigued
5. Take blood sample for GH 30 mins after the onset of exercise

INTERPRETATION

A normal GH response of > 15 mU/l (5.7 ng/ml) absolves the endocrinologist of any further investigation of GH deficiency. It excludes the need for proceeding to the more laborious and hazardous formal tests. A subnormal response (GH < 15 mU/l) means the child should be considered for a formal test though a

repeat exercise test may be valuable (see below).

SENSITIVITY AND SPECIFICITY

A child with GH deficiency will not respond to this test. The percentage of children who are not GH deficient and who show a normal response varies depending on the test used and the peak GH value taken as "normal". Values vary from 68–91%. Repeating the test can also improve the detection rate of normals from 80–92%.

REFERENCE

Milner R.D.G. & Burns E.C., Arch. Dis. Child. 57, 944-947 (1982).

VERSION HISTORY

MLB 12/89

ARGININE STIMULATION TEST

INDICATION

Used in a child with definite growth retardation and a subnormal physiological growth hormone (GH) stimulation test (i.e. GH < 15 mU/l or 5.7 ng/ml).

PREPARATION

Child should be fasting overnight

If the child's bone age is >10 years, the test should be done after sex steroid hormone priming:

M: 100 mg testosterone i.m. 3 days before testing

F: 100 mcg ethinyloestradiol p.o. each for three days before the test.

METHOD

1) Cannulate child.
2) Take blood into a plain tube (red top Vacutainer) for baseline GH measurement (0 mins).
3) Infuse 0.5 g/kg L-arginine monohydrochloride (maximum dose 40 g) as a 10% solution in normal saline over 30 minutes.
4) Take blood for further GH estimation 30, 60, 90, 120 and 150 mins after start of arginine infusion.

INTERPRETATION

- A normal GH response of >15 mU/l (>5.7 ng/ml) excludes GH deficiency.
- A GH response of 7–15 mU/l may indicate partial GH deficiency and should be investigated by a second formal stimulation test.
- A GH response of <7 mU/l (<2.7 ng/ml) should also generally be confirmed by a second test. However, if there are other compatible clinical and auxiliary findings, the child may be directly considered for GH replacement therapy.
- A child with pubertal growth delay may show a subnormal GH response if the test is performed without sex hormone priming. However, there should be a normal response after priming.

SENSITIVITY AND SPECIFICITY

A child with GH deficiency will not respond to this test.

The percentage of children who are not GH deficient and who show a normal response varies from 45 – 93%. Generally, 20% of normal children fail to respond to a formal test and this is the reason for doing 2 tests before proceeding to GH therapy. For example, 71% of normals will respond to both insulin tolerance and arginine stimulation tests. However, the others will respond to at least one test: 13% to insulin, 16% to arginine.

REFERENCE

Raiti et al., Lancet 1183 (1967).

MLB 12/89

FINGER SIZE ASSESSMENT

INDICATION

Finger size is an objective measure of soft tissue over growth. It can be used to follow the response to treatment in Acromegaly.

METHOD

Measurement should be between 0900h and 1000h before any intravenous cannula is inserted. Ring size is assessed on the proximal surface of the proximal interphalangeal joint of the fourth finger. The size is that of the tightest fit. A recording is made from each hand and clearly recorded in the notes. If the finger is too large for size Z then the fifth finger is used.

VERSION HISTORY

ATH 11/89

MEASURING SKIN-FOLD THICKNESS

INDICATION

Skin-fold thickness is used in acromegaly and Cushing's syndrome as an index of skin involvement and therefore disease activity.

METHOD

1. The skin is measured using the skin-fold calliper on the dorsum of the hand over the mid point of the third metacarpal bone.
2. Set the scale on the callipers to zero.
3. Place the patient's hand flat on the table with the wrist in a neutral or extended position.
4. A small skin-fold in the long axis of the hand is lifted up and placed between the blades of the calliper so the fold reaches exactly to the top of the jaw-blades.

INTERPRETATION

- Skin thickness has only a limited role in the diagnosis and the monitoring of acromegaly and Cushing's.
- Mean skin thickness (see reference) in men is 2.8 mm when 20 yrs old decreasing to 1.75 mm when 70 yrs. Women's skin is approximately 0.2 mm thinner than similarly aged men.
- 77% of acromegalics have abnormally thick skin (mean + 2 s.d. in 40 year old males >3.4mm).
- All patients with Cushing's had skin-fold thickness below the mean value but only 42% were abnormally thin (mean - 2 s.d. in 40 year old females <1.5 mm).

REFERENCE

A.D. Wright and G.F. Joplin, Acta Endocrinologia 60, 705-711 (1969).

VERSION HISTORY

ATH 12/89

ORAL GLUCOSE TOLERANCE TEST FOR ACROMEGALY

INDICATION

Used where a clinical diagnosis of acromegaly is suspected.

PREPARATION

Fasting from midnight.
18-20g cannula.
6 Red top Vacutainers.
6 grey top fluoride oxalate tubes

METHOD

1. Take blood sample for GH and IGF-1 (into a red top Vacutainer) and glucose (into grey top tube) at T = 0.
2. Administer 75 grams oral glucose in 300 ml water over about 10 minutes.
3. Take blood for GH and glucose at t=30, 60, 90 and 120 minutes.
4. A synacthen test can be carried out at the end of this test, with samples for cortisol taken at t=120, 150 and 180. Synacthen 250 mcg is administered at t=120.

INTERPRETATION

In normal individuals, GH levels fall following oral glucose, and at least one of the samples during the test should have undetectable GH levels. Failure of suppression or a paradoxical rise in GH suggests acromegaly. Following treatment, “cure” is not an appropriate word. A “safe level” of GH has been thought to be less than 10mU/l (3.8 ng/ml). More recently, this has been revised to 5mU/l (1.9ng/ml).

SENSITIVITY AND SPECIFICITY

False positives sometimes occur in patients with anorexia nervosa, or other causes of chronic starvation, although the IGF-1 level is usually normal.

FOLLOW UP FOLLOWING PITUITARY SURGERY AND RADIOTHERAPY

Following irradiation, endocrine testing should be performed on a yearly basis until failure of a cortisol response is apparent for at least 10 years, and then 5 yearly. Once failure is clear, the patient should be put on hydrocortisone replacement and further insulin tolerance tests are not required.

If patient had pituitary Cushing's, they need LDDST ever 2-3 years to confirm cure.
If acromegaly, and random GH >5, then need annual OGTT + GH to confirm cure. Patients are often on somatostatin analogues following radiotherapy, and once it appears that the radiotherapy has worked, reassessment (OGTT + GH) off these analogues is essential.

Acromegalics should also have a colonoscopy every 3-5 years.

KM/01

POSTERIOR PITUITARY

DIABETES INSIPIDUS

WATER DEPRIVATION TEST

INDICATION

Principle: dehydrate till ADH secretion concentrates urine

Used in differential diagnosis of polyuria, separating Cranial Diabetes Insipidus (CDI), Nephrogenic Diabetes Insipidus (NDI) and Primary Polydipsia/Compulsive Water Drinking (PP).

If in the basal state plasma osmolality > 295 mosmol/kg, plasma Na > 145 mmol/l and urine is hypotonic (< 300 mosmol/kg), PP is excluded and investigation goes straight to DDAVP administration.

CONTRAINDICATIONS

Exclude other causes of polyuria: diuretics, chronic renal failure, hypercalcaemia, hypokalaemia, hyperglycaemia. Anterior pituitary hormone deficiency: renders results meaningless as, in particular, steroid and thyroxine deficiencies impair excretion of a free water load.

PREPARATION

Up to 8.30 hrs:

1. No tobacco/alcohol for 24 hrs before the test
2. Stop interfering medication (e.g. DDAVP (last dose 24 hours before the start of the test), diuretics) but not hormone replacement
3. Light breakfast (do not fast or limit fluids overnight).

Equipment:

a) Blood is taken into yellow top Vacutainers, urine into Sterilin universal containers
b) urine measuring jug.
c) scales.
d) DDAVP: if given intranasally, must acquaint yourself with the spray as it is not easy to use.

Supervision by nursing staff or SHO is essential.

SIDE EFFECTS

If true CDI or NDI, risk of excessive dehydration.

METHOD

Stage 1 (exclusion of PP): 8.30 – 16.30 hrs

1. No fluid allowed but dry food permitted (e.g. toast)
2. Weigh patient at time 0 and hourly intervals: stop test if >3% weight loss (positive test)
3. Urine passed and discarded at time 0; urine then passed hourly and hourly volume estimated
4. Urine specimen taken for osmolality from the total hourly sample passed over 8.30 – 9.30hrs (U1), 11.30 – 12.30 (U2), 14.30 – 15.30 (U3), 15.30 – 16.30 (U4)
5. Blood taken for osmolality at 9.00hrs (P1), 12.00 (P2), 15.00 (P3), 16.00 (P4)
6. Note down urine volumes in chart as shown below (U1-U4).

Stage 2 (differential diagnosis CDI from NDI): 16.30 – 20.30 hrs

7. Patient may now eat and drink freely
8. At 16.30 hrs, administer DDAVP: 20 mcg intra-nasally or 2 mcg i.m.
9. Continue to measure hourly urine volumes and take samples for osmolality from each hourly sample. There is no point measuring plasma samples (or taking any blood), as the patient are now eating and drinking freely, and we are only interested in the effects of the administered DDAVP on urine volume and osmolality.
10. Note down urine volumes in chart as shown below (U5-U8).

TIME	URINE / VOLUME		PLASMA
0830	Discard urine		
0900	**Þ**		**Collect P1**
0930	Collect U1	ml	
1130	Discard urine		
1200	**Þ**		**Collect P2**
1230	Collect U2	ml	
1430	Discard urine		
1500	**Þ**		**Collect P3**
1530	Collect U3	ml	
1600	**Þ**		**Collect P4**
1630	Collect U4	ml	

Now give DDAVP i.m. or intranasally

1730	Collect U5	ml	
1830	Collect U6	ml	
1930	Collect U7	ml	
2030	Collect U8	ml	

INTERPRETATION

1) *Normal*
With dehydration, plasma is concentrated but to <300 mosmol/kg. Urine also concentrates to >600 mosmol/kg.

2) *PP or partial DI*
Start with a low plasma osmolality, which concentrates to normal during stage 1. Urine concentrates, though may be subnormal response (see below).

3) *CDI*
Patient excessively concentrates plasma to >300 mosmol/kg with inappropriately hypotonic urine (U3:P3 or U4:P4 = <1.9). After DDAVP: CDI patient, deficient in ADH, is still able to concentrate urine to >150% of previous highest level. In NDI, patient is unable to respond to ADH or DDAVP, and concentrates urine to <150% of previous highest value.

Diagnosis	After dehydration	After DDAVP
Normal	>750	>750
PP or partial CDI/NDI	300-750	<750
CDI	<300	>750
NDI	<300	<300

Urine osmolality (mosmol/kg)

If there is a partial response, this test does not reliably differentiate between PP and partial CDI or NDI because the response to dehydration and DDAVP may be very similar:

- Polyuria of any origin (e.g. PP or CDI) washes out medullary concentration gradient, blunting maximal urinary concentration
- CDI may increase renal sensitivity to very low levels of AVP. If patient has only a partial deficiency of AVP, dehydration may therefore rapidly increase urine osmolality to maximum of which they are capable.
- Some patients with NDI can concentrate urine if plasma AVP increases to supra-physiological levels, e.g. with exogenous DDAVP.

IF THERE IS A PARTIAL RESPONSE, FURTHER INVESTIGATION IS INDICATED.

SENSITIVITY AND SPECIFICITY

When well performed, the WDT has a sensitivity and specificity of 95% for diagnosing and differentiating severe CDI and NDI. The incidence of false positive and false negative results for PP or partial CDI/NDI is 30-40% (investigate further).

REFERENCE

Vokes et al., Endo. Metab. Clin. N. Amer. 17(2), 281 (1988).

VERSION HISTORY

MLB 10/89; reformatted BK 7/00.

THERAPEUTIC TRIAL OF DDAVP

INDICATION

Used when partial response to water deprivation test to differentially diagnose Primary Polydipsia (PP) and partial Cranial Diabetes Insipidus (CDI) or Nephrogenic Diabetes Insipidus (NDI).

SIDE EFFECTS

Water intoxication in PP

METHOD

1. Admit to hospital
2. Monitor daily: fluid input and output, body weight, U+Es and urine osmolality.
3. Patient observed for 2 days and then 10 mcg DDAVP given intranasally od for at least 2-3 days.

INTERPRETATION

- *Partial CDI*: prompt improvement in thirst and polyuria
- *NDI*: no effect; can be treated for further 2–3 days with a 10 fold increased dose to see if defect partial or complete
- *PP*: decreased polyuria with no change in polydipsia. Causes weight gain, increased urine osmolality and progressive dilutional hyponatraemia, which may develop rapidly and severely (hence need for hospitalisation)

SENSITIVITY AND SPECIFICITY

Small possibility of false diagnosis of PP as hyponatraemia may occur in 5% of CDI who continue to drink excessively on DDAVP because of associated abnormal thirst or prolonged habit

REFERENCE

Vokes et al., Endo. Metab. Clin. N. Amer. 17(2), 281 (1988).

MLB 10/89; reformatted BK 7/00.

ADRENAL INVESTIGATIONS

ADRENAL INSUFFICIENCY

SHORT SYNACTHEN TEST

INDICATION

Used in the diagnosis of hypoadrenalism as a screening test.
It is an increasingly used alternative to the insulin tolerance test to diagnose secondary hypoadrenalism due to pituitary hypofunction.
May also be used to ascertain that the adrenals are functioning normally after a prolonged course of corticosteroids.
Diagnosis and characterization of 21-hydroxylase deficiency and other causes of adrenal hyperplasia.

CONTRAINDICATIONS

Not needed for hypoadrenalism if random cortisol > 550nmol/l. If a random cortisol . 450, patients are very likely to pass the short synacthen test, and some feel that in this circumstance, the test is not warranted.

