

CHAPTER 5 - METABOLIC, NUTRITIONAL AND ENDOCRINE SYSTEMS

1 INTRODUCTION

Metabolic disorders are common and may develop rapidly into an [incapacitation]. Nutritional and [endocrine] disorders are less common and more likely to be slow in development and onset. They may finally become incapacitating [. However] adequate treatment and review should allow safe continuation of flying duties.

2 ENDOCRINE DISORDERS

Although these disorders are not a common aeromedical problem they are frequently insidious in onset and ultimately may endanger flight safety. The effects of modern treatments and the availability of replacement therapy have modified [aeromedical assessment].

3 THYROID DISORDERS

Disease of the thyroid gland can cause []important disturbances in function [and/or goiter].

Diffuse [goiters] with no endocrine imbalance have only a cosmetic or rarely a mechanical need for treatment. Nodular [goiters], more common in women over 50, can produce both [mechanical] symptoms and hyperthyroidism, but exclusion of malignancy is the most difficult problem and that may require [extensive expert] investigation.

3.1 Hyperthyroidism

This condition usually occurs in connection with diffuse [goiter] (Graves Disease) and has an [auto-]immunological basis. [Antibodies] against the TSH receptor []stimulate the autonomous over-production of thyroid hormone [and glandular growth]. Toxic nodular [goiter] or toxic adenoma also over produces thyroid hormone, but not on an auto immune basis.

a *Symptoms*

Sweating, palpitations, nervousness, irritability, insomnia, tremor, hyperactive bowels, weight loss (with appetite apparently normal), exophthalmus, smooth diffuse non-tender [goiter], tachycardia (possibly atrial fibrillation and high output heart failure). In certain cases exophthalmos may be severe with paresis of eye muscles. There may be personality changes.

b *Diagnosis*

Clinically the florid case is unmistakable. Confirmation may be obtained by:

- i determination of TSH level [(decreased)];
- ii determination of total serum T4/free T4 [(increased)]; [and/or]
- iii determination of serum T3/free T3 levels [(increased)].

c *Treatment*

Propyl thiouracil, [methimazole] or carbimazole, will control symptoms but the effect is slow, taking some [two] to [four] months. Propranolol may be used for quicker control of symptoms. Anti thyroid drugs should be continued for [9 – 12] months and then withdrawn but only [50% - 70 %] of patients so treated may remain euthyroid.

Partial [or near total] thyroidectomy is practised much less frequently now and is reserved mostly for [therapy resistant] cases [or in patients] with large and/or nodular [goiters].

Radioiodine administration, is an effective treatment and no evidence of adverse mutagenetic effects on the gland has become apparent, even after many years. However, hypothyroidism is a common sequel and the percentage showing reduced or absent thyroid function grows year by year. Lifelong follow-up and appropriate substitution therapy is mandatory.

d **[Aeromedical assessment]**

A hyperthyroid pilot is unfit for flying and must remain so until a stable euthyroid state has been attained. **[A fit assessment]** may be considered by the AMS in any category when they are euthyroid. The individual must be annually reviewed (to include TSH estimation) to guard against recurrence or the development of hypothyroidism. The continued use of anti thyroid drugs, if well tolerated, is consistent with **[aeromedical fitness]**. Where eye involvement has occurred, the pilot must be **[examined and]** cleared by an ophthalmologist as well prior to returning to flying.

3.2 Hypothyroidism

The failure of the thyroid gland to produce sufficient thyroid hormone quantities may be due to decreased hypothalamic production of thyroid releasing hormone (TRH) or insufficient pituitary production of thyroid-stimulating hormone (TSH). However, much more frequently the condition is caused by inflammation or destruction of the thyroid gland, and may be a sequel of surgery or radio iodine treatment of the hyperthyroid state. The destruction of the gland through an auto immune mechanism may lead to apparent spontaneous cessation of function which may be an extremely chronic process.

a **Symptoms**

[Tiredness, weight gain, constipation, thickening and drying of the skin, hoarseness, bradycardia, apathy, slow speech.] These may slowly develop into a frank myxoedema with heart failure and in rare cases into the myxoedematous coma.

b **Diagnosis**

TSH is increased (in primary thyroid failure); T4/free T4 is decreased.

c **Treatment**

Hypothyroidism is perhaps the most satisfactory condition to treat, adequate substitution therapy makes the individual normal in every way. Treatment will usually be L-thyroxine **[0,1–0,15]** mg daily (with caution exercised in increasing to this dosage in cases with cardiac involvement). Treatment should be continued until TSH has dropped to a normal range and the patient is clinically euthyroid, and then continued **[life-long with annual TSH measurement]**.

d **[Aeromedical assessment]**

Florid hypothyroidism requires a temporarily unfit assessment. The candidate may be considered for **[fit assessment]** while euthyroid and taking **[their]** prescribed medication. Annual endocrinological **[control examinations are]** required by the AMS. Some hypothyroid patients cease taking medication, because they feel entirely well, recurrence of the **[disease]** may not be obvious and the typical apathy may lessen the chance of recognition. **[Therefore, annual]** review essential.