SIDE EFFECTS

None

PREPARATION

If on steroids ensure that none is taken the night prior to the test. The final dose should be at 9am, 24 hrs prior to the test.
HRT or any oestrogen should be discontinued for 6 weeks before the test.
In patients in whom the test is being used to screen for 21 hydroxylase deficiency, the test should be done in the follicular phase because progesterone levels rise substantially in the luteal phase, and there is some cross reaction between the 17 OHP assay and the Progesterone assay.
Admission is required if there is a risk of Addisonian crisis (virtually never).
18-20g cannula
Saline flush
10ml syringes x 4
3 red top Vacutainers for cortisol (same samples for 17-OH progesterone)
1 EDTA tube (purple top Vacutainer) for ACTH basal sample.
1 ampoule of 250 micrograms tetracosactrin (Synacthen)

METHOD

1. 0900h: take 7 ml blood for cortisol (red top Vacutainer) and ACTH (purple top, on ice to lab immediately).
2. Give 250micrograms tetracosactrin IM (ideally) or IV.
3. 0930h: Take 7 ml blood for cortisol.
4. 1000h: Take 7 ml blood for cortisol.

5. For the diagnosis of congenital adrenal hyperplasia the samples taken for cortisol are also analysed for 17-OH progesterone to exclude 21-hydroxylase deficiency. In some cases 17-OH pregnenolone is measured to differentiate between 21-OH and 3ß-HSD deficiency.

INTERPRETATION

Normal response if test done at 0900h (considerable diurnal variation):

Stimulated plasma cortisol >550 nmol/l

Incremental rise of at least 170 nmol/l

- If impaired cortisol response, and ACTH >200 ng/l then diagnosis is primary adrenal failure.
- If ACTH <10ng/l then diagnosis is secondary adrenal failure
- Response of 17-OH progesterone in suspected 21-hydroxylase deficiency (cryptic): marked rise after ACTH stimulation (>20nmol/l), which varies according to whether the patient is homozygous or heterozygous. Reference for nomogram: New et al., JCEM 57, 320-326 (1983).

SENSITIVITY AND SPECIFICITY

A normal cortisol response does not exclude adrenal failure, since impending adrenal failure might be associated with a much greater loss of zona glomerulosa function. The latter would be suggested by an elevated plasma renin activity.

If equivocal result and no urgency, repeat test after a few weeks.

An abnormal response is consistent with primary or secondary adrenal failure, and should be investigated further. Consider long synacthen test or pituitary function testing.

REFERENCES

Hypoadrenalism

Clayton R.N., BMJ 298, 271-272 (1989).

Burke C.W., Clin. Endo. Metab. 14, 947-976 (1985).

Adrenal hyperplasia

Savage M.O., Clin Endo. Metab. 14, 893-907 (1985).

VERSION HISTORY

JW 12/89 updated KM 07/01

LONG SYNACTHEN TEST

INDICATION

Confirmation of diagnosis of hypoadrenalism.

Differentiating primary and secondary hypoadrenalism (note that measurement of basal 0900h ACTH levels is far more sensitive than cortisol response in the long synacthen test).

The first 3 samples should give the same result as the short synacthen test.

SIDE EFFECTS

None

PREPARATION

Patients who have already been taking corticosteroids should have the last dose 24 hours before the start of the test. Admit the patient if there is a risk of an Addisonian crisis (virtually never). Patients with pituitary disease are usually safe if they have an intact renin-angiotensin (aldosterone) axis. Once the test has commenced, dexamethasone will not interfere with the cortisol result. (Do not use hydrocortisone or prednisolone, which will interfere with the cortisol assay). Use 0.75 mg for 5mg prednisolone equivalent.

1 mg tetracosactrin (depot preparation). This is not the same as ordinary Synacthen!
18-20g cannula.
6 red top Vacutainers.
1 purple top Vacutainer for ACTH.
Syringes.
Saline flush.

METHOD

0900h		insert cannula and flush
		take blood for baseline cortisol and ACTH
		give 1mg depot synacthen i.m.
0930h	}	
1000h	}	Take blood
1100h	}	for cortisol
1300h	}	measurement
1700h	}	(i.e. additional 2, 4, 8 and 24h)
0900h	}	

INTERPRETATION

- *Normal response*: baseline cortisol >170 nmol/l with rise to >900 nmol/l (peak)
- *Samples at 9*.00, 9.30 and 10.00 can be interpreted as for a short synacthen test.
- *Primary adrenal insufficiency*: little or no response
- *Secondary adrenal insufficiency*: some patients may show a rise in cortisol, which may be delayed (but a subnormal response does not exclude this – measure ACTH levels).
- Patients with a subnormal response can still have their steroids weaned (by 1mg pred per month).

SENSITIVITY AND SPECIFICITY

More sensitive than short synacthen test for primary adrenal insufficiency (for nomogram see Burke et al 1985).

REFERENCE

Burke C.W. et al., Clin. Endo. Metab. 14, 947-976 (1985).

VERSION HISTORY

KM 01/97 updated KM 07/01

ADRENAL TUMOURS

POST OPERATIVE MANAGEMENT OF ADRENAL TUMOURS

Discuss with anaesthetists in advance.

1. Unilateral non cushing's (non cortisol secreting) adenomas (eg Conn's or phaeochromocytomas) do not need hydrocortisone cover for surgery or cortisol monitoring.

2. Unilateral Cushing's patients or bilateral adrenalectomy patients will need steroid cover as follows. Hydrocortisone should be started on day 0 on induction with either 100 mg qds IM or with an IV infusion of 4.2 mg per hour (write up 100 mg over 24 hours). IV boluses are not appropriate, as the half life of cortisol is short, and plasma cortisol levels fall to undetectable levels in between doses in endocrine patients. These are very different from asthmatics, where IV boluses are given in ADDITION to normal adrenal function.

Start infusion with the premed: hydrocortisone for 24 hrs at 4.2 mg/hr i.v.

Post operatively – if no complications:

Day	**Hydrocortisone**	**Fludrocortisone**
0	100 mg/24 hrs i.v. (4.2 mg/hr) **or 100 mg IM** qds	
1	100 mg/24 hrs i.v. (4.2 mg/hr) **or 50 mg IM** qds	50 mcg p.o. od
2-4	20 mg p.o. qds	50 mcg p.o. od
5-6	15mg (6am) + 10 mg (noon) + 5 mg (6pm) PO	50 mcg p.o. od
7+	10mg (6am) + 5 mg (noon) + 5 mg (6pm) PO	50 mcg p.o. od

Cushing's syndrome caused by a unilateral adenoma can cause suppression of both the pituitary and the contralateral adrenal, and this can take over one year to recover. These patients require synacthen tests before hydrocortisone can be discontinued. Obviously bilateral adrenalectomies will require hydrocortisone and fludrocortisone for life.

Post operatively – if complications:

If on day 1 it appears that patient may need prolonged parenteral hydrocortisone, measure plasma cortisol and adjust dose as necessary.

ON DISCHARGE

- Hydrocortisone 10mg / 5 mg / 5 mg.
- Fludrocortisone 50 mcg od.
- They should be given a steroid card.
- An HCDC should be organised at their first clinic visit.
- Further reduction in dose in patients with unilateral adrenalectomies will depend on the result of the short synacthen tests. Careful follow-up is required.

Contact details for MEDIC alert should be given. Bracelet is free if on benefits (£30 otherwise). Full address in index.

HYPERALDOSTERONISM

PLASMA ALDOSTERONE, AND PLASMA RENIN ACTIVITY

INDICATIONS

- Accelerated hypertension.
- Hypertension with hypokalaemia, spontaneous or easily provoked, i.e. by diuretics or sodium loading – consider if plasma potassium is <3.6mmol/L. As the treatment of hyperaldosteronism is far more effective in correcting hypokalaemia rather than the hypertension extensive investigation in normokalaemic patients is not justified.
- Assessment of early/impending adrenal cortical failure (Addison's) – see short synacthen test.

CONTRAINDICATIONS.

None

SIDE EFFECTS

None

FIRST LINE INVESTIGATION:

Random plasma aldosterone/renin ratio

Outpatient procedure

Stop beta blockers for 2 weeks prior to the sample, as beta blockers prevent renin release.

Other drugs need not be stopped unless further investigations are required (see below)

Supply details of all therapy on request form

Ensure adequate salt intake – NOT loading

Correct severe hypokalaemia first, as a low potassium directly will reduce aldosterone secretion.

Method

Sit patient quietly for at least 10 minutes

1 X Lithium heparin sample (green top vacutainer)

Send urgently to lab (within half an hour) – NO ice needed: Ice will cause cryoactivation (conversion of pro-renin into renin), artificially giving a high apparent renin activity).

Analysis

Carried out in Dept of Chemical Pathology, St Mary's Hospital

Contact: Dr P Kyd : Tel. 020 7886 1618 Fax. 020 7886 1904

If clinical details and list of medications are provided then St Mary's are very helpful in supplying a full interpretation of results.

Interpretation of results

Aldosterone/renin ratio

>2000	almost certainly Conn's
800 - 2000	Possibly Conn's, investigate further
<800	excludes Conn's

For diagnosis of Conn's: low renin expected

Plasma renin	<0.5pmol/ml/hr	(ref. 0.5-3.1)
Aldosterone	>250pmol/l	(ref. 100-800) ie. may be normal or high

POSTURAL STUDIES

It is advisable to discuss the results of first line investigations before proceeding with further investigations.

PREPARATION

Remember liquorice ingestion and carbenoxolone may mimic hyperaldosteronism.

Discontinue drugs:

Spironolactone, oestrogens	6 weeks
Diuretics	4 weeks
ACE Inhibitors	2 weeks
NSAIDs	2 weeks
Calcium antagonists	1 week
Sympathomimetics	1 week
Beta-blockers	1 week

If anti-hypertensive therapy needs to be continued then prazosin, doxazosin or bethanidine may be used.

Patient should be on unrestricted sodium intake before admission – in general the salt intake in this part of the world is adequate and patients do not require salt-loading prior to investigation.

Syringes.

A 18-20g cannula.

Saline flushes.

2 EDTA tubes (purple top Vacutainers).

2 Lithium heparin tubes (green top Vacutainers).

Plain 24 hour urine collection bottle for urinary aldosterone.

METHOD

Day 1		Place on liberal sodium intake – 100 mmol/day (e.g. sodium chloride tablets 2g p.o. tds) or ask dietician Take blood for electrolytes – get results on same day. If potassium is low (<3.5 mmol/l) then give oral potassium supplements. Discuss diet with dieticians.
Day2	0700h 0800h 1200h	Cannulate peripheral vein. Tell patient to remain in bed until told otherwise. Take blood with patient supine (for at least 30 mins) for: Electrolytes and cortisol. Plasma aldosterone (clotted, red topped sample) Plasma renin activity (Lithium heparin NOT on ice. Take to lab immediately). Plasma ACTH (purple topped bottle on ice). Start 24 hour urine collection for aldosterone. Ask patient to get up and mobilise at least from 11.30 for 30 minutes. Take blood for plasma aldosterone, plasma renin activity.

INTERPRETATION

Primary hyperaldosteronism	**Normal ranges**
Suppressed upright renin <2.8 pmol/ml/hr	2.8–4.5 pmol/ml/hr *upright* 1.1–2.7 pmol/ml/hr *supine*
Raised supine aldosterone >450 pmol/l	100-450 pmol/l *supine* variable range *upright*
Raised urinary aldosterone >50 nmol/24 hrs	10-50 nmol/24 hrs

- If plasma and urine aldosterone are low then consider other causes of hypokalaemia.
- If aldosterone is raised but plasma renin activity is not suppressed then the diagnosis is likely to be secondary hyperaldosteronism.
- It is possible to differentiate the two main causes of primary hyperaldosteronism on the basis of the response to time and posture. In bilateral hyperplasia there is a >33% rise in aldosterone on rising (at noon) while in an adrenal adenoma there is an anomalous fall in aldosterone.

SENSITIVITY AND SPECIFICITY

The tests have greater than 90% accuracy of correctly diagnosing primary hyperaldosteronism.
The changes with posture may help in the differentiation between adenoma and bilateral hyperplasia but should be interpreted in the light of the results of CT scanning. Interpret results with caution in patients with renal impairment.

REFERENCE

Melby J.C., Clin. Endo. Met. 69,4; 697-703 (1989).

JW 11/89; revised BK 7/00. revised EM 07/01

SELENIUM CHOLESTEROL SCANNING FOR CONN'S TUMOURS

INDICATIONS

For functional lateralization of Conn's tumours. Now only available on a named patient basis.

CONTRAINDICATIONS

Caution if diabetic.

PROTOCOL

1. Admit. Start dexamethasone 2mg daily at Day -2, i.e. two days before the injection. Monitor blood glucoses qds. Continue dexamethasone to Day +11.
2. On day 0 nuclear medicine will inject 8 MBq of 75Se Scintadren and image.
3. Start 5mg bisacodyl for 2 days.
4. Discharge home once dexamethasone completed.
5. Nuclear medicine will arrange for further images on Day 4, 7 and 11.
6. A cortisol on any morning should be undetectable if the dexamethasone the previous day is suppressing the HPA axis adequately, and may be useful to check compliance. Without adequate dexamethasone suppression, one can wrongly diagnose bilateral adrenal hyperplasia, which is simply an indication of normal cortisol production. Remember that cortisol secretion rates are 1000 times higher than aldosterone secretion rates, so even a single missed dose of dexamethsone can jeapordise the results.

INTERPRETATION

The images will be reported by nuclear medicine, but a Conn's tumour should take up label with no uptake on the contralateral side. Bilateral uptake suggests bilateral adrenal hyperplasia.

ADRENAL VENOUS SAMPLING FOR ALDOSTERONE

INDICATION

Differential diagnosis of primary hyperaldosteronism, between aldosterone producing adenoma and idiopathic hyperaldosteronism where CT has demonstrated no definite tumour and when the results of selenium cholesterol scanning are ambiguous.

CONTRAINDICATIONS

Discuss with radiologist:

Bleeding tendency.
Accelerated Hypertension.
Allergy to contrast.
Significant ischaemic heart disease.

SIDE EFFECTS

Bleeding.
Adrenal infarction rarely.

PREPARATION

Remember liquorice ingestion and carbenoxolone may mimic hyperaldosteronism.

Discontinue drugs:

Spironolactone, oestrogens	6 weeks
Diuretics	4 weeks
ACE Inhibitors and NSAIDs	2 weeks
Calcium antagonists	1 week
Sympathomimetics	1 week
Beta-blockers	1 week

If anti-hypertensive therapy needs to be continued then prazosin, doxazosin or bethanidine may be used.

Patient should be on unrestricted sodium intake before admission.

The day before the procedure, check FBC, U + E, INR, G + S.

Consent (risks of bleeding from sheath sites, venous thrombosis). (done by radiology)

Fast overnight.

8 Plain tubes (red top Vacutainers).

Tetracosactrin 250 micrograms (Synacthen).

Arrangements for immediate transfer of samples to laboratory. Two assistants required for this.

METHOD

Catheter inserted via femoral vein and adrenal veins selectively cannulated under X-ray control. Bolus of Synacthen may be given 20 minutes prior to sampling. Samples taken simultaneously for cortisol, DHEAS, androstenedione and aldosterone.

INTERPRETATION

Normal adrenal vein aldosterone 100–400 ng/dl. In aldosterone producing adenoma the ipsilateral value is 1000–10000 ng/dl. Ratio of >10:1 between sides is considered diagnostic.

Confirm that adrenal veins have been cannulated by comparing cortisol and adrenal androgen levels on the two sides.

SENSITIVITY AND SPECIFICITY

The main problem with this procedure is difficulty in catheterising the right adrenal vein, this is because it enters the inferior vena cava at an acute angle and may be multiple. Even in the best hands cannulation is not possible in 26% of patients.

In patients in whom both adrenal veins are successfully cannulated this procedure is 90-95% successful in correctly distinguishing between idiopathic (bilateral) hyperaldosteronism and aldosterone producing adenoma by demonstrating a unilateral increase in aldosterone secretion.

The diagnostic accuracy is improved by measuring Aldosterone/cortisol ratio of the high side divided by Aldosterone/cortisol ratio of the low side. Ratios of >4.0 are diagnostic and ratios >3.0 are suggestive of an aldosterone producing adenoma (APA). (Young et al, Surgery, 2004)

Examples:

	Aldosterone	Cortisol	A/C ratio	Ratio
RAV	870	2432	0.36	
LAV	33000	1013	32.6	102
IVC	603	253	2.38	

Diagnosis: L sided APA

	Aldosterone	Cortisol	A/C ratio	Ratio
RAV	161000	4130	39	
LAV	151000	2100	72	1.8
IVC	57000	2720	21	

Diagnosis: BAH

REFERENCES

Young W.F. Jr., Klee G.G., Endo. Metab. Clin. N. Am., 17,2; 367-395 (1988).

Melby J.C., J. Clin. Endo. Met., 69,4; 697-703 (1989).

PHAEOCHROMOCYTOMA

MANAGEMENT OF SUSPECTED PHAEOCHROMOCYTOMA

Before any procedures involving IV contrast:

- Patients should be well filled prior to administration of alpha blockade with crystalloids (e.g. 1l 0.9% saline). Complete alpha blockade is achieved at 3 days. Warn patient of side effects of alpha blockade including postural hypotension, nasal stuffiness.
- Alpha blockade with phenoxybenzamine (0.5 mg/kg i.v. over 2-4 hours in 500 ml normal saline).
- Within 24 hours, beta blockade should be commenced with either metoprolol 50 mg tds or propranolol 80 mg tds. Side effects of beta blockade include: cold peripheries, bradycardia, postural hypotension.
- In the event of a crisis, use i.v. phentolamine (0.5 – 1mg) boluses, which can be repeated until BP controlled. This works rapidly. If patients are not well filled, this can precipitate severe hypotension and a watershed cerebral infarction. Rehydration with crystalloid must therefore be started at the same time.

PENTOLINIUM SUPPRESSION TEST

INDICATION

To try and exclude the diagnosis of phaeochromocytoma in patients with hypertension and borderline changes in plasma catecholamines or 24 hour urinary catecholamines.

CONTRAINDICATIONS

No absolute contraindications but beware frail patient and patients with severe coronary or carotid vascular disease.

SIDE EFFECTS

May cause severe transient hypotension

PREPARATION

Order the Pentolinium from pharmacy (difficult to obtain). It comes as 10 mg/ml.
Stop hypotensive treatment (incuding labetalol) for at least 24 hours before the test (especially centrally acting drugs such as methyldopa).
Fast overnight. (Large meals can cause variation in catecholamines).
Quiet environment.
Sphygmomanometer or Critikon BP monitor.
Cannula, 18-20g.
Ice.
Lithium heparin tubes (green top Vacutainer).
Contact biochemistry laboratory who measure catecholamines before doing the test, enquire how they would like the samples taken and arrange for their delivery.

METHOD

1. Patient should empty bladder before lying down as they might not be allowed to stand for a while.
2. Insert cannula and flush.
3. Rest for 1/2 hour.
4. Monitor BP and pulse at onset and every time blood taken.
5. Take 2 baseline samples at 5 minute intervals for catecholamines. Blood needs to be taken into Lithium heparin, kept on ice, spun at 4°C, frozen until assay.
6. At time 0, give 2.5 mg Pentolinium i.v.
7. Take blood at one hour.

INTERPRETATION

Pentolinium is a sympathetic ganglion blocker. Normal subjects may show an initially elevated plasma adrenaline and noradrenaline but these will fall to within the normal plasma range with Pentolinium. In contrast the autonomous secretion of a phaeochromocytoma will not suppress.

SENSITIVITY AND SPECIFICITY

This test has a low false positive and false negative rate as determined in series of known phaeochromocytomas and normals but published information is very scanty. The most likely theoretical problem is a fall in plasma catecholamine levels in a phaeochromocytoma patient whose tumour is only secreting episodically.

REFERENCES

Brown MJ et al. Lancet 1981; 1: 174-7

VERSION HISTORY

SGG 1/90; revised BK, KM, RB and JT 7/00.

CLONIDINE SUPPRESSION TEST

INDICATION

To try and exclude the diagnosis of phaeochromocytoma in patients with hypertension and borderline changes in plasma catecholamines or urinary catecholamine metabolites.

CONTRAINDICATIONS

Frail patient with a history of hypotensive episodes or severe coronary or carotid disease.

SIDE EFFECTS

Hypotension and sedation.

PREPARATION

Order the clonidine from pharmacy (readily obtainable).
Stop hypotensive treatment for at least 24 hours before the test if possible.
Fast overnight.
Quiet environment.

Sphygmomanometer or Critikon monitor.
Cannula, 18-20g.
Ice.
Lithium heparin tubes (green top Vacutainers).
Contact biochemistry laboratory who measure catecholamines before doing the test, enquire how they would like the samples taken and arrange for their delivery.

METHOD

1. Insert cannula.
2. Rest for 1/2 hour.
3. Monitor BP and pulse at onset and every time blood taken.
4. Take 2 baseline samples at 5 minute intervals.
5. Give, at time 0, 0.3 mg clonidine hydrochloride orally.
6. Take blood at hourly intervals for 3 hours.

INTERPRETATION

Clonidine acts via the alpha pre-ganglionic receptors to reduce catecholamine secretion.
In normals, even if they are anxious, the plasma catecholamines will suppress into the normal range 3 hours after clonidine (noradrenaline 0.2–0.8 ng/ml, adrenaline 0.04–2 ng/ml). Phaeochromocytoma patients should not.

SENSITIVITY AND SPECIFICITY

This test gives similar information as the Pentolinium test; there have been no formal comparisons of the two tests. Case reports (see Halter et al., New Engl. J. Med. 306, 49-50 – 1982) have illustrated false negatives. The 24 hr urinary metanephrines/catecholamines have replaced VMAs as the cornerstone of screening for phaeochromocytoma. If a dopamine secreting phaeochromocytoma is suspected on the basis of normo- or hypotension then urinary dopamine and its metabolites should be assayed

REFERENCES

Bravo E.L. et al.. New Engl. J. Med. 305, 623-626 (1981)
SGG 1/90

Genetic screening for phaeochromocytomas

Is it worthwhile ?

Family history is essential. Those who have a family history are at risk of:
NF1 (clinically obvious with café au-lait patches and neurofibromas),
MEN2a (medullary thyroid carcinoma highly penetrant, so screen with calcitonin in the first instance and then a calcium because of the risk of primary hyperparathyroidism in 20%) or
MEN 2b (clinically obvious with Marfanoid habitus and mucosal neuromata, and also calcitonin)
VHL (clinically might have cerebellar signs, brainstem neuromata, so careful neurological exam is essential. Retinal haemangiomas can be screened for by fundoscopy.
SDHD
SDHB

If they don't have a family history, the risk of all of these is low, although some feel screening is justified (ref:Neumann etal NEJM 2002: 346: 1459 – 1466). If you want to screen for VHL, SDHD and SDHB, a sample can be sent to Birmingham, which screen for all three in a single sample. The cost is £1268 (or £634 for VHL only, and £634 for SDHB and SDHD) and samples should be sent to:

West Midlands Regional Genetics laboratory,
Birmingham Women's Hospital, Metchley Park Road, Edgbaston, Birmingham. B15 2TG
Tel: 0121 627 2710 Fax: 0121 627 2711.

For MEN, details of possible screening services is given in the section on medullary thyroid carcinoma.

(From Bryant et al: J. Nat. cancer Inst. August 2003. 59 (16) 1196-1204)

MIBG SCAN

INDICATION

The ^{123}I MIBG scan is a useful, qualitative, method of locating the site of a phaeochromocytoma.
It should not be undertaken without biochemical evidence for a tumour being present (24 hour urine VMA, circulating catecholamines, clonidine or pentolinium test), and should be backed up by ultrasound, CT scanning, and, where indicated, venous sampling. It is particularly useful for extra-adrenal and metastatic or residual phaeochromocytoma.

CONTRAINDICATIONS

No absolute contraindications except pregnancy or its possibility, allergy to iodine.
Caution in any patient with any drug allergies.
Many drugs may interfere with the study – nuclear scanning have a list. These include tricyclic antidepressants, SSRIs, calcium channel antagonists, catecholamine receptor agonists and antagonists, phenothiazines, butyrophenones (e.g. haloperidol etc.), guanethidine and reserpine.

PREPARATION

Liase with nuclear medicine at least 1 week in advance of planned scan.
Avoid IV phenoxybenzamine, although p.o. phenoxybenzamine is OK.
Thyroid uptake should be blocked by **potassium iodide 60 mg bd** for 48 hours beforehand and for 5 days afterwards.

METHOD

^{123}I metaiodobenzylguanidine is injected intravenously (this molecule is similar to noradrenaline, transported in similar fashion and stored in catecholamine vesicles). The patient is scanned twice at 24 and 48 hours.

INTERPRETATION

Spots of increased uptake on scanning are the tumours. Most common sites: adrenals, organ of Zuckerkandl (usually pelvis). May be multiple.

SENSITIVITY AND SPECIFICITY

In patients with a proven phaeochromocytoma but uncertain site the scan has 90-96% sensitivity and 98-99% specificity (Shapiro et al., Cardiology 1985; 72: suppl. 1, 137-142).

REFERENCES

Sisson J.C. et al., New Engl. J. Med. 305: 12-17 (1981).

VERSION HISTORY

SGG 11/89

Thyroid and Parathyroid.

Protocol for the post-radioiodine treatment telephone clinic

AIM:

Our aim following radio-iodine treatment is to render patients hypo(eu)thyroid. The purpose of the telephone clinic is to rapidly determine when thyroxine replacement should be started, thus avoiding unnecessary outpatient appointments or leaving patients with untreated hypothyroidism, which has many undesirable effects, including possible worsening of thyroid eye disease. See http://radioiodine.info.

THYROID EYE DISEASE.

Worsening of thyroid eye disease only occurs in smokers. There is thus no indication for the use of prophylactic steroids in non-smokers. Even in smokers, the number of patients needed to treat with high dose steroids (40 mg prednisolone daily for 1 month, then taper) means that there will be many patients given steroids with radioiodine for no benefit. All patients should be referred to Veronica Ferguson if there is any doubt (consultant ophthalmologist at Charing Cross). It is preferable to avoid steroids in the majority, and treat the few who develop worsening eye signs with steroids at that stage. Smokers may have a 25% risk of worsening eye disease however.

WHO IS SUITABLE FOR TELEPHONE FOLLOW-UP?:

This service is **only** available to patients who;

- Are contactable by telephone during office hours (9am – 5pm).
- Speak reasonable English and are able to follow instructions regarding medications.
- Consent to regular blood tests, preferably at the hospital phlebotomy department.

HOW DO I ARRANGE FOR RADIO-IODINE TREATMENT:

Antithyroid drugs should be stopped as soon as the decision to use radioiodine is made. Ideally they will be stopped for at least a week. If you know roughly when the patient wants radioiodine, further planning can be made. If it is clear that the patient will defer treatment for more than 2 months, then the antithyroid drugs should be continued until closer to the date of RAI. As a guide, the antithyroid drugs should be stopped at least 1 week and at most 2 months before RAI.

Give the patient an appointment for list M30 at Charing Cross Hospital as soon as possible. If you are at Hammersmith, you will need to give the patient an appointment on **M30** and also write on the frontsheet for SUE BROWN to actually book this on the Charing Cross system (she normally works at CX, but is based at Hammersmith Hospital on Wednesdays).

Send a referral letter (or fill in web form on http://meeran.info) to:
Radioiodine clinic (c/o Dr. Meeran),
c/o Dept of Endocrinology
9th Floor, East Wing, Charing Cross Hospital (Fax: 020 8846 1862).

Make sure to include as many **contact telephone numbers** as possible in the letter.

WHAT IS THE PROTOCOL FOR RADIO-IODINE TREATMENT?:

Day –7	Thyroid function tests. Information session & signing of consent form in Department of Nuclear Medicine, Charing Cross Hospital. Send information letter to patient's GP. Stop anti-thyroid medication.
Day -3	Start Lithium carbonate (Priadel) 800mg nocte.
Day 0	Thyroid function tests. Lithium level. Radio-iodine treatment.
Week +1	Thyroid function tests. Lithium level. STOP lithium treatment.
Week +3	Thyroid function tests. Lithium level.
Week +6	Thyroid function tests.
Week +9	Thyroid function tests.
Week +12	Thyroid function tests.
Week +14	Outpatient clinic visit.

If the patient agrees to take part in the randomized placebo controlled trial, they might receive placebo instead of lithium. These patients should collect the drugs from Charing Cross pharmacy when they attend nuclear medicine there 7 days before their RAI.

WHAT DO YOU NEED TO GIVE THE PATIENT?:

1. Information sheet on Radio-iodine treatment.
2. Give the patient an appointment for list M30 at Charing Cross. Everything else (below) is for information only, and will be carried out from that clinic.