4 PITUITARY DISORDERS

4.1 Diseases of the anterior pituitary

a **Over-production of adrenocorticotrophic hormone (ACTH)**

An over-production of ACTH, usually by a basophil micro adenoma of the pituitary gland, can cause Cushing's Disease by over-stimulating the adrenal cortex to produce an excess of adrenal hormones.

- i Features. Obesity, hypertension, myopathy, diabetic tendency, osteoporosis, plethoric facies (moon face), easy bruising, poor wound healing, striae, change in appearance.
 - ii Diagnosis. Urinary free cortisol and serum cortisol are increased. Serum potassium is decreased. Dexamethasone administration will not suppress the over-production of ACTH.
 - iii Treatment. Transphenoidal removal of the microadenoma.
 - iv [Aeromedical assessment]. Applicants with acute Cushing's Syndrome are unfit for flying and must be assessed [as] temporarily unfit until a normal hormone balance is restored, by whatever means. After adequate surgery it may take six months or more for the symptoms and signs to subside and for the adrenal to resume normal production of cortisol. [Fit assessment] by the AMS is dependent on satisfactory reports from, and supervision by, an endocrinologist.
- b *Over-production of prolactin*

[Over-production of prolactin, usually] from an macro- or microadenoma of the pituitary, is now recognised as the most common hormonal abnormality [or] pituitary neoplasia. The adenoma may be large enough to distort the sella turcica and cause pressure signs on adjacent structures, especially compression of the optic chiasm [with subsequent defect of the visual field].

- i Symptoms. Galactorrhoea, amenorrhoea or irregular cycles in females; impotency and loss of libido in men. Headache and visual field defect in cases with macroadenoma.
- ii Diagnosis. The adenoma is diagnosed by MRI or CT of the pituitary gland. Serum prolactin (PRL) is elevated and usually a level above 100 ng/ml is a diagnostic parameter for [an] adenoma [secreting prolactin].
- iii Treatment. Many tumours respond to dopamine agonists such as bromocriptine and this treatment should be continued, if tolerated, on a long-term basis. On cessation of therapy, the hormonal overproduction will most likely recur. Cases which do not respond or those with local pressure symptoms, may require surgical intervention.
- iv [Aeromedical assessment]. An applicant with macroadenoma and associated pressure signs is unfit.

Many individuals on long term medication without side effects or following successful surgery may be considered [for fit assessment] by the AMS. [Current evidence indicates that] treatment [has to be continued] lifelong[]. Annual review must include ophthalmic and endocrinological examination.

c *Growth hormone [(GH)]*

Hyper-secretion of GH by a pituitary adenoma produces acromegaly in the adult.

- i Features. Increase in bone size and soft tissues of hands, feet, supraorbital ridges, sinuses, mandible. Skin thick and coarse; tongue, lips and ears may be enlarged. Any adult with significant changes in appearance or size of extremities requires investigation. MRI or CT imaging may be used for a pituitary tumour. The biochemical diagnosis is based on elevated serum glucose levels which cannot be suppressed, an oral glucose tolerance test (OGTT), and an increased insulin like growth factor I (IGF I) level.
- ii Treatment. In the majority of cases, surgery is the [] treatment [of choice]. Irradiation and/or [] treatment [with somatostatin analoga] may also be required.
- iii [Aeromedical assessment]. Any pilot with a GH secreting tumour producing symptoms is unfit (also see [Chapter 17] Oncology with regard to assessment).

After operation or irradiation of the tumour, an individual must be very carefully reviewed over an extended period to determine whether he or she is fully recovered. Anyone with gross physical changes, most of which do not regress, is unlikely to be assessed fit [for] Class 1 or 2. Specialist ophthalmological and endocrinological review

will be required before consideration by the AMS. Annual review is necessary [for those] assessed as fit.

4.2 Disease of the posterior pituitary

a *Diabetes insipidus (DI)/ failure to secrete ADH*

A condition marked by polyuria (partial or complete failure of vasopressin [(ADH)] secretion by the posterior pituitary).