They will be given:

1. An X-Ray request form to Nuclear Medicine for I-131 Therapy.
2. Seven (7) request forms for TFTs (Weeks –1, 0, +1, +3, +6, +9, +12 as above).
3. 2 request forms for a lithium level (week 0 and +1 as above).
4. A prescription for lithium 800mg (specify **Priadel**) nocte for 10 days.
5. A prescription for thyroxine 100 cg, **NOT** to be started until they are telephoned.
6. An appointment for the out-patient clinic, 14 weeks after treatment.
7. Make sure to note the **patients' telephone number** in the notes and on the X-Ray form. If they need to ring and enquire regarding results/treatment they should be given the switchboard number and bleep 3509.

WHO WILL FOLLOW PATIENTS UP BY TELEPHONE?:

All computerised results are updated and reviewed on a weekly basis by a designated Endocrine/Clinical Chemistry Specialist Registrar and patients telephoned if they become either biochemically hypo- or hyperthyroid following treatment.

WHAT HAPPENS IF A PATIENT DEVELOPS SIGNIFICANT SYMPTOMS AFTER RADIOIODINE?

If at any stage a patient becomes symptomatic or develops Grave's opthalmopathy the Department of Endocrinology can be contacted by either the patient or the GP and arrangements made to review the patient urgently at the next outpatient clinic.

WHEN WILL THYROXINE BE STARTED.

Blood samples will be checked on the day of RAI, and 1 week later for lithium levels. Thyroid function tests will also be monitored, but no action taken (as the FT4 may be lowered by the lithium).
When the Ft4 falls to 14.5 pM or less, then thyroxine will be commenced by telephone. Samples will be collected at 3,6,9 and 12 weeks, and the patient should see someone at about 14 weeks. If they are still toxic, further telephone appointments can be made at 15, 18 and 21 weeks.

If at review (after 12 weeks), the TSH is still not detectable, then this is either due to excess thyroxine, or due to failed RAI. A FT3>5 suggests autonomy, and the thyroxine should be discontinued. If the FT3<5.0, then the dose of thyroxine can be slowly lowered with 3 weekly phone reviews.

EM 07/01, KM 01/03

Instructions for those running the phone clinic.

Patients will be expecting phonecalls to tell them whether or not to start thyroxine.

First look on computer for results of FT3/ FT4/TSH. Ask someone else to phone for lithium level, and let Dr. Meeran know if they are lithium toxic. Some will have a zero level.

Ask the patient their weight in kilograms (or stone/lbs and convert).

Find out how they feel. Ask specifically about nausea. Check that they have been compliant with the lithium/placebo. How many tablets did they take? Which ones did they miss?

If the patient feels toxic (tremor, tachycardia etc), and the FT4 > 40pM, then suggest atenolol 100 mg daily until next (3 weeks) review, as they might still rapidly become hypothyroid.

If FT4< 14.6, then start thyroxine 100 mcg daily. The patient should have a supply of these at home, and should be able to start these the day you make the phonecall.

After week 12, if TSH suppressed, then check FT3. If FT3>5, then stop thyroxine. If FT3<5, then reduce thyroxine slowly.

This page to be filled in with each phonecall in the thyroid clinic made and stored in the thyroid file.

Name:

Hospital Number:

Date of phoncall:

Date of blood test:

Date of RAI:

Weeks since RAI:

Results: FT4

FT3

TSH

Lithium level checked (yes/no). Do NOT get result.

Phone call:

Comments about how patient feels:

Weight of patient (at home).

How many lithium tablets did you take and how many did you forget? Which ones did you forget? (Get exact dates).

Do you smoke ? How many?

What tablets are you CURRENTLY taking:

If FT4 < 14.6pM, then start thyroxine 100mcg daily. Advice given: start thyroxine or wait until further samples taken:

If FT4>30 and patient feels unwell (tremor, tachycardia etc), then consider atenolol 100 mg daily.

After week 12, if TSH suppressed, then check FT3. If FT3>5, then stop thyroxine. If FT3<5, then reduce thyroxine slowly.

PATIENT INFORMATION (RADIOIODINE)

What is radio-iodine treatment?

Your consultant has asked us to see you about iodine (iodine 131) therapy for thyrotoxicosis. Iodine therapy uses a form of iodine that is radioactive. Iodine is taken up by the thyroid gland and the radioactivity will "slow down" the thyroid's production of certain hormones. Radio-iodine therapy has been used for more than 40 years and is a well-established technique. We have been using radioactive iodine therapy in this Department for many years and are highly satisfied with the results.

Where else in the body does radio-iodine go?

Most of the radio-iodine goes to the thyroid. The rest will pass from your body, mostly in the urine, during the first few days.

How is the radio-iodine given?

The radio-iodine is given as a capsule to swallow with water. This is similar to any other tablet and is taken in much the same way. Occasionally the radio-iodine can be given as a drink which tastes just like water.

Is there any preparation before the treatment?

Yes, and it is important to follow the instructions exactly otherwise the treatment may not be effective.

- Medication - You must tell us about all the medication you are taking, even health products or supplements bought over the counter.
- **It will be necessary to stop taking certain medication before the treatment - for example carbimazole (CBZ) and propyl-thiouracil (PTU) must be stopped at least seven days before the treatment. You will start the Lithium (for which you will have been given a prescription) for a total of 10 days, starting 3 days before the RAI, and continuing 7 days after. You will also have been given a prescription for thyroxine. Hold this until told to start taking it.**
- Food - Do not eat any fish or seafood for two days before the treatment. A low iodine diet is repeated on page 58.
- On the day - You may have a light breakfast but no lunch. You should drink normally.

Can I have treatment if I am pregnant or breast-feeding?

No. Women who are pregnant or breast-feeding must not be given radio-iodine. If there is any possibility that you may be pregnant, you must tell us. **You are advised not to become pregnant for at least four months following the treatment. You must take adequate contraceptive care.**

Will there be any danger to my family or friends?

We wish to keep all radiation levels as low as reasonably practical. We aim to ensure that your family and friends will not receive radiation above the levels experienced by members of the public in their daily lives. We will discuss with you in detail how you can achieve this. The essential precautions to reduce radiation are:

- Avoid non-essential close contact with babies, young children and pregnant women. For people with day to day contact this can be for a period of 2-4 weeks. At consultation we will discuss how this can be practically carried out.

- You may need to take some time off work depending on your specific job.
- You will need to avoid close contact with other people for several days
- You must sleep alone for one week after treatment.
- Please check if you can travel by public transport. Usually there will be no restriction.
- Women should not become pregnant nor men father a child in the 4 months after treatment

On the day of treatment you will be given specific advice about these precautions. The exact length of time for which these precautions apply depends on the amount of radioiodine the doctor prescribes.

Investigations that will be needed during the course of treatment.

You will need several blood tests, as follows:

- On the day of the preliminary consultation
- On the day of treatment
- One week after treatment
- 3,6,9 and 12 weeks after treatment

You will have been given request forms for all these tests by the Clinic Doctor, and they will be numbered.

Will I need to see a doctor after the radioiodine treatment?

Yes, either the doctor you saw at the clinic or your GP. Blood tests will be required to monitor the effect of the treatment on your thyroid. Full instructions will be given at the time of treatment.

How many treatments will I need?

Usually one treatment is enough, although sometimes more than one is needed. The blood tests will help decide.

Are there any side effects?

Very occasionally after receiving the radio-iodine you may get a sore throat. This should last for only a few days and if it does happen to you, it can be relieved by drinking plenty of fluids and sucking boiled sweets. Your thyroid may become underactive. This could happen within a few months or many years after the treatment. Again the blood tests will check the state of your thyroid. If it does become underactive you will be given thyroxine tablets.

What should I do if I cannot keep my appointment?

Please contact the Nuclear Medicine Department on the telephone number below if you are unable to keep an appointment. The radio-iodine has to be ordered specially for each patient and it would be appreciated if any unavoidable appointment cancellation or rearrangement could be made at least one week before the appointment date so that the order for your dose can be changed accordingly.

If you have any questions at all or need further advice please do not hesitate to ring the telephone number given below:

Telephone: 020 8746 8412 or 020 8846 1428
Dr. Meeran's secretary: 020 8846 1065.

JF 07/01

Preparation of thyrotoxic patients for thyroidectomy

Patients will ideally be rendered euthyroid before surgery. In all cases, one must always balance the risks of delay against the benefit of being euthyroid pre-operatively. In an emergency, the following combination of drugs can be used to try and achieve this in approximately ten days:

1. Beta blockade. Propranolol 80mg tds is favoured historically. Atenolol 100mg or Nadolol 160mg can be administered only once daily and hence might improve compliance

2. Propylthiouracil 250 mg qds. This is a higher dose than used normally, but in emergency higher doses more frequently are required in view of the fact that the liver increases the metabolism of these drugs. The PTU should be administered an hour before any iodide as the PTU will prevent organification of the administered iodine.

3. An excess of iodide or iodine (KI 60 mg tds or 0.3 ml Lugols iodine tds). Potassium iodide 60mg tds is by far the easiest to administer (ref NEJM 1980 (Vol 302) 883-885)

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PENTAGASTRIN TEST FOR MEDULLARY THYROID CARCINOMA

CALCITONIN.

Calcitonin may be secreted by C-cells on the thyroid gland. High levels may suggest medullary thyroid carcinoma. In very early disease (eg on screening for familial syndromes), levels may not be raised, but may be stimulated either by calcium or pentagastrin. It is suggested that borderline baseline levels (which no longer need be fasting) are further investigated by a stimulation test.

INDICATIONS

Suspected medullary carcinoma of thyroid.
Screening of families with medullary carcinoma of the thyroid.
Patients with suspected MEN type 2. Remember to inform the MEN2 registry.
Patients with basal CT level >12ng/L (males) and 5ng/L (females).

CONTRAINDICATIONS

Allergy/anaphylaxis on repeat administration.

SIDE EFFECTS

Nausea, epigastric discomfort

PREPARATION

Check electrolytes and serum calcium.
Cannula, 18-20g.
Pentagastrin 0.5 mcg/kg body weight.
6 x 7 ml Lithium heparin tubes (green top Vacutainers) with 0.2ml Trasylol added.
Centrifuge.
Ice or facilities to transfer samples immediately to lab

METHOD

1. Patients should be fasted, as food can increase calcitonin.
2. Insert cannula and flush.
3. Take baseline sample for calcitonin.
4. Give bolus i.v. of pentagastrin 0.5 mcg/kg body weight and flush cannula.
5. Take samples at 1, 2, 3, 5 and 10 minutes for calcitonin.
6. Take immediately to lab on ice.

INTERPRETATION

In patients with a stimulated CT 30-100ng/L- follow-up screening recommended.
In patients with a stimulated CT 100-200ng/L- probable C-cell hyperplasia or early MTC.
In patients with a stimulated CT >200ng/L- MTC very likely.

Karges W. et. al. Calcitonin measurement to detect medullary thyroid carcinoma in nodular goitre. Exp. Clin. Endocrinol. Diabetes 2004;11:52-58

Biegelmeyer et. al. Screening for MTC
Wien Klin Wochenschr (2002) 114/7:267-273

Surgical treatment should be considered especially if there is a family history. Potentially affected family members should be screened biennially until 65.

SENSITIVITY AND SPECIFICITY

Pentagastrin stimulates calcitonin best in medullary carcinoma, whereas calcium infusion is best in normals.

Combining two studies only two out of 25 patients with medullary thyroid carcinoma had normal responses to pentagastrin. Many normals have been described with an exaggerated response to pentagastrin and the reproducibility of this test is poor.

Reference: McLean G.W. et al., Metabolism 33, 790-796 (1984).

CALCIUM INFUSION TEST FOR MEDULLARY CA THYROID

INDICATIONS

Suspected acalcitoninaemia.
Suspected medullary carcinoma of thyroid.
Screening of families with medullary carcinoma of the thyroid.
Patients with suspected MEN type 2.

CONTRAINDICATIONS

Bleeding disorders

SIDE EFFECTS

Unpleasant flushing sensation
No major side effects

PREPARATION

Patient should fast overnight.
Check electrolytes and serum calcium.
Cannula, 18-20g.
Saline flush.
Calcium gluconate 10% (10 - 20 ml required).
6 x Lithium heparin tubes (green top Vacutainer) with 200 µl Trasylol.
Syringes.
Ice and facilities to transfer samples immediately to lab.

METHOD

Insert cannula and flush.
Take baseline sample for calcitonin.

Give calcium gluconate 0.2 ml/kg body weight i.v. over 1 minute.
Flush cannula.
Take samples at 1, 2, 3, 5 and 10 minutes for calcitonin.
Send immediately on ice to the lab for centrifugation and freezing.

INTERPRETATION

In medullary carcinoma of the thyroid there is often a raised fasting serum calcitonin (>90 ng/l) but this may be in the normal range. Provocative tests improve the sensitivity of calcitonin measurement. Normal range for peak calcitonin following calcium infusion is 100 to 200 ng/l

SENSITIVITY AND SPECIFICITY

In the study quoted below 8/12 subjects with medullary thyroid carcinoma had increased responses to calcium infusion. Two of the four who failed to respond had a raised baseline calcitonin. There is a high false positive rate especially in young men. The pentagastrin test is better in this situation.

REFERENCES

Charib H. et al., Mayo Clinic Proc., 62, 373 (1987).

VERSION HISTORY

JW 12/89

Screening for mutations of MEN1, MEN2a, MEN 2b or FMTC.

Huw Dorkins and Angela Brady (consultant clinical geneticists) will consent and screen patients (and send off the blood) if referred: They are at the Kennedy Galton centre, Watford Road, Harrow, Middlesex, HA1 3UJ: Tel: 020 8869 2797; Fax 020 8869 3106).

Because thyroidectomy prevents medullary thyroid cancer provided it is performed before the age of 5, children must be screened for the MEN2 gene before they develop thyroid cancer. Send 10 ml blood in an EDTA tube to: Dr. J Whittaker, East Anglian Medical Genetics Service, Molecular Genetics laboratory, Box 158, Addenbrookes Hospital, Hills Road, Cambridge. CB2 2QQ. Tel: 01223 217971/217973.

An alternative laboratory for **MEN1**, and MEN 2 genetic screening runs in Exeter under the auspices of Dr. Andrew Hattersley. Tel : 01392 403089. Fax: 01392 403027. E-mail: A.T.Hattersley@ex.ac.uk: Screening for MEN1 costs £400, for MEN2a, £250 and for MEN2b, £100. Testing for a known mutation in a family member costs £75 for both conditions. Lab contact: S. Ellard (01392 402910).
A request form is available via http://meeran.info
KM 01/03

FINE NEEDLE ASPIRATION OF A THYROID NODULE (FNA)

INDICATION

Investigation of thyroid nodule(s). 80% of all thyroid nodules are "cold" on technetium or iodine scan, and 85 to 90% of these cold nodules are benign. Thus the prime aim of FNA is to exclude malignancy (note however that 9% of nodules that are apparently functioning on isotope scanning turn out to be malignant,

i.e. scanning alone is a poor test to exclude malignancy and may be becoming obsolete as a first line investigation of nodules).

CONTRAINDICATIONS

None

PREPARATION

None

SIDE EFFECTS

Rarely: local bleeding. Avoid by applying local pressure

METHOD

1. Contact cytology department who will come almost immediately and bring their prepared slides.
2. Lie patient in supine position with neck flexed backwards.
3. Insert 25 gauge needle into nodule and aspirate (usually more than one pass). Local anaesthesia is usually necessary. The needle should just be passed in and out. Don't draw back as this results in a bloody tap.
4. At Charing Cross, if the nodule is palpable, draw a clear diagram of where it can be felt, and book the patient to return the following Thursday at 1.30 pm on list M70. The FNA is usually performed by Dr. Naomi Livni, consultant cytopathologist, who teaches endocrine SPRs how it is done.

INTERPRETATION

Possibilities are:

1) "Negative" or benign: obvious epithelial cells ± colloid
2) Hashimoto's (hypercellular)
3) Suspicious of neoplasm: papillary etc.
4) Diagnostic of neoplasm
5) Non-diagnostic: insufficient cells to make a diagnosis

ACTION

1) and 2) do nothing, ?follow up if necessary. No indication for T4 treatment to "suppress" nodule unless function tests show raised TSH (i.e. "subclinical hypothyroidism").

3) Repeat FNA, radioisotope scan: if focal abnormality refer to Mr Lynn

4) Refer Mr Lynn

5) Consider repeat FNA. Do isotope scan ± ultrasound.

SENSITIVITY AND SPECIFICITY

Depends on the centre. At the Hammersmith we have as yet little experience and cannot say. Experienced centres report 98% sensitivity and over 99% specificity. The major limiting factor may be the quality of the sample.

REFERENCES

Gabib H et al., Endo. Metab. Clin. N. Am. 17, 511-26 (1988).

VERSION HISTORY

SG 10/89 KM 07/01

POST OPERATIVE INVESTIGATION OF THYROID CARCINOMA

Patient age <40 yrs and non-invasive papillary or follicular carcinoma less than 3 cm

- Subtotal thyroidectomy
- Ablation dose ^{131}I, day 5 post-operatively, 2 hours after i.v. TRH
- Replacement therapy (T4) started 3 days post ablation, and increased to 200 mcg daily.
- Follow-up, with TSH and thyroglobulin levels. Thyroglobulin levels are done in Birmingham (0121 6271627 x52284).
- ^{131}I scan only if recurrence suspected clinically.

Extrathyroidal papillary carcinoma, non-invasive papillary carcinoma if age > 40 yrs or follicular carcinoma

- Subtotal thyroidectomy
- Ablation dose ^{131}I
- Replacement therapy (T3) started 3 days post ablation, and increased to 20 mcg twice daily
- Regular follow-up with ^{131}I scanning (3 and 6 months, and then at years 1, 2, 3, 5 and 7)
- If no evidence of recurrence after 2nd ^{131}I scan, switch to T4 suppression (200mcg daily).
- T3 needs to be discontinued 8 days prior to ^{131}I scan and TSH measured on day of scan to ensure appropriate interpretation.

VERSION HISTORY

AP 1/98

LOW IODINE DIET

This diet is used for patients who have previously been treated for papillary or follicular thyroid carcinoma and who have had a total thyroidectomy. In these patients, it is taken for 2 weeks prior to a whole body iodine scan, as the smallest amount of iodine might cause reduced uptake. It can also be used (for 2 days) before radioiodine ablation in hyperthyroid patients, but this is less critical. The dose of radioiodine is much less than used in thyroid carcinoma.

Please avoid the following foods that have a high iodine content:

- Iodised salt, including sea salt and processed meat products, which all contain iodised salt and red food colourants
- All foods containing red food colourants (E127). Please look on the product label for this food dye, which is found in things like glacee cherries, red biscuits, etc.
- Seafood, including fish, shellfish, kelp and seaweed
- Try and restrict your intake of milk, since milk contains iodine. Use soya milk instead

In general, check all food labels for additives, and if possible avoid those containing iodides, iodates, algin, alginates, agar, and carraganeen.

HYPERPARATHYROIDISM

ESTABLISH DIAGNOSIS

- Elevated corrected Ca^{2+}.
- Low PO_4^{3-}.
- Normal alkaline phosphatase.
- Normal or elevated serum PTH.
- Exclude vitamin D deficiency
- High 24 hr urinary Ca^{2+}.
- To exclude Familial Hypocalcuirc Hypercalcaemia (FHH), the calcium clearance to creatinine clearance ratio should be > 0.01. This is calculated as follows:

Calcium Clearance
[Urine Calcium (mmol/l) x urine volume (ml)] / [Plasma Calcium (mmol/l) x 1440]

Creatinine Clearance (This may be calculated already)
[Urine Creatinine (mmol/l) x urine volume (ml)] / [Plasma Creatinine (mmol/l) x 1440]
Plasma creatinine is normally expressed in umol/l and needs to be converted to mmol/l by dividing by 1000.

However, this ratio can be reduced to

$$\frac{\text{Urine Calcium (mmol/l) x [Plasma Creatinine (umol/l) / 1000]}}{\text{Plasma Calcium (mmol) x Urine Creatinine (mmol/l)}}$$

For example
FHH

Urine calcium 1.0 mmol/l
Urine creatinine 6.2 mmol/l
Plasma creatinine 130 umol/l
Plasma calcium 2.65 mmol/l

$$\text{Ratio} = \frac{1.0 \times [130/1000]}{2.65 \times 6.2} = 0.0079$$

Primary Hyperparathyroidism

Urine calcium 2.2mmol/l
Urine creatinine 1.4 mmol/l
Plasma creatinine 74 umol/l
Plasma calcium 3.3 mmol/l

$$\text{Ratio} = \frac{2.2 \times [74/1000]}{3.3 \times 1.4} = 0.035$$

LOCALISATION OF PARATHYROID ADENOMA

None of the techniques are reliable and often a combination of methods are used.

- Ultrasound of neck.
- Sesta-MIBI scanning.

- ^{123}I and sesta-MIBI double isotope scan (higher sensitivity, ask nuclear medicine).
- MRI of neck.
- CT neck (+ upper mediastinum).
- Selective venous sampling for PTH is not routinely used and reserved for difficult cases. Patient requires hospital admission, and investigation needs to be booked with Dr Jackson well in advance.

MANAGEMENT PRIOR TO PARATHYROIDECTOMY

- Usual pre-operative bloods, including U+E, Ca^{2+}, PO_4, alkaline phosphatase, albumin.
- Maintain adequate hydration.
- Replace deficit and maintain 3-4 l fluids /day i.v. and then orally if patient able to drink.
- If above measures do not reduce corrected Ca^{2+} <2.8 mmol/l give bisphosphonates (e.g. pamidronate 30 mg in 1l 0.9% saline over 4 hrs). This will not start to work for 24hrs, with maximum effect 5-6 days. Plan in advance to avoid severe post-operative hypocalcaemia.

MANAGEMENT AFTER PARATHYROIDECTOMY

- Enquire for symptoms of hypocalcaemia (paraesthesiae, cramps etc.).
- Trousseau's and Chvostek's test daily or whenever blood pressure is checked.
- Daily U+E and corrected Ca^{2+}.
- If mild symptoms and corrected Ca^{2+} >1.9 mmol/l, give effervescent Ca^{2+} (Sandocal 1000; two tds suggested).
- If severe symptoms and corrected Ca^{2+} <1.9 mmol/l, give Ca^{2+} infusion (calcium gluconate 15 mg/kg i.v. in 1l 0.9% saline over 4 hours). [1gram which is 10 ml of 10% calcium gluconate in a 70 kg patient. Neat calcium gluconate (10ml 10% can cause necrosis if it extravasates, so either administer it yourself through an obviously patent large venflon, or use a central line). Diluting it in a liter of saline is another option.
- If hypocalcaemia persists, start oral Sandocal 1000 (up to 4 tabs qds might be needed) and introduce alfacalcidol (125 ng od). This is a low dose and patients may require 1 – 2 mcg twice daily eventually.
- The amount of calcium needed depends on how hungry the patients bones are, and initially can be quite large.
- Monitor PTH. If detectable, and parathyroid recovery occurs, try to wean off alfacalcidol. If PTH remains undetectable, it is likely that they will stay on alfacalcidol for life. In that situation, the long term risk is nephrocalcinosis as the calcium-phosphate product will be high. Thus long term aim is for a low-normal calcium.

VERSION HISTORY

AP 1/98 updated SS 07/01

PANCREAS

DIABETES

GLUCOSE TOLERANCE TEST

INDICATIONS

- Suspected diabetes mellitus. An oral glucose tolerance test is not required if the diagnosis of diabetes is not in doubt or if a fasting venous plasma glucose is greater than 7.0 mmol/litre or a random venous plasma glucose is greater than 11.1 mmol/l.
- In acromegaly, to establish the diagnosis and to follow patients after treatment with surgery or irradiation.
- Suspected reactive hypoglycaemia.

CONTRAINDICATIONS

None

SIDE EFFECTS

Nausea and occasional vomiting

PREPARATION

The subject should have been on a diet containing an adequate amount of carbohydrate (250g/day) for at least 3 days before the test
Overnight fast.
75g anhydrous glucose.
Fluoride oxalate tubes x 3 (grey top Vacutainers).
18-20g cannula.
Saline flush.
Syringes x3.

METHOD

- *Diabetes*
  Insert cannula.
  Take a baseline glucose at time 0.
  Give oral glucose load (75 g anhydrous glucose in 250–350ml water).
  Repeat blood samples at 60 and 120 min after glucose load.
- *Acromegaly*
  See under “growth hormone” above.
- Reactive hypoglycaemia
  Take blood for glucose AND GUT HORMONES (to measure GLP-1) at -15, 0, +15, 30, 45, 60, 90, 120, 150, 180, 210, 240, 270 and 300 min.

INTERPRETATION

WHO (established June 2000) for diabetes and impaired glucose tolerance

Plasma Glucose (mmol/l)	Fasting	2 hrs after glucose load
Diabetes mellitus	≥7.0	≥11.1
Impaired glucose tolerance		>7.8 – 11.0
Impaired fasting glucose	>6.1 – 7.0	
Normal	6.1	7.8

75 g oral glucose tolerance test.

In the absence of diabetic symptoms at least 2 abnormal values are necessary to establish a diagnosis of diabetes mellitus

Gestational diabetes: women who have IGT in pregnancy should be treated as if they have GDM.

SENSITIVITY AND SPECIFICITY

These criteria were revised by the WHO in 1997 and remain arbitrary. Remember that acute illness (e.g. myocardial infarction) and drugs may affect glucose tolerance.

In acromegaly it is very rare for GH to suppress to the normal range with a glucose load. In fact there is often a paradoxical rise in GH. Some normals especially if stressed do not suppress. The definition of "cure" in acromegaly is very difficult. Patients may show dramatic clinical improvement but not suppress with glucose.

REFERENCES

Keen H., Medicine International May, 2672-2675 (1989).

Diabetes Care, 21 S1, 5-19 (1998).

AUTONOMIC FUNCTION TESTS

INDICATIONS

Suspected diabetic autonomic neuropathy.

Shy-Drager Syndrome.

Suspected autonomic failure from other causes.

CONTRAINDICATIONS

Patients with proliferative retinopathy should not perform the Valsalva manoeuvre because of the risk of retinal haemorrhage.

Atrial fibrillation (tests uninterpretable, except postural hypotension and handgrip tests).

SIDE EFFECTS

None

PREPARATION

Sphygmomanometer.

Mouthpiece to attach to sphygmomanometer (5ml syringe minus plunger).

ECG machine (old fashioned type as long rhythm strips recorded).

Tests of cardiac parasympathetic damage

1. *Heart rate response to the Valsalva manoeuvre*

   Start ECG machine (limb leads only, use lead II)

   Patient blows into sphygmomanometer and maintains pressure at 40mmHg for 15 seconds, continue recording for 30 seconds after release of pressure.

   Measure shortest R-R interval during manoeuvre and longest after.

   Valsalva ratio = longest after/shortest during.

   Take mean of three readings.

2. *Heart rate variation during deep breathing*

   Start ECG machine

   Ask patient to breathe quietly at a rate of six breaths over one minute (5 seconds in and 5 seconds out).

   Mark ECG at start of each inspiration and expiration.

   Measure maximum and minimum R–R interval for each cycle and convert to beats/min.

   Result is mean difference (max – min) for heart rate during deep breathing.

3. *Heart rate response to standing*

   Start ECG recording with patient lying.

   Ask the patient to stand, continue recording ECG for 1 minute.

   Measure shortest R–R interval around the 15th beat after standing and the longest around the 30th beat.

   Calculate longest/shortest = 30:15 ratio.

Tests of sympathetic damage

Blood pressure response to standing

Measure blood pressure lying and then 2 minutes after standing

Record postural difference

INTERPRETATION

TESTS	Normal	Borderline	Abnormal
Valsalva ratio	1.21	1.11-1.20	1.10
(max–min) HR	>15	11-14	<10
(30:15 ratio)	>1.04	1.01-1.03	1.00
fall in BP	10	11-29	30

These tests can be used to determine the degree of abnormality present: if two or more of the parasympathetic tests plus the sympathetic tests are clearly abnormal then this indicates significant autonomic damage, earlier damage is signified by abnormalities in at least two parasympathetic tests.

SENSITIVITY AND SPECIFICITY

Caution should be taken in interpreting these tests in patients who are poorly co-operative and in the elderly.

REFERENCE

Clarke B.F. and Ewing D.J., BMJ 285, 918-920 (1982).

GUT HORMONE TUMOURS

INSULINOMAS

Patients with hypoglycaemic symptoms may have an insulinoma or reactive hypoglycaemia should have a prolonged (5 hour) oral glucose tolerance test before their supervised fast. Therefore both protocols are given below. (If both negative, consider EEG and CT brain, as temporal lobe epilepsy also occurs with this presentation).
If the patient is on diazoxide it should be discontinued a week before admission.