- i *Diagnosis.* Fluid deprivation tests are diagnostic. If dehydration raises the serum osmolality to 295 mOsm/kg but the urine remains [diluted], the diagnosis is diabetes insipidus.
- ii *Treatment.* Desmopressin (DDAVP), is effective and convenient. The dose must be individualised.
- iii [Aeromedical assessment]. Each case must be considered individually by the AMS with full specialist reports. An individual, who is well controlled, using vasopressin or desmopressin, may be considered for [fit assessment for] initial Class 2 applicants and Class 1 and 2 [applicants at revalidation / renewal] with regular specialist [follow-up].

5 DISEASES OF THE SUPRARENAL GLAND

5.1 Hypoadrenalism (Addison's disease)

a [Aetiology] and pathogenesis

The adrenal cortex fails to produce hormones or adequate quantities of hormones. Most cases are due to an autoimmune process which eventually destroys the adrenal cortex. In the past destruction of the gland by tuberculosis was a frequent cause.

b Features

The patient may complain of weakness, anorexia and weight loss. The onset is usually gradual, though a sudden onset may be precipitated by unrelated diseases, classically acute infections. Hyper-pigmentation may be seen. The blood pressure will be low in crisis. Hypovolaemia is present. Serum potassium is elevated and serum sodium depressed in crisis. The ECG may show changes related to the raised serum potassium.

c Diagnosis

Low plasma cortisol and decreased urinary cortisol excretion which do not rise after administration of ACTH. Elevated serum ACTH level.

d Treatment

Using cortisol and cortisone in low doses. Additional medication is needed for infection or stress. An individual receiving adequate substitution therapy has no immediate risk of incapacitation. However, any minor infection or stress can quickly induce a [crisis and incapacitation].

e [Aeromedical assessment]

Fully stabilised cases may be considered by the AMS for [a fit assessment at revalidation / renewal]. A multi-pilot limitation (Class 1 'OML') or safety pilot limitation (Class 2 'OSL') may be required. Regular specialist review will be required.

6 DIABETES MELLITUS

This carbohydrate metabolic disorder [,characterised by absolute or relative lack of insulin] is associated with many complications which may produce sudden incapacitation or grossly reduced performance and thus cause a serious risk to air safety.

6.1 Diagnostic criteria

Typical symptoms are weight loss, polyuria and polydipsia. The findings of 2% glycosuria and an elevated blood sugar are diagnostic. However, the difficulty arises when mild glycosuria and subsequent abnormal blood glucose levels are found in a symptomless applicant during routine medical examinations. An abnormal blood glucose requires glucose tolerance testing. 75 gram glucose loading in a minimum of 250 ml of water is given to a fasting subject who has eaten a normal diet containing 250 gram of carbohydrate for the previous few days. Fasting whole blood glucose levels and those two hours after glucose loading are [tested]. [The] WHO agreed levels [in venous full blood] are outlined below [(please find the levels in capillary full blood in brackets)].

	Fasting		2 hours post	
Normal []	< 6,1 mmol/l 110 mg/100ml	(< 6,1 mmol/l)(< 110 mg/100ml)	< 7,8 mmol/l < 140 mg/100ml	(< 7,8 mmol/l) (< 140 mg/100ml)
Impaired glucose tolerance	< 6.7 mmol/l < 120 mg/100ml	(6,1 - 6,7 mmol/l) (< 120 mg/100ml)	<6,7- 10,0mmol/l <120-180mg/100ml	(7,8 - 11,1mmol/l) (140-200mg/100ml)
Diabetes Mellitus	≥ 6,7 mmol/l ≥ 120 mg/100ml	(≥ 6,7 mmol/l) (≥ 120 mg/100ml)	≥ 10,0 mmol/l ≥ 180 mg/100ml	(≥ 11,1 mmol/l) (≥ 200 mg/100ml)

These results are valid for venous whole blood glucose [(please find the levels in capillary full blood in brackets)]. Differing laboratories and methods using capillary blood or plasma glucose may require minor changes to these figures. Diagnosis should not rely on one abnormal OGTT result and all borderline tests should be repeated.

6.2 Classification

The accepted modern classification is:

Type 1 Insulin Dependent (IDDM)	Genetically associated with T-cell dependent auto immune disease and HLA factors. Very low or absent endogenous insulin. Liable to keto-acidosis. Onset typically under 30.
Type 2 Non-insulin dependent (NIDDM)	Related to obesity and [family history of NIDDM]. Endogenous insulin always present and often hyperinsulinaemic with insulin resistance. Rarely if ever ketotic. Onset 40+. There is a non-obese sub-group which have different aetiology and [hereditary family factors].