GLUCOSE TOLERANCE TEST

PREPARATION

The subject should have been on a diet containing an adequate amount of carbohydrate (250g/day) for at least 3 days before the test thus the OGTT must NOT follow the prolonged fast.
Overnight fast.
75g anhydrous glucose.
Fluoride oxalate tubes x 14 (grey top Vacutainers).
Lithium heparin with trasylol (0.2 ml) x 14
18-20g cannula.
Saline flush.

METHOD

Take blood for glucose AND GUT HORMONES (to measure GLP-1) at -15, 0, +15, 30, 45, 60, 90, 120, 150, 180, 210, 240, 270 and 300 min.

PROLONGED SUPERVISED FAST

INDICATION

Used to demonstrate fasting hypoglycaemia and diagnose insulinoma if not shown spontaneously or after an overnight fast.

PREPARATION

Admit to perform test under close supervision with glucose (p.o./i.v.) available.
Leave a copy of this protocol sheet in the nurses' notes and a copy above the patient's bed.

METHOD

- Cannulate patient and commence 72 hr fast.
- Water/non-caloric beverages allowed. Patient should be active during waking hours.
- Blood glucoses should be done at regular (4–6 hr) intervals and whenever the patient has symptoms suggestive of hypoglycaemia. Decrease to 2 hr intervals if the patient consistently has glucoses <3.0 mmol/l.
- If blood glucoses are 2.2 mmol/l or symptoms are convincing:

  - Take blood for glucose, insulin and C-peptide in a plain clotted tube (7 ml) and a fluoride oxalate tube.
  - Take blood and spot urine for sulphonylurea screen in a plain clotted tube (7 ml) and a Sterilin universal container.
  - Take to chemistry labs to be separated and frozen within 30 mins. Ring biochemistry up for an urgent glucose.
  - Do not reverse hypoglycaemia until the lab confirms hypoglycaemia, or unless the patient becomes unconscious or fits.
- If no symptoms during the fast, finish with 15-30 mins exercise, e.g. a brisk walk around the hospital.
- Take final samples for glucose, insulin and C-peptide, sulphonylurea screen.

INTERPRETATION

- Normals do not become hypoglycaemic, although young women can run glucoses in the region of 2.2–3.0 without symptoms.
- True hypoglycaemia must be demonstrated (glucose 2-2.2 mmol/l), before we are able to either interpret insulin results or consider insulinoma.
- If hypoglycaemia with raised insulin but low C peptide, consider self administration of insulin.
- If hypoglycaemia with raised insulin, and raised C-peptide, make sure sulphonylurea screen is negative! Tel (Guildford lab 01483 571 122 x 4696).
- With hypoglycaemia, insulin and endogenous insulin production (estimated by C-peptide) should be low.
  - Insulin >6 mU/l (>50 pmol/l); C peptide >300 pmol/l = insulinoma (check ratio of c-peptide to insulin high enough).
  - Insulin >3-6 mU/l (25-50 pmol/l); C peptide 100-300 pmol/l = possible insulinoma but needs further tests
  - Insulin <3 mU/l (<25 pmol/l); C peptide <75 pmol/l = normal response
- Ketones should be suppressed with insulinoma even though patient is fasting because of the excess insulin.

SENSITIVITY AND SPECIFICITY

By 24 hrs, 66% insulinomas develop hypoglycaemia and by 48 hrs, >95% insulinomas can be diagnosed. After 72 hrs fast plus exercise, if no hypoglycaemia, insulinoma is very unlikely.

REFERENCE

Friesen, S.R. Surg. Clin. N. Amer. 67(2). 379 (1987).

VERSION HISTORY

MLB & PJH 10/91

MANAGEMENT OF STABLE INSULINOMAS PRIOR TO SURGERY

ALTERNATIVES INCLUDE:

1. Dietician review. Multiple, regular, small meals usually help.

2. Guar gum 5g tds also helps by slowing gastric absorption.
3. Diazoxide 50–200 mg tds, but beware of hypokalaemia and severe oedema
4. NG feeding can be considered.
5. Steroids can help for a short period.
6. Octreotide can be helpful but beware hypoglycaemia if glucagon levels are suppressed.
7. Calcium channel antagonists may be useful for nesidioblastosis.

GASTRINOMAS

GASTRIC ACID SECRETION

INDICATION

Used in the diagnosis of Zollinger-Ellison syndrome. Rarely needed now as an endoscopy can give evidence of acid hypersecretion (multiple ulceration) and usually can distinguish achlorhydria.
Consider syndrome if:

1) Raised gastrin (>40 pmol/l) in the absence of other causes (e.g. H2 antagonists, PPIs, pernicious anaemia, other causes of achlorhydria, renal failure).
2) Associated upper gastrointestinal disease, i.e. peptic ulcer disease with poor response to treatment; multiple duodenal or jejunal ulcers; peptic ulcer disease with unexplained diarrhoea; fulminant peptic ulcer disease (perforation, haemorrhage, oesophagitis and stricture); ulcer in upper part of ligament of Treitz.

Measuring gastric output distinguishes secondary hyper-gastrinaemia (due to achlorhydria) from primary hyper-gastrinaemia. Administration of pentagastrin i.v. does not improve the diagnostic accuracy.

PREPARATION

Book with endoscopy suite since the end couch next to the apparatus will be required.
Liase with Gastro research fellow to ensure that equipment is not being used.
Stop H2 antagonists for 72 hrs and stop PPIs for 2 weeks.
Stop antacids 24 hours before blood sample.
Patient should be fasting.
Check that the autotitrator is available, otherwise you will need to obtain a burette, conical flask, pH meter and 0.1M NaOH.

METHOD

1. Pass the special double lumen naso-gastric tube (obtained from sister in endoscopy) with plenty of Xylocaine spray to the nose and throat, and lignocaine jelly to the nose. Pass the NG tube as far as the 50cm mark at the nostril.
2. Ask the patient to drink 50mls of water and then aspirate this via the NG tube to check that it is in the most dependent part of the stomach.
3. Connect NG tube to the pump and collect four samples of gastric juice, each over 15 min into polystyrene cups. Alternatively, aspirate regularly and periodically with a 50ml syringe to collect gastric juice over each 15 min period.
4. Measure total volume of each sample. Decant 10mls of each into a fresh polystyrene cup and titrate against 0.1M NaOH with the automated titrating equipment, or carry out a standard neutralisation titration manually.
5. Calculate the acid production of each 15 min collection:

   $A = (N/100) \times V$

   A = mmol of acid production

   N = volume (ml) of 0.1M NaOH solution needed to neutralise 10mls of gastric juice

   V = volume (ml) of gastric juice in 15 min collection

A sum of the acid production for each 15 min will give the total hourly production.

INTERPRETATION

Spontaneous basal acid outputs of 20 - 25 mmol/hr are almost diagnostic, >10 mmol/hr is suspicious. Post ulcer surgery >5 mmol/hr is indicative.

SENSITIVITY AND SPECIFICITY

Hypergastrinaemia and raised gastric acid are also found with:

1. gastric outlet obstruction: resolves with NG decompression
2. massive small bowel resection: resolves a few months post op
3. antral G cell hyperplasia: excess cells on histochemistry

REFERENCE

Deveney et al., Surg. Clin. N. Amer. 67(2) 411 (1987).

VERSION HISTORY

MLB & PJH 2/91; corrected equation BK 7/00.

INTRAVENOUS SECRETIN TEST

INDICATION

The intravenous secretin test should, whenever possible, be performed only after the results of basal plasma gastrin and acid output – both performed off PPIs for 2 weeks, H2 blockers for 3 days and fasted - are available.

The indications for the test are:

1. Strong clinical suspicion of a gastrinoma with equivocal results of acid studies and fasting gastrin.
2. Inability to wean patients off antisecretory therapy for long enough to perform acid studies and gastrin estimation because of recurrence of severe symptoms.

PREPARATION

Warn fasting gut hormone lab (34549/33949) 48 hours in advance.

Fast overnight. If possible, stop antisecretory therapy for 24 hours.

Secretin (Kabi) ordered in advance from Pharmacy.

7 x 7 ml Lithium Heparin tubes (green top Vacutainers) with 200 l Trasylol labelled before the study.

Syringes.

Ice.

Arrangements to transfer for immediate spinning.

METHOD

1. Site indwelling cannula.
2. Take two baseline samples at T = -15 and 0 mins.
3. Secretin 2U/kg injected as bolus at T = 0.
4. Blood samples taken at T = 2, 10, 15, 20 and 30 minutes.
5. Samples stored on ice and spun within 15 minutes.

6. All samples assayed for gastrin.

INTERPRETATION

The criteria for diagnosing a gastrinoma are based on gastrin assays from other laboratories where results may not be directly comparable. The best criterion is a rise in gastrin of 200 pg/ml – equivalent to about 100 pmol/l. This gives a sensitivity of 85% when performed on all patients with a fasting gastrin of less than 400 pmol/l. A rise of 50% over basal values gives a sensitivity of 78%. Gastrin levels FALL in normal individuals in response to secretin.

Few false positives have been reported, but massive rises occasionally occur in association with achlorhydria and common duodenal ulcer disease, hence the need to have acid studies and fasting gastrin as the initial investigations, if possible.

REFERENCE

Frucht et al., Ann. Intern. Med. 111, 713-722 (1989).

LOCALIZATION OF GASTRINOMAS AND INSULINOMAS

IMAGING.

CT or MRI.

Octreotide scan

Endoscopic ultrasound is performed at the Middlesex Hospital by Dr. Z Amin. This can be booked by contacting the gastro (hepatobiliary) registrar at UCLH (tel: 020 7387 9300 bleep 2010 or 2128). Alternatively (if bleeps difficult, contact the secretary on X 9011).

Preparation for endoscopic ultrasound (EUS)

Patients need to fast from 4 am, but insulinoma patients are at risk of hypoglycaemia and will require admission for an iv dextrose infusion from at midnight. Transport needs to be booked for the patient to arrive at the Endoscopy department at the Middlesex Hospital for 9am (usually a Thursday morning). They require a nurse escort (organised by the ward).

SELECTIVE ARTERIAL INJECTION

INDICATION

This investigation is performed in conjunction with highly selective angiography for patients with proven gastrinomas or insulinomas, whose tumours are too small (usually less than 1 cm) to be detected by CT or USS. This comprises about 50% of patients with these syndromes. Gastrinomas can be stimulated with intra-arterial secretin or calcium; insulinomas with intra-arterial calcium. Much better results are obtained with calcium, and secretin is no longer really available.

CONTRAINDICATIONS

(Discuss with radiology S.R.)

Allergy to contrast dye.

Ischaemic Heart Disease
Orthopnoea
Bleeding tendencies (severe)

PREPARATION

Order Secretin (Kabi) or 10% calcium gluconate in advance from Pharmacy.

Warn fasting gut hormone lab (34549/33949) or endocrinology lab (34681) 48 hours in advance.

Stop diazoxide 7 days before procedure. Patients on PPIs or H2 antagonists need not have them discontinued (unlike fasting gastrin measurements for diagnosis).

Consent patient (may have flushing, nausea and hypoglycaemia following calcium injection, risks of bleeding from sheath sites, thrombosis/dissection of femoral artery and visceral arteries, dye allergy). This should be done by the radiologist.

Blood for FBC, U+Es, clotting, and G+S should be taken the day prior to the procedure.

Fast for at least 4 hours and run in 5% dextrose to maintain blood glucose at about 3.0 mmol/l.

2 people to attend to assist sample processing.

7 tubes per arterial run (prepare 5 runs and have more tubes to hand):

7 ml Lithium Heparin tubes (green top Vacutainers) containing 200 µl Trasylol marked before the study starts for *gastrinoma*.

7 ml plain bottles (red top Vacutainers) for *insulinoma*. (for insulin AND c-peptide).

Syringes.

Ice.

Stopwatch.

Arrangements to transfer for immediate spinning.

SIDE EFFECTS

No serious complications of this procedure have been reported in the 30 patients reported in the literature. Flushing and nausea may follow calcium injection. One of our insulinoma patients had a hypoglycaemic episode following injection of calcium and so BMs should be monitored and the glucose maintained at 3 - 5 mmol/l with dextrose infusion if necessary. The other potential side effects are those of the angiography itself.

METHOD

1. A catheter is placed in the right hepatic vein prior to routine highly selective visceral angiography.
2. Following angiography each artery (usually proximal gastroduodenal, proximal splenic, hepatic and superior mesenteric) is recatheterised in turn, preferably starting with the vessels least likely to be supplying the tumour. Occassionally the dorsal pancreatic artery is also catheterised.
3. Take two baselines at T = -120 and 0 secs.
4. At T = 0 secretagogue is rapidly injected as a bolus into the artery – 30U secretin in 5ml normal saline or 1 ml of 10% calcium gluconate as appropriate.
5. Blood is sampled at T = 30, 60, 90, 120 and 180 secs (give a 10 sec countdown before each sample).
6. Samples for gut hormone assay should be stored in ice and spun within 15 minutes, and samples for insulin assay should be separated within 30 minutes. Do not store insulin samples on ice unless procedure is very prolonged. A Clinical Chemistry form needs to be completed with details of arteries sampled, times and hormones that you want assayed.

INTERPRETATION

- *Secretin injection*: localization to a specific region of the pancreas or duodenum (regionalization) is based on a gradient of greater than 50% on the 30 sec sample. Using these criteria the NIH group successfully regionalized 54% of tumours and in combination with angiography, 77% of lesions were localized.
- *Calcium injection*: 4 patients have been reported in the literature (by the NIH group). All were localized using the criterion of a two-fold rise in insulin in the 30 or 60 sec hepatic vein samples. There has also been one report of a PPoma being localized by selective arterial calcium injection.

REFERENCES

Secretin: Doppman J.L. et al., Radiology 174, 25-29 (1990).

Calcium: Doppman J.L. et al., Radiology 178, 237-241 (1991), Fedorak I.J. et al., Surgery 113, 242-249 (1993), O'Shea et al., JCEM (1996): 81(4): 1623-1627

Turner etal (2002): Clin End (Oxf). Calcium stimulation tests for localisation of gastrinoma.

Dhillo etal (2005): Eur. J. Gast Hep.

PJH 9/93; minor corrections BK 07/00, KM 07/02

CARCINOID AND NEUROENDOCRINE TUMOURS

FOODS TO AVOID DURING 24 HOUR URINE COLLECTION FOR 5-HIAA

Avocados, bananas, plums, walnuts, pineapples, tomatoes, aubergines, cough medicine.

HEPATIC EMBOLIZATION OF METASTASES

DEFINITION

The liver has a dual blood supply (hepatic artery and portal vein) so that interruption of hepatic arterial supply by its embolization using foreign substances (e.g. polyvinyl alcohol) in the presence of a patent portal circulation (necessary to sustain liver function). Undertaken under local anaesthetic by Professor Jackson's radiology team.

INDICATIONS

1. Palliation of clinical consequences of hormone production from hepatic secondaries in the carcinoid syndrome and other neuroendocrine tumours. Diagnosis should be fully established.
2. More controversially: reduction of tumour load in these patients to improve the well being of the patient or to reduce local symptoms (e.g. "dragging" abdominal pain from hepatomegaly).

CONTRAINDICATIONS

Prolonged prothrombin time
Non-patent portal circulation
Obvious end-stage illness
Ischaemic heart disease
Contrast allergy

SIDE EFFECTS

Arterial thrombosis (e.g. femoral artery).
Bleeding from sites of sheath insertion.
Malaise, mild hypotension and fever due to the release of tumour necrosis factor and other vasoactive compounds from necrotic tissue. This can last for weeks after the procedure.
Occasionally life threatening hypovolaemia with renal failure due to severe vasodilatation. This is now rare when octreotide is used, but patients must be well hydrated pre- and immediately post-embolization.
Rarely infarction of other intra-abdominal organs including the gallbladder.
Rarely infection introduced during procedure and rarely abscesses in the liver, which can develop late.
Rarely tumour lysis syndrome, which is why allopurinol has been added to protocol.

PREPARATION

1 week before procedure:

- Dual-phase contrast CT abdomen to establish baseline for size, location of metastases.
- *Optional* Doppler USS liver to establish portal vein patency (this is always established by Prof Jackson immediately before embolization).

- Take blood for FBC, U+Es, clotting, G+S.
- CXR, ECG.
- Echocardiogram if carcinoid and no previous echo.

Day before:

- May need to put in central venous catheter and urinary catheter (low threshold).
- Insert three large cannulae, if not using central venous catheter.
- Document foot pulses.
- No evidence of infection.
- Informed consent.
- Premed (discuss with radiologist).
- Discuss with anaesthetic SR on call regarding possible need for ITU bed.
- Start 1l 0.9% saline with 20 mmol KCl from midnight before procedure.
- Write up protocol medication:

PROTOCOL MEDICATION

Start on admission:

- Allopurinol 300 mg p.o. od for 10 days.
- Cyproheptadine 4 mg p.o. tds (histamine blocker – in *carcinoids*) for 72 hrs post procedure.
- Nicotinamide no longer used as it causes extreme flushing in carcinoids. It can be used in lower doses chronically to avoid Pellagra.

To start on morning of procedure and continue for 48 hrs:

- Octreotide: 1600 mcg in 48 ml 0.9% saline, i.v. at 6 ml/hr (i.e. 8 hrs). Write up 6 syringes.
- Trasylol (aprotinin): 50 ml neat (10,000 U/ml) i.v. at 5 ml/hr (i.e. 10 hrs). Write up 5 syringes.

One hour before procedure:

- Methylprednisolone 1g i.v.
- Premedication (discuss with Prof Jackson).

Antibiotic cover:

Pre-procedure

- Amoxycillin 1g i.v. (or Teicholplanin 400 mg 12 hourly if penicillin allergic).
- Metronidazole 500mg i.v.
- Gentamicin 120mg i.v.

Post-procedure

2 further doses of

- Amoxycillin 1g i.v. 8 hourly
- Metronidazole 500mg i.v. 8 hourly

Have available:

- Hydralazine i.v. for hypertension (alternatively nitroprusside, labetalol).
- Colloids for hypotension.
- Methylprednisolone.

POST-EMBOLIZATION

Usual post angiogram observations (i.e. foot temperature, peripheral pulses, Tº, BP and HR).

Careful attention to fluid balance is needed.

Daily biochemistry including GGT, CRP, and haematology for at least 3 days.

Monitor specific tests, e.g. urinary 5-HIAA in carcinoid syndrome or gut peptides, every other day.
Expect pyrexia and malaise for up to ten days but perform blood cultures daily until pyrexia subsides.
If abdominal symptoms persist, arrange appropriate investigations (erect and supine X-rays, U/S abdomen) and ask for a surgical opinion.

RESULTS OF TREATMENT

In approximately 60%-80% of patients who have symptoms from secreting hepatic secondaries there will be an improvement with embolization. Revascularisation will occur with a recurrence of symptoms after weeks, months or years. Embolization can be successfully repeated.
Hepatic embolization is not known to prolong life – this is purely a palliative procedure.

REFERENCE

Allison D.M., Br. J. Hosp. Med. 20, 707-715 (1978).
Adjani J.A. et al., Ann. Intern. Med. 108(3), 340-4 (1988).

VERSION HISTORY

SGG 11/89; revised BK 7/00 and SS 07/01

CHEMOTHERAPY FOR NEUROENDOCRINE TUMOURS

Coordinate with oncology: Prof Waxman's team.

INDICATIONS

Patients with established neuroendocrine tumour, to reduce tumour bulk and improve symptoms

INVESTIGATIONS

(to monitor renal, hepatic and bone marrow function, and response to treatment)

- 24.hr urine for creatinine clearance: chemotherapy contraindicated if <60 ml/min.
- Urinalysis twice daily during treatment and abandon if persistent proteinuria.
- FBC and biochemical profile on alternate days.
- Gut hormone screen and urinary 5HIAA before and after treatment.
- CT scanning and ultrasound where appropriate.

TREATMENT PROTOCOL

Streptozotocin 500 mg/m^2 | on alternate days
5-Fluorouracil 400 mg/m^2 | for 10 days

Chemotherapy given during 2nd litre saline, each drug diluted in 10ml normal saline and administered slowly (1ml/min) via a fast-flowing drip.

Administered with:

1. 0.9% saline i.v. – 3 litres over 12 hours
2. Lorazepam 2mg i.v. | after 1st litre saline
3. Dexamethasone 4mg i.v. | and 30 mins before
4. Metoclopramide 1mg/kg i.v. over 15 minutes | treatment commences

RESULTS OF TREATMENT

3–4 courses of chemotherapy are given every 2–3 months.

Response of the tumour is assessed after a further 6 months

Partial response occurs in

25% carcinoid

20% gastrinoma

60% malignant insulinoma

80% VIPoma

REFERENCE

Oberg et al., Acta Oncol. 28, 425 (1989).

OVARY

SCREENING FOR OVULATION

INDICATION

To confirm ovulation in a woman WITH PERIODS presenting with infertility.

BACKGROUND

1. LH and FSH rise for approximately 48 hours ("surge") at the onset of the ovulatory phase of the menstrual cycle.
2. Progesterone production rises in the ovulatory phase to a maximum during the luteal phase.
3. Basal body temperature rises by >0.5ºC during the ovulatory phase peaking about 8 days after the LH surge.

PREPARATION

Confirm menstruation. Exclude other causes of infertility including hyperprolactinaemia, chromosomal problems, and thyroid dysfunction.

METHOD

1. Arrange for blood to be taken on days 18, 21 and 24 for progesterone. Should be undertaken for at least 2 cycles.
2. A more intensive screening regimen is undertaken in the IVF clinic, and referral is an alternative option.
3. Blood for progesterone is taken in red top Vacutainers and may be posted to the lab.

INTERPRETATION

Progesterone >30 nmol/l between days 18 and 24 indicates an adequate luteal phase (production of progesterone by granulosa cell).

Evidence of ovulation and adequate luteal phase should prompt further investigation of causes of infertility unrelated to ovulation or menstrual cycle (husband's sperm count, tube problems etc.). A postcoital test should be considered if there is no evidence for any of these.

If there is no evidence of ovulation: review screening tests for other systemic causes of infertility or consider clomiphene test.

REFERENCE

Sverdloff R.S. et al., Endo. Metab. Clin. N. Amer. 17, 301-332 (1988).

Progesterone challenge:

Medroxyprogesterone 10 mg po QD x 5 days to induce uterine bleeding

If patient has bleeding within one week of stopping progesterone, then she has both a sufficient amount of estrogen to stimulate endometrial growth and a normal outflow tract, but she is lacking in progesterone. Anovulation is the cause. These women are at risk for endometrial hyperplasia from

unopposed estrogen. They should be treated with cyclic progesterone to induce withdrawal bleeding periodically (4 times per year), or alternatively OCPs can be prescribed if no pregnancy is desired. If pregnancy is desired, clomiphene can be used to induce ovulation.

If patient has no bleeding, she either has an outflow-tract defect or is estrogen-deficient from ovarian failure or dysfunction of the hypothalamic-pituitary axis. You can use a combination oral contraceptive pill for 21 days to induce menses; if no bleeding-- the patient likely has outflow tract obstruction-- although this diagnosis is usually easily made by history alone.

CLOMIPHENE TEST

INDICATION

Demonstration of the capacity for ovulation to be induced in a woman with infertility and anovulation, using clomiphene, a selective oestrogen receptor modulator.

CONTRAINDICATIONS

Pregnancy.

PREPARATION

Timing of cycle needs to be explained (first day of period = day 0).
Women without cycles have to start test at an arbitrary time.

SIDE EFFECTS

Rarely causes abdominal bloating. Small risk of multiple pregnancy.
Rarely, ovarian hyperstimulation with cardiovascular collapse, ascites and pleural effusions.

METHOD

1. Give clomiphene for 5 days at dose of 50 mg/day starting at day 5.
2. Blood is taken for baseline measurements on day 6 and at 2 day intervals between days 18 and 24, measuring LH, FSH, progesterone and oestradiol.
3. Keep a temperature chart.
4. If the test is unsuccessful over 2 cycles, repeat using higher doses of clomiphene (100 and 200 mg/day), cautiously. (best refer for follicle tracking).

INTERPRETATION

A rise in LH and FSH occurs, probably as a consequence of an anti-oestrogen effect giving a rise in GnRH. This in turn leads to follicular maturation, oestrogen production, LH release, and ovulation.
Thus a positive result is a:

rise in LH (to >20 U/l). rise in FSH (to >10 U/l).
rise in progesterone to >30 nmol/l.
rise in temperature by >0.5ºC to help confirm ovulation.

SENSITIVITY AND SPECIFICITY

The sensitivity and specificity is poorly defined. The difficulties with this test are:

a variable response to a given dose

the mechanism of clomiphene action is not known

therefore no clear-cut guidelines for a negative result

The potential value is that a positive result confirms relatively minor hypothalamo-pituitary dysfunction causing anovulation that should resolve spontaneously or be easily treated.

REFERENCE

Sverdloff R.S. et al., Endo. Metab. Clin N. Amer. 17, 301-332 (1988).

HYPOGONADOTROPHIC HYPOGONADISM

Fertility possible, but may need subcutaneous gonadotrophins:

Gonal F: 75u twice weekly (=FSH) + profasi (=hCG) 500 u twice weekly.

Referral to gynaecologists for follicular tracking essential.

PCOS

REVERSE CIRCADIAN PREDNISOLONE (dexamethasone).

Steroid levels are usually peaking at about 6am, and this can be suppressed by 0.5mg of dexamethasone last thing at night. If this is given, there may be borderline deficiency of steroid first thing in the morning, so administer 0.25 mg dexamethasone on waking. The nightime dose will suppress not only adrenal cortisol, but also androgen production, and the morning dose will prevent hypoadrenalism in the morning.

Method
Day 1: at 9am take blood for cortisol, testosterone, DHEA, androstenedione, SHBG, LH and FSH. Give the patient 0.25mg dexamethasone in the morning and 0.5mg dexamethasone in the evening for the next 5 days.
Day 6: at 9am take blood for cortisol, testosterone, DHEA, androstenedione, SHBG, LH and FSH.

Interpretation:
The androgens should fall into the normal range.
The cortisol should be undetectable if the patient has taken all of the dexamethasone tablets correctly.

HIRSUTISM

In a hirsute woman, an adrenal or ovarian androgen producing tumour must be excluded if testosterone > 5nM (unlikely anyway, so some authors ignore this and simply repeat testosterone). Tumour can be excluded if testosterone is suppressed to <3nM after 1 week of reverse circadian prednisolone. Congenital adrenal hyperplasia should also be excluded by doing a Short Synacthen test with 17-hydroxyprogesterone measurements (see Short Synacthen Test section).

If ovulation does not occur in confirmed PCOS (suggested by LH:FSH ratio>3, low SHBG, testosterone between 3 and 5 nM), give reverse circadian prednisolone. Start with a 3 month course.

Reduce prednisolone as follows if pregnancy occurs:
Change to normal circadian prednisolone (5mg mane + 2.5 mg nocte) for 1 week.
Then reduce to 2.5 mg twice daily for 1 week.
Then reduce to 2.5 mg once daily for 1 week.
Then stop prednisolone (within 3 weeks therefore of discovering pregnancy).

If no pregnancy after 3 months, add clomiphene, 50 mg daily for 5 days of each cycle.
If this also fails, try 100 mg clomiphene daily for 5 days each cycle.
If this also fails, refer for a gynae opinion.

Metformin can be helpful at regularising menstruation, but this drug is not licenced for PCOS. Metformin must be stopped before the end of the first trimester if pregnancy occurs. Metformin is poor in patients looking for reduction in hirsutism.

TESTIS

Idiopathic gynaecomastia is best treated with liposuction by a Plastic surgeon. Suggest Adam Searle or Mr Percival at Charing Cross.

Induction of fertility in patients with hypogonadotrophic hypogonadism

Male patients who are on regular testosterone replacement must have this discontinued. Where the cause of infertility is hypogonadotrophic hypogonadism replacement with LH and FSH is carried out.

Dosing regimen for hypogonadism to induce spermatogenesis

1. HCG (Pregnyl) 2000iu 2 x per week for 3 months
2. THEN carry out sperm count
3. If still azoospermic, add to above FSH (Puregon) 150iu 2 x per week
4. Combination treatment can be continued for 18 months

(N.B. Profasi has been discontinued)

Testosterone levels will be monitored every 8 weeks. LH stimulates the Leydig cells to make testosterone while FSH will hopefully induce spermatogenesis.

As it takes about 3 months for spermatogenesis to result in mature sperm, sperm counts should be checked 3 months after this has been commenced.

Should the testosterone be above the limit of the normal range (26 nmol/l), the dose of both of the above can be halved.