6.3 Complications

Macro-angiopathic vascular damage is the common background for the coronary, cerebral and peripheral arterial disease which can constitute a major aeromedical risk and may be related to the hyperlipidaemic effects of diabetes.

Estimates of the risk of Type 2 diabetes vary, but it is clearly significant and increases with the duration of the condition. Microangiopathy is associated with progressive retinal and renal damage. Neuropathy is probably related to the long term effects of the metabolic abnormality and can involve motor, sensory and autonomic functions. Cataract is common in older patients. All complications tend to be found in long term diabetes, especially those which are poorly controlled, but can also appear early in the disease – retinopathy in particular can be an initial finding.

6.4 Management

- a Type 1: it should be noted that an apparent remission of insulin requirement invariably ends in relapse and the applicant should not be [assessed as fit] during such a remission or 'honeymoon period'.
- b Type 2 requires:
 - i optimum weight
 - ii dietary control and/or oral hypoglycaemic drugs (insulin in occasional resistant cases is disqualifying)
 - iii satisfactory control of blood glucose levels, lipids, blood pressure, and any other risk factors.

6.5 Treatment [of Type 2 diabetes mellitus (NIDDM)]

Reduction of carbohydrate and total calorie intake in the obese may be sufficient in many cases to reduce blood glucose levels [to an acceptable level]. Other dietary modifications may include an increase in dietary fibre and a reduction in animal fat. Glucose levels are now usually assessed by home monitoring with meters or sticks. Routine urine testing is unreliable for treatment management because of the wide variation in renal threshold for glucose, especially in old people. Glycosylated haemoglobin (HbA1) or serum fructosamine estimations are of good value as indicators of average blood glucose over periods of weeks.

The ideal result of dietary management would include:

- Blood glucose control appropriate to diabetes management
- HbA1 within normal range
- Body mass index less than 25
- Regular exercise and no smoking
- Lipid control appropriate to diabetes management

Type 2 diabetics may need oral hypoglycaemic drugs to supplement dietary treatment. This is especially likely in the non-obese sub-group. Quar-gum may be used as a dietary adjunct.

In selected cases, the use of oral hypoglycaemic drugs may be acceptable:

Medication	Class 1 'OML'	Class 2
Biguanides	Yes, [without limitation]	Yes, [without limitation]
Alpha-glucosidase Inhibitors	Yes, [without limitation] if used as single therapy	Yes, [without limitation] if used as single therapy
Sulphonylureas	Not acceptable	Yes, with 'OSL'
Thiazolidinedione		
Rosiglitazone	Not acceptable	Yes, when combined with a biguanide or sulphonylurea, with an 'OSL'
Pioglitazone	Not acceptable	Yes, when combined with a biguanide or sulphonylurea, with an 'OSL'
Repaglinide	Not acceptable	Not acceptable

6.6 Long term monitoring of Type 2 diabetes [(NIDDM)]

- a. The monitoring process should consist of:
 - i careful examination to exclude common complications of diabetes;
 - ii assessment of the degree of control;
 - iii regular weight measurements;
 - iv blood glucose measurements;
 - v urine test results (limited value).
- b. Air crew should undergo careful review of the following in addition to the periodic medical examination:
 - i regular [ophthalmological examination with] ophthalmoscopy after pupillary dilation to check for retinopathy and [and slit lamp examination of the] lens [for] vitreous opacities;
 - ii [neurological] examination for evidence of neuropathy;
 - iii periodic blood tests including biochemistry, [HbA1], renal function, liver function and plasma proteins, plus fasting blood lipids and cholesterol;
 - iv cardiological review with consideration of exercise electrocardiography;
 - v periodic urinary tests for detecting early renal damage (microalbuminuria).

6.7 [Aeromedical assessment]

Type 1 diabetics requiring exogenous insulin are unfit to fly. The intrinsic risks of the disease itself are further increased by that of hypoglycaemia. No present injection regime or insulin infusion pumps are sufficiently efficient to act as an artificial pancreas. Nevertheless, progress in such developments as islet transplantation may require consideration in the future.

Type 2 diabetics fully controlled on diet alone may be [assessed as] fit [for] Class 1 and Class 2 [without limitations], subject to detailed follow-up at periodic medical examinations or at least annually. Those requiring [treatment with] biguanide or alpha-glucosidase inhibitors []in addition may be acceptable [with a multi-pilot (Class 1 'OML') limitation for Class 1 applicants] and [without limitation for] Class 2 [applicants,] but the follow-up would need to be more stringent, namely 6 monthly. The use of sulphonylureas is unacceptable except for Class 2 [with a safety pilot (Class 2 'OSL') limitation].

This Assessment applies to Class 1 and Class 2.

Impaired glucose tolerance often represents a pre-diabetic state that may convert to the full condition at a rate of around 4% per year. Cases may need dietary treatment and will require prolonged and detailed follow-up in order to [preserve aeromedical fitness in the long run].

[The international aeromedical literature presents examples of assessing pilots with Type 2 diabetes (NIDDM) and being insulin dependent as fit under strict regimes and strict selection, either Class 2 or even Class 1 or military pilots. European experts discuss whether protocols may be useful in the future to gain scientific evidence in this field in Europe as well.]

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7 GOUT

Gout is a term representing a heterogeneous group of disease which in their full development are manifested by:

- a an increase in the serum [] concentration [of uric acid (hyperuricaemia)];
- b recurrent attacks of a characteristic acute arthritis in which crystals of monosodium urate monohydrates are demonstrable in leukocytes of synovial fluid;
- c aggregated deposits of monosodium urate monohydrate (tophi) chiefly in and around the joints of the extremities and sometimes leading to severe crippling and deformity;
- d renal disease involving interstitial tissues and blood vessels;
- e uric acid nephrolithiasis (renal stones). These may occur singly or in combination.

The full natural history of gout comprises four stages.

7.1 Asymptomatic hyperuricaemia

This is especially common in overweight and hypertensive men who may be taking diuretics. Only a minority will progress to clinical gout. However, it carries a small risk of urate stone or nephropathy, potentially preventable by prophylactic treatment with allopurinol. In practice the inconvenience and other disadvantages of indefinite drug treatment outweigh any benefits. Low purine diets are rarely practicable but general health measures such as weight reduction, alcohol restriction, and a review of need for diuretic treatment should be attempted.

7.2 Acute gouty arthritis

Acute gout, often recurrent, usually of the metatarso-phalangeal joint of a great toe, is not uncommon in air crew. Familial or constitutional factors are more important than obesity or alcohol, but combinations of predisposing and precipitating factors are usual. Acute gout and its immediate drug treatment should preclude flying duties which may be resumed 24-hours after [termination] of treatment. The inconvenience of this restriction often leads to maintenance treatment with allopurinol, which may precipitate acute gout early in the course of treatment so prophylactic treatment with an anti-inflammatory drug, such as indometacin, is usually prescribed simultaneously for the first few weeks of treatment. Allopurinol may disturb liver functions and rarely causes more serious side-effects, usually early in treatment. In practice it is generally well tolerated, normalising the serum uric acid, preventing attacks of gout and development of complications. This treatment can, and usually should, be continued indefinitely with periodic follow up.

7.3 Intercritical period

The initial, acute attack of gout may last only a day or two up to several weeks, but characteristically subsides spontaneously. [Usually, there are no sequelae] and resolution is complete. An asymptomatic phase termed 'the inter critical period' then commences. The patient is totally free of symptoms during this stage, a feature that is diagnostically important. While approximately 7[%] never have [another] attack, approximately 60[%] experience a recurrence within 1 year. However, the inter critical period may last up to 10 years and is terminated by successive attacks, each of which may last longer and resolve less completely than its predecessors. Later attacks tend to be polyarticular, more severe, more prolonged and associated with fever. In this stage gout may be difficult to differentiate from other types of polyarticular arthritis such as rheumatoid arthritis. Rarely patients progress directly from the initial acute attack to chronic polyarticular disease with no remissions.

7.4 Tophic and chronic gouty arthritis

Effective therapy alters the natural history of the disease. Since the advent of effective anti-hyperuricemic therapy only a minority of patients develop visible tophi, permanent joint changes or

chronic symptoms. Tophi, if present, will occur in the helix or antihelix of the ear, along the forearm, as enlargement of the Achilles tendon or at other pressure points. This stage of the disease is [only rarely preventing aeromedical fitness].

7.5 **[Aeromedical assessment]**

- a Asymptomatic hyperuricaemia is not disqualifying.
- b Acute gout and the associated treatment require **[a]** temporarily unfit **[assessment]** until 24 hours after cessation of treatment.
- c Tophic and chronic gouty arthritis should be assessed individually, depending upon the strength, range of movement, pain and medication used.
- d The possibility of nephrolithiasis at any stage must be considered.

This Assessment applies to Class 1 and Class 2.

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