FSH should induce an increase in testicular volume to the normal 15 mls bilaterally, which can occur over the course of a year.

The hospital undertake to check regular sperm counts and testosterone levels and to inform the GP of any change in dose required.

Normal semen analysis results

Parameter		Reference value
Volume		> 2.0ml
Viscosity		Normal
pH		7.2-8.1
Sperm conc (million/ml)		>20
Motility %	Rapid progressive	>25%
	Total	>50%
Sperm morphology (normal forms)		*
Vitality (% live / dead)		>50%
MAR IgG (direct sperm antibody)		Neg
Nucleated / round cells millions / ml		<1
Leucocytes per ul (cyturtest)		<25-75

- International reference values are presently under review due to the introduction of ‘strict criteria’ used in the definition of ‘Normal morphology’ & a lack of between laboratory consensus.

Post vasectomy	2 separate samples with ‘no sperm present’

OTHER MISCELLANEOUS CONDITIONS

SYSTEMIC MASTOCYTOSIS

METHOD

1. Collect a sample of urine shortly after an attack for urinary methyl histamine, which will be excreted in the following hour. A spot urine is adequate.
2. Also collect a clotted sample of blood for serum tryptase.
3. Collect a further sample of urine and blood 24h later to serve as a baseline for comparison.

– Thus two samples of serum and two samples of urine should be sent together for assay of urinary methyl histamine and serum tryptase to Chemical Pathology on a white miscellaneous form.

– Assays for urinary methyl histamine and serum tryptase are carried out by Dr John Watkins, Department of Immunology, Northern General Hospital, P.O. Box 894, Sheffield S5 7YT. Tel: 01742 434343 ext 5728 Fax: 01742 619893

INTERPRETATION

Normal methyl histamine:	5–20 ng/ml.
Typical patient with systemic mastocytosis:	>100 ng/ml
Typical patient following beesting:	>2000 ng/ml
Normal plasma tryptase	<1

VERSION HISTORY

KM 7/94

ISCHAEMIC LACTATE TEST

INDICATIONS

Suspected metabolic muscle disease.

This protocol is from Professor Land at Queen's Square.

Contact numbers: 020 7837 3611 / 020 7833 9391.

CONTRAINDICATIONS

None.

PREPARATION

Warn biochemistry 24 hrs prior to test that assays for pyruvate, ammonia and lactate will be required.

Tubes for pyruvate:	Tubes prepared in the lab by the addition of 2mls perhexilene and refrigerated overnight. Add 1ml of blood to each tube accurately. Specimens for pyruvate must be handled carefully and placed on ice and taken to the lab immediately.
Tubes for lactate:	Grey top fluoride oxalate bottles (samples stored on ice).
Tubes for ammonia:	9 paediatric lithium-heparin tubes (samples stored on ice). The 9th tube is a control, to measure the background ammonia levels in the samples.

METHODS

1. Fast from midnight.
2. The patient must spend the day relaxing, not doing any exercise.
3. 2 people needed to assist with sampling.
4. Insert i.v. cannula into large forearm vein with a three-way tap.
5. All specimens should be free flowing blood.
6. Take baseline bloods (-2 min) for lactate, pyruvate, ammonia, CK, phosphate and uric acid.
   - *At each time point discard 3mls of blood from the cannula, take 1ml for pyruvate in a 2ml syringe so that the volume is accurate, and 6mls in a 10ml syringe for the rest. Flush the cannula with normal saline and put the bottles on ice immediately.*
7. Place sphygmomanometer on the cannulated arm and inflate the cuff above systolic pressure. The patient exercises the arm rhythmically by squeezing some rolled up paper towels or a ball. The hand must be fully extended between squeezes. Exercise the hand for 2 minutes.
8. Release the cuff, this is time = 0.
9. At time 0, 1, 2, 4, 6, 8 and 10 min take blood for lactate, pyruvate and ammonia as above.

INTERPRETATION

- Normally the lactate rises by 3–5 x baseline.
- The ammonia rises from 40 µmol/l to about 100 µmol/l.
- The normal lactate:pyruvate ratio is 10-20 which rises to 30-40 on exercise.

The lactate test is positive when the patient exercises and they can't open their hand fully. The lactate level remains unchanged, as glycogenolysis is defective. The ammonia level rises dramatically to 300-400 µmol/l. The lactate to pyruvate ratio is 10-30 and does not change on exercise.

VERSION HISTORY

AP, LS 01/98

REFERENCE RANGES

Compound [MW]	Conditions	Reference range	Sample
	STEROIDS & RELATED		
Oestradiol [272]	Early follicular	<300 pmol/l	A
	Late follicular	400 – 1500 pmol/l	A
	Luteal	200 – 1000 pmol/l	A
	Pre–ovulatory	420 – 1470 pmol/l	A
	Post–menopausal	<250 pmol/l	A
	Male	<250 pmol/l	A
Oestrone	Post menopausal	<260 pmol/l	A
Testosterone [288]	Female	<3.0 nmol/l	A
	Male	10 – 28 nmol/l	A
5-dihydrotestosterone	Female	<1.0 nmol/l	A
	Male	1.0 – 3.0 nmol/l	A
Androstenedione	Female	<10 nmol/l	A
DHEAS	Female	<10 mol/l	A
Sex Hormone Binding Globulin	Male	20–40 nmol/l	A
	Female	40–80 nmol/l	A
Progesterone	Follicular	<8 nmol/l	A
	Luteal	30 – 70 nmol/l	A
	Post–menopausal	<8 nmol/l	A
	Male	<8 nmol/l	A
17-OH progesterone		<10 nmol/l	A
11-deoxycorticosterone		18–51 nmol/l	A
Compound S [345]	Basal	<23 nmol/l	A
	After metyrapone	230 – 725 nmol/l	A
Cortisol [362]	0900h	200 – 700 nmol/l	A
	2400h	<55 nmol/l	A
Not acid bottle unless cats also	24h urine free (plain bottle)	55 – 270 nmol/24hr	U1
	ANTERIOR PITUITARY		
ACTH [4500]	0900h	<30 ng/l	C
	2400h	<10 ng/l	C
-hCG	non-pregnant	<2.0 U/l	A
LH [28000]	Follicular	2 – 10 U/l	A
	Luteal	4 – 14 U/l	A
	Mid–cycle	20 – 60 U/l	A
	Postmenopausal	>50	A
	Male	4 – 14 U/l	A
FSH [28–41,000]	Follicular	1.5 – 8 U/l	A
	Luteal	1.5 – 8 U/l	A
	Mid-cycle	9 – 12 U/l	A

	Postmenopausal Male	>20 U/l 1.5 – 8 U/l	A A
Prolactin [21000]	Female Male	125 – 625 U/l 75 – 375 U/l	A A
GH [21500]	During ITT During GTT	>20mU/l <2mU/l	A A
THYROID			
TSH [27000]		0.3 – 3.8 mU/l	A
Free T4 [711]		10.0 – 26.0 pmol/l	A
Free T3		2.5 – 5.7 pmol/l	A
Thyroglobulin		<1 g/l	A*
Thyroxine binding globulin		7 – 17 mg/l	A
CALCIUM METABOLISM			
Calcitonin		<5 ng/l (female); <12 ng/l (male)	D
Intact PTH *25-OH vitamin D*	Urgent to lab.	1.1 – 6.8 pmol/l 7 – 50 g/l	C B
PEPTIDE HORMONES			
Insulin [5807]	Fasting	3 – 20 mU/l (20 – 140 pmol/l)	B
C-peptide	Fasting	~30 – 75 x insulin	B
IGF-1	Age 41-60 Dependent on age and sex	7.1 – 30.0 nmol/l	A
Somatostatin *GAWK* *Proglucagon* *Gastrin* *VIP* *Neurotensin* *Pancreatic polypeptide*	Fasting Fasting Fasting Fasting Fasting Fasting Fasting	<150 pmol/l <150 pmol/l <50 pmol/l <40 pmol/l <30 pmol/l <100 pmol/l <300 pmol/l	E E E E E E E
OTHER ADRENAL HORMONES			
Renin	Erect Supine	2.8 – 4.5 pmol/ml/h 1.1 – 2.7 pmol/ml/h	F F
Aldosterone	Supine	100 – 450 pmol/l	A
24 hr urine adrenaline *24 hr urine noradrenaline* *24 hr urine dopamine*		0.03 – 0.10 mol/24 hrs 0.12 – 0.50 mol/24 hrs 0.65 – 2.70 mol/24hrs	U2 U2 U2
CARCINOID SYNDROME			
24 hr urine 5-HIAA		15.0 – 40.0 mol/24hrs	U3

BLOOD

A. 7 ml blood into a plain glass tube (red top Vacutainer) delivered to the lab the same day or kept in a refrigerator overnight

B. 7 ml blood in a plain glass tube (red top Vacutainer) delivered to the lab within 30 minutes
C. 4 ml blood in EDTA (purple top Vacutainer) delivered to the lab IMMEDIATELY to be spun, separated and frozen.
D. 7 ml blood in a lithium heparin tube (green top Vacutainer) brought to the lab IMMEDIATELY on ice to be separated and frozen.
E. 7 ml blood in a lithium heparin tube (green top Vacutainer) containing 200 l Trasylol (10,000 KIU aprotinin/ml) brought to the lab immediately on ice.
F. As for D but NOT on ice.

*Samples analysed off site. Specimens dispatched once a week on Monday.

URINE (U)

Two main types of bottles are available for 24 hour urine collections.

1. *No Preservative:* ELUC (Na^+, K^+, urea, creatinine), creatinine clearance, total protein, uric acid, amylase, cortisol, urinary steroid profile.
2. *10% HCl:* (hydrochloric acid): ELUC (Na^+, K^+, Urea, Creatinine), creatinine clearance, calcium, phosphate, magnesium, oxalate, catecholamines, VMA, 5HIAA, cortisol
3. *25% Acetic Acid:* 5-HIAA is no longer used.

Since an acid bottle can be used for most tests, provided you are not measuring total protein, uric acid or amylase, an acid bottle should be requested.

URGENT SAMPLES AND LOCALISATION STUDIES

- Requests must be made in person to a Clinical Scientist (Dr Mandy Donaldson or Mrs S Fernandez) extension 34681.
- For localisation studies:
  Give at least 1–2 days notice
  Provide lab with patients name and type of study and starting time.
  Keep lab informed if samples likely to arrive after 5 pm, or if procedure cancelled.
  If the samples are to be delivered within an hour of collection, it is not necessary to collect samples for PTH and insulin on ice.
  ACTH and gut peptides must be collected on ice.

USEFUL NAMES AND ADDRESSES

Diabetes UK	10 Queen Anne Street London W1M OBD Tel: 020 7343 1531
Society for Endocrinology	17/18 The Courtyard Woodlands Bradley Stoke Bristol BS32 4NQ Tel: 01454 201612
The British Thyroid Foundation	Mrs J Hickey PO Box HP22 Leeds LS6 3RT
National Osteoporosis Society	Dr J A Dixon PO Box 10 Radstock Bath BA3 3YB Tel: 01761 471771
The Pituitary Foundation	17/18 The Courtyard Woodlands Bradley Stoke Bristol BS32 4NQ Tel: 01454 201612
National Society for the Relief of Paget's Disease	1 Church Road Eccles Manchester M30 0DL Tel: 0161 707 9225
CAH Support Group	The Child Growth Foundation 2 Mayfield Avenue, Chiswick London W4 1PW Tel: 020 8995 0257
MEDIC alert foundation.	1 Bridge Wharf, 156 Caledonian Road, London N1 9UU Tel: 020 7833 3034

Sheets for tests

OGTT FOR ACROMEGALY

Date:

Patient SURNAME: **Patient First name:**

Hospital Number: **Date of Birth:**

Telephone Number(s):

Next Endocrine OPA:

Diagnosis:

Drugs:

OGTT

Time	Glucose	GH (and basal IGF-1)
0		
30		
60		
90		
120		
150		
180		
210		
240		
270		
300		

LDDST/ HDDST

Date:

Patient SURNAME: **Patient First name:**

Hospital Number:

Date of Birth:

Telephone Number(s):

Next Endocrine OPA:

Diagnosis:

Drugs:

24hr urinary free cortisols:

midnight cortisol:

9am cortisol:

LDDST

	cortisol	**ACTH**
9am (“2+0”) basal:		
48 hr(“2+48”)		
50 hr (“2+50”)		
post CRH (2+50+CRH)		

HDDST

9am (“8+0”)		
(may be same as “2+48”)		
48 hr(“8+48”)		

24hr Urinary free cortisol during HDDST:

Hydrocortisone Day Curve (HCDC)

Date:

Patient SURNAME:

Patient First name:

Hospital Number:

Date of Birth:

Telephone Number(s):

Next Endocrine OPA:

Diagnosis:

Drugs:

Hydrocortisone dose with timings:

HYDROCORTISONE DAY CURVE

	Time	cortisol
On arrival		
Pre 2nd dose		
Post 2nd dose		
Pre 3rd dose (or 6pm)		
Post 3rd dose		

Short / Long Synacthen Test

Date:

Patient SURNAME:

Patient First name:

Hospital Number:

Date of Birth:

Telephone Number(s):

Next Endocrine OPA:

Diagnosis:

Drugs:

SST

Time	Cortisol	ACTH (basal only)
0		
30		
60		

(LST continues:)

2 hrs		
4hrs		
8hrs		
24hrs		

Water Deprivation test.

Date:

Patient SURNAME: **Patient First name:**

Hospital Number: **Date of Birth:**

Telephone Number(s):

Next Endocrine OPA:

Diagnosis:

Drugs:

TIME	**URINE / VOLUME**		**PLASMA**
0830	Discard urine		
0900	Þ		**Collect P1**
0930	Collect U1	ml	
1130	Discard urine		
1200	Þ		**Collect P2**
1230	Collect U2	ml	
1430	Discard urine		
1500	Þ		**Collect P3**
1530	Collect U3	ml	
1600	Þ		**Collect P4**
1630	Collect U4	ml	

Now give DDAVP i.m. or intranasally

1730	Collect U5	ml	
1830	Collect U6	ml	
1930	Collect U7	ml	
2030	Collect U8	ml	

Pamidronate infusion

Date:

Patient SURNAME:

Patient First name:

Hospital Number:

Date of Birth:

Telephone Number(s):

Next Endocrine OPA:

Diagnosis:

Drugs:

Dose pamidronate given:

Calcium 3 days later: