

An Introduction to Endocrinology - University of Leeds

1. Hypothalamic pituitary function page 2
Dr. P Belchetz
2. Pathology - the pituitary gland and its connections page 6
Dr JW Ironside
3. Pituitary disease page 8
Dr. P Belchetz
4. Thyroid hormone synthesis and control of thyroid hormone secretion
page 11
Dr. P Belchetz
5. Thyrotoxicosis page 15
Dr. RM Pope
6. Hypothyroidism page 22
Dr. RM Pope
7. Clinical adrenal disease page 25
Dr. P Belchetz
8. Adrenal function page 28
Dr MJ Levell
9. Testes and related clinical problems, male hypogonadism and infertility
page 29
Dr. P Belchetz
10. Hyperlipidaemia page 30
Dr' JN Harvey
11. Ovarian Endocrinology page 34
Mr. K Hancock
12. The menopause page 36
Dr. M Jones
13. Parathyroid hormone secretion and vitamin D metabolism and their diseases
page 47
Dr. P. Belchetz
14. Puberty and growth page 50
Dr. Buckler
15. Aetiology of diabetes page 51
Dr. HJ Bodansky
16. Diabetes mellitus page 52
Dr. HJ Bodansky
17. Management of diabetes page 55
Dr. PJ Grant
18. Chronic complications of diabetes page 59
Dr. PG Wiles
19. Diabetes in children and adolescents page 62
Dr. JN Harvey
20. Diabetes - acute complications page 64
Dr. PG Wiles
21. Special problems in diabetes page 67
Dr. RM Pope
22. Catecholamines page 71

INTRODUCTION__ TO THE ENDOCRINOLOGY COURSE

Endocrinology is a fast moving field of medical science, the expansion being based on improving methods of measuring hormones in body fluids, and relating changes in the levels of these hormones to clinical disease or symptoms. There has also been a greater understanding of the biochemical changes produced by hormones within cells. Clinical Endocrinology deals with diseases which affect the integration of body function, for few hormones produce their effect in isolation and can give rise to some of the most complex problems seen in clinical practice.

At present, increasing emphasis is being given to arriving at an earlier diagnosis of endocrinological disease before the classical syndromes occur (which are often untreatable) the difficulties in understanding endocrinological disease arise at present from:

1. inaccurate measurements of very small quantities of hormones in blood and urine;
2. translation of results in animal experiments to man; and
3. difficulty in knowing the limits of normality.

This course is not a comprehensive review of clinical endocrinology, but is a brief introduction into present day attitudes to the common endocrinological diseases.

Students must read up the subjects presented to complete the course

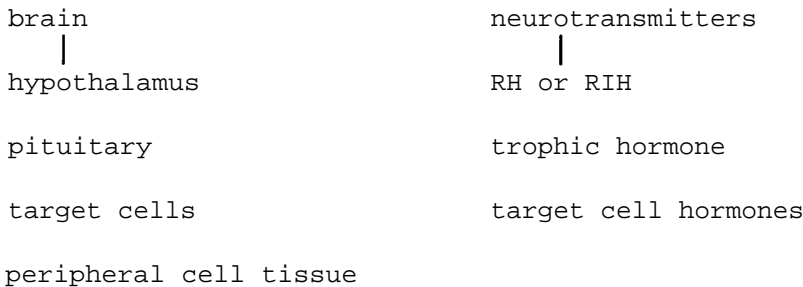
Basic textbook used: Fundamentals of Clinical Endocrinology (1980) Hall, Anderson and Smart, Pitman Medical 3rd Edition.

Both the anterior and posterior pituitary are under hypothalamic control. The **stimulus to posterior hormone secretion involves neurological processes, whereas hypothalamic control of the anterior pituitary is effected by a portal capillary system which transports the hypothalamic secretions from the median eminence to the vascular sinusoids surrounding pituitary cells.** These hypothalamic secretions are termed hypothalamic regulatory hormones (either releasing hormone, RH, or release-inhibiting hormone, RIH). Some have been isolated, characterised and synthesized, and two (TRH and LHRH) are available commercially.

The **hypothalamic hormones are regulated by the higher centres involved in establishing time-dependent rhythms, by psychological stress factors, by feedback mechanisms, and by reflex responses mediated by peripheral nerves.**

Hypothalamic hormones act on pituitary cells to stimulate the synthesis of pituitary trophic hormones in amounts 10 to 10 times greater than the stimulating hormone. The pituitary hormones in turn act on the target gland to produce 10 to 10 times as much hormone again, thus producing a "cascade amplifier" effect. Target gland hormone levels interfere with the action of hypothalamic hormone on the pituitary (negative feedback) and also influence the hypothalamic hormone itself. Some interaction occurs between different hypothalamic-pituitary-target axes, thus for example, thyroid hormone deficiency influences hypothalamic-pituitary-gonadal function.

General Scheme of Control Mechanisms



Anterior-pituitary hormones

Basophil cells - glycoprotein hormones - TSH, FSH, LH, ACTH
 - B lipotropin (LPH)

Acidophil cells - protein hormones - prolactin, GH

Investigation of endocrine disturbances

A. Basal hormone measurements

Many hormones can now **be directly measured in the blood, usually by radioimmunoassay.** This had led to many advances in endocrinology and greatly simplifies investigation. However basal measurements alone may not **distinguish between normal and abnormal states and will not usually indicate the precise abnormality.** Hence the need for:-

B. Dynamic (stimulation or suppression) test

By giving the hormone at one step in the control pathway it is possible to test the effect on the axis, e.g.

- (a) to test pituitary function, stimulate with RH, or block (via the negative feedback) with target cell hormone,
- (b) to test target cell function, stimulate with trophic hormone. For some hormones this is still in a developmental stage, so the pattern cannot be followed entirely to its logical conclusion.

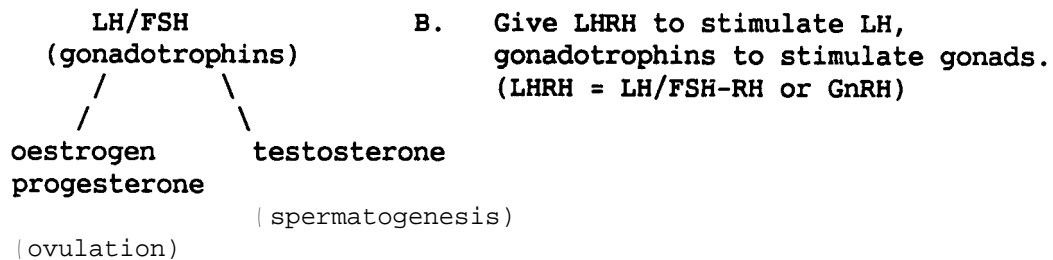
1. Hypothalamic-pituitary-thyroid (HPT) axis

- | | |
|-----|---|
| TRH | A. Basal - measure T ₄ , T ₃ , TSH |
| TSH | B. Dynamic - can give TRH, TSH or suppress with T ₃ . In practice, T ₄ T ₃ use TRH, measure TSH (0+ 30 mins) or T ₄ T ₃ later |

Applications: Primary myxoedema - T₄ and T₃ , TSH , TRH ++
hypopituitarism - T₄ and T₃ , TSH , TRH peg.
hyperthyroidism - T₄ and T₃ , TSH , TRH NEG

2. H-P-gonadal axis

- | | |
|------|---|
| LHRH | A. Measure oestrogens, progesterons, testosterone, (indices of ovulation and spermatogenesis) LH, FSH |
|------|---|



Applications: hypopituitarism - LH , FSH , Gonadal hormones gonadotrophin test normal
gonad failure - LH , FSH , Gonadal hormones

3. H-P-adrenal axis

CRF A. measure cortisol, ACTH

ACTH

Cortisol

- B. a) ACTH test, measure cortisol
- b) metyrapone test, inhibits cortisol synthesis and stimulates ACTH
- c) dexamethasone test, suppresses ACTH
- d) insulin stress test - hypoglycaemia stimulates ACTH via CRF, measure cortisol + ACTH (CRF not yet available).

Applications:

Addison's disease - cortisol , ACTH , ACTH test

Cushing's disease - cortisol , ACTH variable Dexamethasone fails to suppress

Hypopituitary - cortisol , ACTH , ACTH test normal or partial metyrapone and insulin tests - no response.

4. Growth hormone and prolactin follow slightly different pattern because mainly inhibitory control.

GHRH A. measure GH, glucose

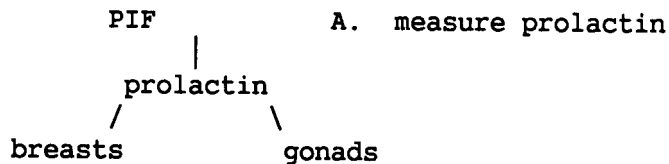
GH B. **Insulin, arginine, exercise tests**

Somatomedin

Application: Acromegaly - GH in GTT fails to suppress or paradoxical rise

Hypopituitary - stimulation tests negative

5. Prolactin



6. B lipoprotein

Precursor of endorphins. Control and clinical significance not yet known.

7. Posterior Pituitary

AVP (ADH)	A. Measure plasma and urine osmolality
Kidneys	B. Test - Dehydration

8. Combined pituitary function test

Use TRH, LRH, Insulin followed by DDAVP (IV or Intranasal)

Anatomy

The pituitary gland lies within a convexity of the sphenoid bone known as the sella turcica. The gland is covered by the diaphragm sellae, a **dura mater-like structure through which passes the infundibular stalk containing the portal blood vessels to the anterior pituitary and hypothalamic nerve fibres to the posterior pituitary.** The sphenoidal air sinuses lie below the gland, while above are the optic chiasm, hypothalamus and III ventricle. **The cavernous sinuses and their contents lie laterally and superiorly.**

Normal histology

The old classification of anterior pituitary cells based on tinctorial properties has been superseded by one which recognises the main hormones produced by the cells - Growth Hormone (GH), Prolactin (PRL), Adreno corticotrophic Hormone (ACTH), Thyroid Stimulating Hormone (TSH), Follicle Stimulating Hormone (FSH) and Luteinising Hormone (LH). It is now recognised that some cells can produce more than one hormone, e.g. GH and PRL.

Pathology

Clinical symptoms of pituitary disease can be produced in 2 ways:

- 1) Mechanically (by pressure on adjacent structures, or as an intracranial space-occupying lesion)
- 2) Hormonally (excess or deficient hormone production)

These will be dealt with in detail in clinical lectures.

Disease processes affecting the pituitary gland can be considered in several main groups:

1. Genital Abnormalities
e.g. hypoplasia, agenesis. These are rare.
2. Depositions
e.g. amyloid, mucopolysaccharidoses. These are rare.
3. Inflammations
e.g. Bacterial infections (including tuberculosis)
Viral and Fungal infections
Sarcoidosis
Lymphocytic (autoimmune) hypophysitis
4. Atrophy
e.g. the 'empty sella' syndrome

5. Haemorrhagic necrosis and infarction

- Post infective
- Post traumatic
- Post partum (Sheehan's post partum necrosis)

6. Benign Neoplasms

A **Adenomas** These are common, and account for around 10% of all intracranial neoplasms. They are classified according to the cell of origin and the hormones produced, e.g. GH adenoma, ACTH adenoma. Occasional adenomas are nonfunctional, e.g. "null-cell" adenomas.

B Craniopharyngiomas These are rare, but usually occur in children and young adults. An origin from remnants of Rathke's pouch is suggested; these tumours have a histological resemblance to odontogenic cysts and tumours.

7. Malignant Neoplasms

A Pituitary carcinoma. These are rare.

B Metastatic carcinoma, e.g. lung or breast carcinomas.

8. Lesions in adjacent and connected structures

It must be remembered that any disorders affecting the pituitary stalk, hypothalamus or III ventricle can cause secondary pituitary dysfunction. Lesions affecting the hypothalamus may interfere with release of antidiuretic hormone or oxytocin; the former is of greater clinical significance (diabetes insipidus). Primary hypothalamic disorders are rare; the commonest include:

- A. Congenital malformations and hamartomas.
- B. **Acute and chronic inflammatory diseases.**
- C. Wernicke's encephalopathy (Thiamine deficiency).
- D. Primary neoplasms, e.g. astrocytoma, ganglioneuroma.

HYPOPITUITARISM

Pituitary failure usually develops gradually and the symptoms are insidious. Failure of gonadotrophin, and growth hormone secretion occurs earlier than TSH and ACTH, in hypopituitarism secondary to pituitary tumours.

Isolated deficiencies of individual pituitary hormones may occur rarely probably resulting from hypothalamic releasing hormone defect.

Causes:

Pituitary adenomas
Cranio-pharyngiomas
Pituitary infarction including post-partum necrosis
Irradiation
Trauma, including surgery
Infections (encephalitis, meningitis, T.B., syphilis)
Granulomata (Sarcoid, eosinophilic granuloma) idiopathic

Clinical features

Loss of secondary sexual features: **amenorrhoea, loss of libido, impotence**; fine skin; depigmentation; hypoglycaemia; hypotension; hypothyroid, small stature in children; hyponatraemia; susceptibility to stress, coma.
Failure of lactation;

Diagnosis:

1. Basal Thyroid function tests including TSH, LH/FSH, Testosterone (men), Oestradiol (premenopausal women), Prolactin.
2. Combined Pituitary Test: (i) Insulin tolerance test. Nadir Glucose < 2.2 mmol/l - cortisol > 550 nmol/l, GH > 20 mU/l contraindicated if 0900h cortisol < 180 nmol/l, cardiac abnormality (ECG), epilepsy. Can use Glucagon s.c. instead. (ii) GnRH test. (iii) TRH test.
3. X-ray of pituitary fossa. PA & R lateral film.

Management:

1. Treatment of cause, e.g. adenoma
2. Replacement therapy - hydrocortisone
- thyroxine
- gonadal steroids or gonadotrophins

PITUITARY TUMOURS

Symptoms are caused by local pressure effects or by endocrine syndromes resulting from hypersecretion of pituitary hormones; clearly these two types of symptoms may coexist.

Type of tumour

1. Adenoma of anterior pituitary

non-functioning	local pressure, hypopituitarism
secreting GH	acromegaly or gigantism
secreting prolactin	amenorrhoea/galactorrhoea
secreting ACTH	Cushing's disease

2. Craniopharyngioma (not true pituitary tumour)

3. Posterior pituitary tumours (very rare)

Local pressure effects: **headache, visual field defects (typically bitemporal hemianopia), enlarged pituitary fossa, cranial nerve palsies, hypopituitarism, diabetes insipidus, hypothalamic disturbance**

ACROMEGALY

Usually due to acidophil adenoma

Clinical features: gigantism or bony and soft tissue overgrowth, headache: **excessive sweating; diabetes; hypertension; enlarged pituitary fossa and field effects.** Diagnosis and assessment: GTT with GH determinations; X-ray

Management

1. Surgical hypophysectomy - transphenoidal: **transfrontal**
2. Pituitary irradiation - conventional, heavy particle, implantation
3. Medical - Bromocriptine, Sandostatin

CUSHING'S DISEASE (pituitary dependent adrenal hyperplasia)

Due to basophil hyperplasia or adenoma

To be discussed in separate lecture

After adrenalectomy for Cushing's syndrome pigmentation may increase with rising ACTH levels (Nelson's syndrome) due to a chromophobe adenoma.

HYPERPROLACTINAEMIA

Causes:

physiological	- pregnancy, suckling
drugs	- centrally acting drugs
	- oestrogens
tumours	- prolactin - secreting adenoma (eosinophilic)
	- tumours blocking hypothalamic inhibition

Clinical features:

- hypogonadism - menstrual disturbance
- infertility
- impotence

galactorrhoea
headaches,
field defects

Diagnosis : repeatedly high serum prolactin
pituitary tomography (tumours often very small)

Management : medical - suppression of prolactin secretion with
dopamine agonist, bromocriptine

ablation - for local pressure effects
- if patient subsequently intends to become
pregnant

The thyroid gland arises from the midline endoderm between the first and second branchial pouches. In the adult, it straddles the trachea just below the cricoid cartilage. Histologically, the thyroid consists of acini (spherical clusters of cells surrounding a cavity filled with protein "colloid").

Iodine Metabolism. 95% of body iodine is stored in the thyroid gland. The uptake of iodine into the thyroid gland is an active process, the energy being supplied by ATP.

Iodine deficiency may cause enlargement of the thyroid gland (goitre), and sometimes hypothyroidism, while iodine excess may be used to cause temporary suppression of the thyroid. Dietary iodine supplementation in iodine deficient areas has been effective in preventing this form of endemic goitre but an increase in the incidence of thyrotoxicosis has been observed, e.g. Tasmania, 1967.

Thyroid Hormone Synthesis is shown diagrammatically in Fig. 1

The Thyroid Hormones. The active hormones produced by the thyroid are thyroxine, -3, 5, 3', 5', tetraiodothyronine (T 4) and triiodothyronine -3, 5, 3', triiodothyronine (T 3). Circulating T 4 and T 3 are almost entirely protein bound. The main binding protein is Thyroxine Binding Globulin (TBG) but a small percentage is bound to albumin and to a thyroxin-binding pre-albumin.

At tissue level T 3 appears to be the active hormone presumably in the free form. Although the thyroid produces both T 4 and T 3 , the major amount of T 3 is derived from circulating T 4 by deiodination. The T 4 can therefore be considered as a form of pro-hormone.

T 4 is deiodinated to the active (3, 5, 3') T 3 and to an inactive 3, 3'5' form called Reverse T 3 (rT 3). It appears that the appropriate rate of T 3 production is achieved by varying the ratio of deiodination of T 4 between T 3 and rT 3 . By itself rT 3 appears to have no known specific function and it is rapidly removed.

The concentration of T 4 and T 3 in the plasma is dependent, as would be expected, on the rate of production by the thyroid (and the rate of utilisation) but it is also dependent on the concentration of binding protein which can vary considerably (e.g. pregnancy, oral contraceptive oestrogens etc.) For a given level of thyroid function a constant proportion of available protein binding sites are taken up. Consequently, if the binding protein concentration is higher than normal the concentration of hormone in the plasma will be high and vice versa. Free (unbound) hormones-active form.

Control of Hormone Secretion The hypothalamus, pituitary and thyroid form a self modulating system. The concentrations of T 3 and T 4 , resulting from TSH 'drive' on the thyroid, themselves exert a negative feedback on the hypothalamus and pituitary.

The hypothalamus stimulates pituitary TSH production through Thyrotrophic Releasing Hormone (TRH), a tripeptide which is easily synthesised but is not

measurable in the plasma; there is also evidence that dopamine produced in the hypothalamus may have an inhibitory effect.

Fig. 2 shows normal feedback control (a) and the abnormal situations in (b) Graves Disease (thyrotoxicosis) (c) primary thyroid failure and (d) primary pituitary failure. Occasionally (not illustrated) TSH or TSH-like substances produced ectopically can stimulate excessive T₃ T₄ production, and, very rarely, excessive and unmodulated TSH secretion by pituitary adenoma (acidophil) can cause T₃ and T₄ secretion.

Thyroid Function Tests

1. Plasma thyroid hormone concentration (radioimmunoassay)

Total thyroxine (TT₄) nmol L⁻¹ (ref. 60-140)

Total triiodothyronine (TT₃) nmol L⁻¹ (ref. range 1.6-3.0)

Thyroid Hormone Distribution Index (THDI) (ref. range 1.2-2.0)

"Free Thyroxine Index" (FT₄ I) (ref range 1.3-3.2)

Free T₄ (FT₄) 8-24 pmol/l Free T₃ (FT₃) 0.9-3 pmol/l (not available at LGI).

Reference range is for L.G.I. Laboratory; may vary in other laboratories.

THDI gives an indication of the concentration of protein, which itself directly affects the plasma total T₄ (and T₃) concentrations (see below). FT₄ I is a ratio of TT₄ to THDI which corrects for this.

Examples: 1.	TT ₄ = 100 nmolL ⁻¹ (normal)	Normal
	THDI = 1.8 (normal)	
	FT ₄ I = 1.8 (normal)	
2.	TT ₄ = 180 nmolL ⁻¹	Normal but high
	THDI = 1.0 (low)	TBG (pregnancy or
	FT ₄ I = 1.8 (normal)	oral oestrogens
3.	TT ₄ = 50 nmolL ⁻¹	Normal but low TBG
	THDI = 3.0 (high)	(chronic illness,
	FT ₄ I = 1.8 (normal)	other plasma protein
		abnormalities).

All the above represent normal thyroid function states: TT₄ is influenced by the amount of binding protein.

In other laboratories the method for indirect estimations of TBG may vary (e.g. "T₃ resin uptake test") but all have the effect of correcting TT₄ value for TBG variation. TBG can now be measured directly but is relatively expensive and indirect methods are usually satisfactory.

Plasma thyroid hormone measurement and plasma TSH measurement (see below) are now standard and in most cases give all the information required in thyroid function assessment.

Direct measurement of 'free' T₄ and T₃ is now available in most centres, may be best for monitoring.

2. Plasma TSH concentration (radioimmunoassay)

Plasma Thyrotropic Hormone (TSH) $\mu\text{L-1}$ (ref. range < 8)

Reference range and units are for L.G.I. laboratory; may vary in other laboratories.

TSH is most sensitive indicator of primary thyroid failure, and is frequently raised when plasma thyroid hormone is equivocal. A 'compensated failure' state can sometimes be detected, the thyroid hormone concentration being maintained within the normal range by continuous high TSH drive.

Low thyroid hormone concentrations together with low TSH are seen in hypopituitarism (and sometimes in the ill elderly patient).

The effective *maintenance* dose of T 4 in hypothyroidism is that which suppresses the **plasma TSH to the normal level.**

Highly sensitive TSH assays of great value can be used in diagnosis of thyrotoxicosis.

3. Isotope thyroid scan and uptake

With the exception of thyroid imaging for detection of 'cold' nodules (? carcinoma), 'hot' nodules (autonomous adenoma - 'toxic nodules') or retrosternal thyroid, and for special *investigations* of dysmorphogenesis, uptake tests are no longer used.

^{131}I (Half Life 8 days) has been supplanted by ^{123}I (HL 13 hrs.) or, where not possible due to shipping difficulties, $^{99\text{m}}\text{Tc}$ (technetium). $^{99\text{m}}\text{Tc}$ is concentrated by the thyroid cell in the same way (though not to **the same degree**) as iodine. The radiation dose to the **thyroid is much reduced compared with ^{131}I and the radiation energies are more suitable for modern imaging devices (gamma cameras).**

4. Thyrotrophin Releasing Hormone (TRH)

Not measurable in plasma (see above) but easily synthesised. 200 μg . i.v. will cause a rise of plasma TSH by at least 50% above basal level within 20-40 minutes in normals. Can be used as a test of thyroid and pituitary function.

- a) In thyroid function. A 'flat' (no response) curve will be obtained in thyrotoxic state, and more importantly, where plasma thyroid hormone concentrations are equivocal. Especially useful in 'Ophthalmic' Graves Disease - that is, where patient has eye signs without apparent toxicity. In borderline hypothyroidism where TSH level is equivocal (it usually is not), an exaggerated response is seen.
- b) In pituitary function. A 'flat' or reduced response is seen in thyroid hypofunction secondary to pituitary TSH failure. Sometimes useful where plasma thyroid hormones seem rather low, and TSH is not raised (usually seen in chronic illness due to other causes).

5. Tests of Overall 'Tissue Response'

- a) BMR
- b) Plasma creatinine
- c) **Plasma cholesterol (always raised in myxoedema)**
- d) **Tendon jerk speed**

All **measure some aspect(s) of end organ response to** thyroid hormone. None are now used in normal diagnosis and management of thyroid disease because non-specific, difficult, and/or laborious.

6. Other Tests

13 suppression. A daily dose of T 3 (80 mcg) for one week will suppress the normal thyroid but not the abnormally hyperfunctioning thyroid (largely supplanted by TRH test but still useful in some situations).

TSH stimulation. Almost never performed.

Thyroid stimulating immunoglobulins/antibodies. (TSI or TSAb) **Usually raised in Graves Disease and is the cause of the thyrotoxicosis.** May have considerable value in **future for early prediction of 'responders' and 'non responders' to medical (drug) treatment.** Currently not readily available. Cloning of the TSH receptor may allow cheap diagnostic tests in future. Thyroid **antibody tests detect thyroid microsomal antigen=thyroid peroxidase** enzyme. Antibodies may fix complement probably involved in gland destruction. Thyroglobulin antibodies not complement fixing probably not pathogenic directly. Other antibodies reported; not usually tested for.

Thyroid biopsy

Incidence of all forms of **thyroid disease favours females about 8:1.** Strong family incidence. Not single gene. **Probably complex inheritance.**

Three types of disease giving rise to thyrotoxicosis are generally recognised: Graves disease, toxic multinodular goitre, and toxic adenoma.

Graves Disease classically consists of triad - enlarged thyroid, thyrotoxicosis, and exophthalmos, (first two may be referred to as 'toxic diffuse goitre'). May be wide variation in the prominence of individual components of the triad, e.g. "Ophthalmic Graves Disease" ophthalmopathy without a previous history of hyperthyroidism. However, thyroid gland function is rarely normal, e.g. when tested by T3 suppression. **Also frequently evidence of thyroid autoimmunity (antibodies, etc.).** Orbital complications not related to thyroid status. Usually develops within 18 months of hyperthyroidism but there may be a gap of many years between the two. True relationship of components of the triad is also widely variable - e.g. Ophthalmic Graves may develop toxic diffuse goitre later: toxic diffuse goitre, initially without exophthalmos, may develop exophthalmos later, often irrespective of whether the thyrotoxicosis has been treated or not.

Apart from rare cases of pituitary disease, thyrotoxicosis, (whatever the pathogenesis) is never accompanied by high TSH, - in fact when measured plasma TSH is low or absent. Generally, the ophthalmopathy of Graves disease occurs in an older age group. Graves' disease often is accompanied by evidence of other organ specific autoimmune disease (gastric parietal cell antibodies - increased evidence of pernicious anaemia - adrenal antibodies - occasionally Addison's Disease - vitiligo). There is an increased incidence of Hashimoto's Disease, insulin-dependent-diabetes, pernicious anaemia, Addison's Disease, and myasthenia, in families of patients with Graves Disease.

Since 'Long Acting Thyroid Stimulator' (LATS) was discovered in a mouse bioassay, and later defined as an immunoglobulin, there has been considerable progress. **Thyroid Stimulating Antibodies (TSAB) have been identified and a number of assay methods (none entirely satisfactory) using human thyroid cell have been derived. It seems likely that there are a family of Thyroid Stimulating Immunoglobulins (TSI) which bind at or close to the TSH receptor and then stimulate the thyroid cell. Also, rarely thyroid blocking antibodies which can cause hypothyroidism in patients with Graves Disease.** TSH receptor recently cloned using molecular biology techniques; likely that better diagnostic tests will follow in the near future. There can now be no doubt, that Graves Disease is an autoimmune disease. The correlation between levels of TSI (as at present assayed) and exophthalmos is only partial: **it seems possible that specific immunoglobulins and likely that cell mediated immune mechanisms (not yet fully defined) are responsible.**

Other factors - notably stress (e.g. domestic strains, accidents) seem to have some causal relationship, though very difficult to prove.

Toxic multinodular goitre occurs in older age group (40-60). Usually in long standing euthyroid nodular goitres. Two different types (a) uneven distribution of hyperplastic, overactive gland between nodules and (b) multiple overactive nodule with adenoma-like properties. Rest of gland appears to function normally.

Toxic adenoma- usually a single nodule which is overactive ('toxic nodule', 'hot nodule') showing the feature of an adenoma (i.e. independence of usual feed-back homeostatic mechanisms). Consequently the rest of the gland (which is not independent) is usually in a quiescent, hypofunctioning state which 're-awakens' if the adenoma is removed.

All forms of thyrotoxicosis may be **accompanied by upper lid retraction ('Stare') and lid lag**: only Graves Disease (by definition) includes exophthalmos. Difficulties in categorisation in cases of apparent toxic diffuse goitre without nodules and without exophthalmos.

Other (rare) forms of thyrotoxicosis: thyrotoxicosis factitia (hooked on thyroid tablets): thyrotoxicosis due to TSH-like secretion by choriocarcinoma: thyrotoxicosis due to the thyroid tissue in Teratomas. In **subacute and chronic lymphocytic thyroiditis (when usually transient)**.

'Special' thyrotoxic states:

Neonatal thyrotoxicosis (relationship to maternal Graves disease with high circulatory TsAb):

Juvenile thyrotoxicosis (often presents as behaviour problems: usually growth outstrips weight).

Thyrotoxicosis in Pregnancy (difficulty in diagnosis and problems with treatment).

Thyrotoxic crisis ('storm') .

Thyrotoxicosis in the elderly (often 'cryptic' **and presenting as cardiac failure**, usually with **atrial fibrillation**).

Iatrogenic e.g. drugs such as amiodarone (iodine content and thyroid hormone-like structure), can rarely cause iodine-induced thyrotoxicosis (Jod-Basedow's Disease).

Modes of presentation: 'acute' or '**subacute**' onset 'chronic', 'chronic remittent' or '**chronic**' with **remissions and relapse** due to intermittent treatment with thyroid blockers.

Systems_ involved:

Associated with increased metabolic rate

Fat and muscle (loss of weight). High cardiac output fast pulse rate \pm AF; pulse pressure stroke volume muscle blood flow (cardiac failure). Heat production (sweaty, skin blood flow, pyrexia).

Associated with increased catecholamine sensitivity

Tremor; hyperglycaemia; tachycardia

Central Nervous System: 'nervousness', emotional lability, hyperkinesia, hyperreflexia (and fast jerks): tiredness.

Skin: Smooth and soft; fine hair (sometimes hair loss); pink and wet; skin blood flow (sweaty), increased pigmentation. Plummer's nails.

Muscle: weakness and fatiguability, proximal myopathy (common).

Skeletal: osteoporosis urinary calcium and hydroxyproline; bone resorption, calcium absorption. \$~

G.I. Tract: Motility frequency of BO **sometimes diarrhoea; sometimes malabsorption and steatorrhoea; sometimes abdominal pain, nausea and vomiting.** Then anorexia instead of usual appetite.

Lungs: (cardiac failure) - but also increased shortness of breath on exertion without cardiac failure, apparently due to some increase in lung "stiffness".

Endocrine: oligomenorrhoea, subfertility.

Renal: thirst (sweating) but also polyuria, sometimes due to glycosuria, hypercalcuria.

Ocular signs: **Lid lag, lid retraction and mild exophthalmos very common; often subside spontaneously.** Proptosis often asymmetrical. Diplopia may be transitory, usually on upward and outward gaze. Severe exophthalmos-chemosis risk of optic neuropathy high - pressure on optic nerve from enlarged eye muscles (uncommon 3-5%: treatment surgical/high dose steroids/DXT).

Associations: myasthenia gravis: pernicious anaemia (as above).

Differential diagnosis: Little difficulty in full-blown Graves Disease; but exophthalmos may be absent, and goitre may be inconspicuous. Then differential diagnosis will be related to the most obtrusive features of thyrotoxicosis in a particular case: commonest differential - anxiety state with or without (euthyroid) goitre. But also:- other causes of cardiac failure in the elderly; other causes of diarrhoea and/or steatorrhoea; other causes of hyperglycaemia (including diabetes mellitus); other causes of proximal muscular weakness; other causes of high pulse rate and high peripheral blood flow - e.g. liver disease, phaeochromocytoma - other causes of pyrexia - legion.

TREATMENT OF THYROTOXICOSIS

1. Reversible ('medical'): Blockers: Carbimazole (methimazole), thionamides (propylthiouracil)
2. Irreversible ('destructive'): surgery (subtotal thyroidectomy); radioactive iodine.

Secondary or ancillary blockers beta-blockers (propranolol), tranquilizers (chlordiazepoxide, diazepam).

Other (related to 'complications') e.g. digoxin and diuretics in cardiac failure; oral calcium supplements (osteoporosis); symptomatic treatment for diarrhoea.

Diagnosis must be confirmed before treatment is started Some objective evidence of the thyrotoxic state required If tests doubtful clinical state usually also in doubt. If so, allow time to elapse A 'therapeutic trial' is permissible. but should very rarely be necessary, and only where there is strong clinical conviction in spite of dubious biochemistry.

'Philosophy' of treatment. Some patients with thyrotoxicosis are cured - i.e. they do not relapse after treatment is stopped - by a course of blocking drugs, provided that it is carefully maintained, and is given for a long enough period. Assuming that other (destructive) therapy has intrinsic disadvantages, it is logical to treat all thyrotoxicosis initially with a course of blocking drugs, reserving destructive therapy for those not cured.

Exceptions to this rule are patients with large goitres which increase rather than diminish in size on blockers; patients who cannot be trusted to take tablets and those with very high initial free thyroid hormone levels where, perhaps, surgery is the preferred treatment.

Disadvantages of prolonged therapy are: need for careful supervision because dose requirements change, and need for serial biochemistry to monitor thyroid state; unwanted side effects of drugs (nausea and vomiting, rashes, (common) polyarthrititis, but occasionally agranulocytosis and aplastic anaemia); tendency for some goitres to increase in size progressively; difficulty in treating patients who will not take tablets reliably.

These are perhaps small disadvantages compared with destructive therapy which should therefore be reserved for non-responders.

Medical Treatment

Commonest blocker in this country - carbimazole, converted in the body to methimazole. Advantage in using one drug for all patients unless it has to be changed due to sensitivity. **First alternative - propylthiouracil (PTU); second alternative - perchlorate** (KC10 4). No apparent cross-sensitivity; not dose-dependent. **Perchlorate very rarely needed and best avoided if possible.** Carbimazole probably works both by inhibiting thyroid hormone synthesis and by local immunosuppressant effect.

Treatment regimens

1. 'Blocking/Replacement' Carbimazole 40mg daily (once daily dosage) plus T4 0.1-0.15 mg daily after the first 4 or 5 weeks. Advantages: once daily treatment, theoretical benefit of high dose carbimazole throughout treatment period in view of immunosuppressant action. Duration of treatment probably 12 months (controversial).
2. Titrated Dose Therapy. 45-60 mg **carbimazole daily, decreasing to maintenance doses dependent on thyroid function.** Duration of therapy 12-18 months. **Best indicator of duration of therapy may be level of thyroid stimulating antibodies (when assay more readily available may become routine test, currently only available in some centres).**

Treatment should always be stopped after 18 months; if patient relapses 'destructive' therapy without further ado.

Surgery always preceded by control with blockers - surgery always on euthyroid patients. Some surgeons also favour use of iodine (KI or Lugol's). Thyrotoxic storm after operation then a rarity. Radiation (radioiodine), usually preceded by control with blockers.

Most thyrotoxics adequately treated as out-patients from the outset and many able to carry on working throughout. However, moderate thyrotoxics need

rest (no work) and severe thyrotoxicosis need bed rest (probably hospital). Palpitations, tachycardia and tremor can be controlled with beta-blockers (propranolol, atenolol), but not always necessary (improvement on carbimazole is rapid). Cardiac failure treated with bed rest, digoxin, diuretics and if necessary, blockers). Cardiac failure commonest in the elderly.

Treatment of other forms of thyrotoxicosis

Thyrotoxicosis factitia: **prevention of access to thyroid tablets (not easy!) psychiatric treatment.**

Abnormal TSH-like substances. Treatment of cause, meanwhile blockers.

Toxic ectopic thyroid (teratomas). Remove. Meanwhile blockers.

Thyroiditis - self limiting. May progress to hypothyroidism.

'Special' Thyrotoxic States

Neonatal thyrotoxicosis: life support, iodide and carbimazole - it's temporary.

Juvenile thyrotoxicosis: avoid risks of destructive therapy. Tendency to relapse is high. May mean continuing blockers, right through puberty to adult. Attempt to withdraw at age 21 yrs. Surgery only when driven to, when adult (tendency to relapse is less when adulthood is reached). Radio iodine: never.

Thyrotoxicosis in preanancy: do not use **blocking replacement therapy** (carbimazole crosses placenta, thyroxine does not) risks of blockers to mother and foetus less than risks of surgery (said to be at least in 2nd trimester). Smallest amount of blocker which will keep mother well and gaining weight normally. Continuance of blocker afterwards. **Cannot breast-feed (though perhaps not absolutely contraindicated with carbimazole if required dose is small).**

Thyrotoxic storm: **main problems:- water and electrolyte loss through sweating, diarrhoea, vomiting - circulatory failure and pre-renal failure. Hyperpyrexia, cardiac failure, cardiac rhythm disturbance.**

Treatment: **water and electrolyte replacement; cooling down, treatment of cardiac failure (not diuretics) and rhythm abnormalities.** Propranolol in large doses, i.v. hydrocortisone, antithyroid drugs - oral blocker, i.v. iodide. Sedation.

Thyrotoxicosis in the elderly: energetic treatment of thyrotoxicosis (overtreat rather than undertreat) bed rest, digoxin diuretics.

Surgical Treatment

Complications:

1. Bleeding at operation
2. Bleeding after operating - emergency
3. Recurrent laryngeal nerve palsy
4. Hypoparathyroidism (1)



cont'd.

5. Thyrotoxic storm (2)
6. **Recurrence of thyrotoxicosis (3)**
7. **Thyroid failure (myxoedema) (4)**

- 1) May be temporary. Treatment oral calcium supplements and Vit. D (1,25 dihydroxy D or calcitriol).
- 2) Should never occur if euthyroid on blockers before operation
- 3) Percentage recurrence inversely proportional to extent of surgery. Better the surgeon, lower the relapse rate.
- 4) Thyroid failure sometimes predictable if thyroid ('destructive') antibodies in high titre present before operation. Better to treat such patients medically only.

RADIOACTIVE IODINE TREATMENT

Relies on self-irradiation of (thyroid) cells which are capable of concentrating iodide from the plasma.

Used in treatment of thyrotoxicosis and certain forms of thyroid carcinoma. **Radioisotope used is ^{131}I** (although ^{125}I can be used).

Radioiodine, as with surgery, is a form of 'destructive' therapy for thyrotoxicosis. Aim is to reduce mass of thyroid cells to that which will give normal overall function.

Doses are usually arbitrary.

Advantages compared with surgery; none of the risks of surgery. Usually possible to treat as outpatient.

Disadvantages: (1) cannot calculate a 'correct' dose. Risk of under-treatment (continuing thyrotoxicosis) or over-treatment (myxoedema). Latter risk is very high; up to 60% of patients become myxoedematous in time. Presumably due to ablation of thyroid cell by radiation. Continuing controversy whether to treat with high or low doses.

Limitations: May **not be effective where goitre very large**. Should not be given to patients planning to conceive within 18 months to 2 years. Almost never given to children here (do in the USA).

Probably best used in older patients (> 45 years) where the hazards of surgery are rather greater. Elderly patients with thyrotoxic cardiac failure are best candidates.

Unless thyrotoxicosis is very mild patients should be controlled first with blockers. **Stop carbimazole at least 5 days before dose with radioiodine.**

Thyroid carcinoma Radioiodine is useful only when neoplastic cells retain some functional capacity (i.e. will concentrate radioiodine). **Therefore histologically well-differentiated forms - papillary and follicular**. Aim is to **destroy all cells and very large** (100-200 mCi) doses used. Since even best differentiated carcinomas function less well than normal thyroid cells, the normal thyroid has to be 'ablated' first, either by surgery or by preliminary

doses of radio iodine. Procedure is to give treatment (in-patient, with special precautions) and allow time to elapse. Myxoedema is treated with tri-iodothyronine. At intervals T3 is withdrawn, the high TSH resulting will 'drive' any remaining (tumour) tissue (in neck, lungs, bones or elsewhere) to take up therapy doses. Exogenous TSH may be given for maximal stimulation.

Advantages The well differentiated cells which will take up radio iodine are relatively insensitive to external radiation - hence DXT is ineffective. Chance of destroying cells left after surgery. Metastatic tumours i.e. lungs or bones - are also irradiated.

Disadvantages Ineffective in poorly differentiated carcinoma. Some hazard to bone marrow. Given orally some patients nauseated.

Hypothyroidism may occur as the result of primary failure of the thyroid gland (most frequent) or as the result of pituitary failure. **The 'full-blown' primary thyroid failure presents as myxoedema, which is easy to recognise clinically provided that the diagnosis is thought of.** The diagnosis should not be missed because myxoedema is one of the few completely curable chronic diseases in medicine. Primary thyroid failure is a common disorder affecting approx. 1% of the adult population. The hypothyroidism of pituitary failure is usually (but not always) modified by the coincident failure of other endocrine glands driven by the pituitary, the clinical appearance is then different from that of myxoedema. Confusion occasionally arises because adrenal and gonadal functional depression can occur in association with the hypometabolic state of severe (primary) myxoedema. These, however, are reversible if the myxoedema is treated.

Primary thyroid failure is usually gradual and it has **been shown that there is a continuously variable state from normal, through 'compensated' failure (maintained by increased pituitary drive) and all grades of partial failure to the more-or-less complete failure associated with frank myxoedema.** Partial failure is difficult (and sometimes impossible) to recognise clinically; how much ill-health is due to partial thyroid failure is unknown. The picture is complicated by the fact that obesity and tiredness are often assumed (both by lay and medical people) to be due to hypothyroidism:

thyroid hormone is often given without proof that hypothyroidism exists.

Detection of early hypothyroidism has been greatly facilitated by the development of sensitive plasma TSH assays. It has been shown that nearly normal plasma thyroxine levels may be maintained for a long time in the slowly failing thyroid by sustained and progressive increase in TSH level. Differentiation of primary and pituitary thyroid failure is simplified by direct measurement of TSH and the use of TRH.

Causes of primary hypothyroidism

1. 'Idiopathic'. The thyroid is impalpable and at postmortem a fibrotic, atrophic remnant is found. Since many patients have positive auto-immune antibodies, it seems likely that many of these are end-results of Hashimoto process. This is the usual situation in middle aged and elderly patients.
2. Hashimoto's disease. The thyroid is palpable and may be enlarged. It is firm and usually (but not always) symmetrical. Thyroid antibodies present. Histology shows the characteristic changes of chronic lymphocytic thyroiditis. May occur at any age, but most common in 4th and 5th decades. Hashimoto's may present without hypothyroidism, but it usually develops later.
3. Non-development of thyroid. ('athyretic') most common form of cretinism (sporadic) in this country. Diagnosis in the first few months of life is a must - otherwise mentally subnormal. Neonatal screening along with PKU.

4. **Iatrogenic' .**

- a) **post-thyroidectomy by no means uncommon.** Usually follows subtotal thyroidectomy for thyrotoxicosis. **Characteristically myxoedema plus thyroidectomy scar, but varying degrees of hypothyroidism may be found. After thyroidectomy the gland is very frequently in a state of 'compensated' failure - 'normal' T₄ levels being maintained only by high TSH drive.** Cause of some cases of complete failure after thyroidectomy may be co-existence of thyrotoxicosis and Hashimoto's before operation.
- b) post irradiation (radio iodine) cumulative incidence > 60% in patients treated with ¹³¹I. Presumably irradiation produces a 'sick' clone of thyroid cells which attenuate and eventually die. Gland impalpable.
- c) administration of blocker. Gland palpable, very often enlarged. Thyrotoxicosis overtreated by carbimazole is obvious. **But hypothyroidism plus goitre, can be produced by drugs given for other purposes - e.g. iodide compounds ('Felsol' powders for asthma) PAS (for TB), Lithium (for manic depression).**
5. Subacute and acute thyroiditis. **Subacute thyroiditis (viral) not uncommon (De Quervain's disease).** Gland usually recovers but **sometimes gland atrophies and myxoedema and impalpable thyroid results. Destruction of thyroid by acute (pyogenic) thyroiditis is very rare indeed.**
6. Hypothyroidism with goitre. Goitrous cretinism rare in this country. **More common in central area of land masses where iodide is scarce. A familial tendency probably due to failure to handle scarce iodide as efficiently as normal glands.** A goitre may be present with or without hypothyroidism - a matter of degree.

Families exist in which goitre and hypothyroidism occur in varying degree (sporadic - not associated with iodide lack). **Some of these shown to have blocks to hormone elaboration, presumably genetically determined.** Uncommon. **Main interest is light they throw on steps in hormone synthesis by the thyroid.**

'Special hypothyroid states'.

Cretinism (see above). Need for early diagnosis and treatment.

Juvenile myxoedema: - usually retardation of growth without permanent mental impairment (though often fall in school performance is early sign) very occasionally precocious puberty also.

Association with pernicious anaemia: - **co-existence of gastric parietal cell antibodies with thyroid antibodies.**

Myxoedema heart failure: myxoedema coma (social factors usually precipitate) 'myxoedema madness'.

Modes of presentation. **Normally insidious, unrecognised by patient, relatives and (often) by family doctor for a long time.** Recognition earlier if there is goitre. More rapid development in some iatrogenic forms. Symptoms are often non-specific: tiredness, slowness, aches and pains. Many of the

more specific symptoms due to the complications or associated diseases, (e.g. angina, anaemia). Sometimes the condition is unrecognised (particularly in the elderly) until the patient develops an unrelated disease (e.g. pneumonia).

Systems Involved:

Associated with decreased metabolic rate: Fat (usually only moderate weight gain). Cardiac output (pulse rate, pulse pressure). Heat production (reduced sweating and skin and muscle blood flow) sensitivity to cold - hypothermia.

Central Nervous System. Slowness of thought, sometimes intellectual impairment, occasionally psychotic ('myxoedema madness'), lack of drive. Hypokinesia - sits very still, economy of movement, slow in normal activities such as dressing and undressing; somnolence; slow jerks; median nerve compression ('carpal tunnel syndrome'); peripheral neuropathy; very occasionally cerebellar ataxia.

Skin: dry, cold, thick, esp. about elbows and knees. Thinning dry hair, slowing of growth (and loss of) body hair. No pitting oedema, baggy eyes, (mucoprotein of myxoedema).

Muscles: General fatiguability and slowness and increased fatiguability of repetitive muscle movement. Muscles often appear bigger and firmer than normal. Big tongue. Gruff voice (mucoprotein of myxoedema).

G.I. Tract: Constipation, may be serious problem in the elderly. Rarely causes ascites.

Endocrine: Oligomenorrhoea, amenorrhoea (myxoedema often occurs after, or around menopause), loss of libido; impotence in male. Associated with adrenal suppression, occasionally a marked feature, requiring (temporary) steroid therapy.

'Renal': Usually reduced GFR (renal plasma flow - low cardiac output). Blood urea, serum creatinine, plasma Na (but TE Na normal). Abnormal handling of water and salt load (probably also partially related to adrenal depression).

Treatment

Thyroxine: Orally, gradually increase in dose 0.05 mg/day initially, maintenance dose usually 0.1-0.15 mg/day. NB - **caution in the elderly, in those with ischaemic heart disease (start treatment in hospital)**. Oral T3 also available. Very rarely intravenous T3 (e.g. unconscious, myxoedema coma).

Do not overtreat (bones). Difficult to monitor treatment biochemically if TSH becomes suppressed. Controversial area.

I. HYPOADRENALISM

A. Addison's Disease is a generalised adrenocortical deficiency. At one time it was largely due to tuberculosis, but the majority of cases are now due **to atrophy of the adrenal cortex secondary to autoimmune disease, followed by tuberculosis, carcinomatosis, amyloidosis,** fungal infections and bleeding into both adrenal glands (with anticoagulants, or in meningococcal septicaemia - 'Waterhouse-Friederickson' syndrome).

Clinically the condition presents in an acute or in a chronic form: the latter being very difficult to diagnose at times due to the non-specific nature of the symptoms.

Chronic form: anorexia, nausea, vomiting, weight loss, pyrexia, sodium depletion, hyperpigmentation, hypotension, psychosis, hypoglycaemia."

Acute form: vomiting, abdominal pain, shock, death - 'adrenal crisis'

Treatment:

- a. in emergency: i.v. cortisol with i.v. glucose and saline fluids in plasma, etc.
- b. maintenance: cortisone acetate or cortisol orally plus 9 fludrohydrocortisone as mineralocorticoid both for life.

B Isolated enzyme defect: adrenogenital syndrome

C Diminished ACTH production: in hypopituitarism. This is usually a late feature of this syndrome. It is characterised by the ability of the adrenals to respond to synacthen (synthetic ACTH) but not to other tests of the pituitary/adrenal axis (insulin etc.). The same maintenance therapy is indicated but without mineralocorticoid.

D. Following the cessation of long-term steroid therapy. This is probably the commonest cause of hypoadrenalism and may occur acutely, particularly if stress or infection supervenes and also if patients stop their steroids suddenly, i.e. **onset of vomiting, etc.**

2. HYPERADRENALISM

This condition is called Cushing's syndrome and has several causes, but apart from the iatrogenic variety, is rare. However, in its early stages this condition presents with non-specific **91-vs"and symptoms, such as obesity, hypertension,** and early diagnosis would greatly help morbidity. Diagnosis is difficult and involves two stages:

- (i) establishment of the syndrome - inappropriately high tissue exposure to glucocorticoids;
- (ii) differential diagnosis of the cause of Cushing's syndrome.

The types of Cushing's syndrome can be divided into:

- A. ACTH Dependent:
 - a. Pituitary-dependent bilateral adrenocortical hyperplasia (Cushing's disease).
 - b. Ectopic ACTH syndrome.
 - c. Iatrogenic - ACTH treatment.
- 3. Non ACTH Dependent:
 - a. adenoma or carcinoma of the adrenal cortex.
 - b. Iatrogenic - steroids.

The clinical features of this syndrome are many and varied. The overt syndrome is difficult to miss, early syndrome very easy to miss.

Clinical Features

- 1. Obesity - face, neck, shoulders and trunk
- 2. Hypertension
- 3. Amenorrhoea or impotence
- *4. Skin - hirsuties, striae, acne, poor healing, easy bruising, recurrent infection.
- *5. Proximal myopathy
- *6. Osteoporosis - with pathological fractures.
- 7. Diabetes mellitus
- 8. Polycythaemia
- 9. Psychosis

* indices of protein wasting: very important

In the ectopic ACTH syndrome is mostly commonly due to oat cell carcinoma of lung, pigmentation is occasionally found as in Addison's Disease, with marked hypokalaemia and very high plasma ACTH levels. More indolent ectopic ACTH secretion occurs with other tumours - often hard to differentiate from Cushing's disease.

Investigations are principally aimed at showing an increased steroid production which is **not under the normal physiological control. Plasma ACTH levels help to localize the lesion (if available) and the loss in diurnal rhythm of plasma cortisol is an early sign.** When **one attempts to reduce cortisol secretion with dexamethazone, the response suggests the site of lesion.** Radiology is then used to delineate a pituitary or adrenal tumour and **assist surgical removal etc.**

Treatment

- A. Cushing' disease
 - a. mild
 - pituitary ablation
 - drugs, metapyrone, amino-glutethimide

b. moderate or severe - bilateral adrenalectomy with pituitary ablation
if Nelson's syndrome occurs.

H Adrenal adenoma - surgery

c. Adrenal carcinoma - surgery plus op DDD 6-9g/daily

D. Ectopic ACTH tumour - treat original and if not possible
bilateral adrenalectomy.

The adrenal contains three functional units: **the inner medulla producing catecholamines and the two parts of the cortex - the zona glomerulosa (producing aldosterone) and the zona fasciculata + reticularis (producing cortisol and androgens).**

Destruction of the adrenals affects all parts of the gland and all hormones.

Overproduction will affect only one part of the gland.

Cushing's Syndrome Screening test: urine cortisol. (Midnight plasma cortisol is less useful). Follow-up; Dexamethasone suppression test; plasma ACTH, metyrapone stimulating, imaging.

Addison's Disease Screening test: tetracosactrin ("Synacthen") stimulation test measuring plasma cortisol. (Single measurements of plasma urine cortisol are usually worse than useless). Follow-up: Prolonged stimulation test (which may be carried out while steroids are being given).

Conn's Syndrome There is no cheap screening test. Therefore investigate only when there is a good prima facie case: hypertension with renal disease excluded and a persistently low potassium not due to drugs. Diagnosis depends on showing a high aldosterone and a low renin on **the same occasion**. The difficulties stem from the **number of physiological factors that influence aldosterone and renin.**

Congenital adrenal hyperplasia **Defective enzymes on the biosynthetic pathway to cortisol lead to a compensatory increase of ACTH production and adrenal hyperplasia.** The pattern of steroid production by the adrenals is quite different from normal. This makes diagnosis easy and the method currently favoured is the measurement of plasma 17.-hydroxyprogesterone (which shows a 10- 50-fold increase).

Cortisol assays may mislead in this disease because of poor specificity.

Congenital adrenal hyperplasia is treated with replacement doses of glucocorticoid and mineralcorticoid. Treatment is monitored by observing rate of growth (in **children**) and **steroid** and renin production. There is no general agreement regarding the best steroid to measure. **Plasma 17-hydroxyprogesterone gives a good indication of undertreatment but not of overtreatment.** Plasma androstenedione is useful.

Other causes of androgen over production **Androgen-producing tumours of the adrenal or ovary are very rarely encountered** but the relatively mild androgen excess that leads to female hirsutism is quite common. **Androgen metabolism is complicated because both adrenal and ovary steroids are converted to the active androgens (especially dihydrotestosterone) elsewhere in the body.**

TESTES AND RELATED CLINICAL PROBLEMS MALE HYPOGONADISM AND INFERTILITY

DR. P. BELCHETZ

Basic Physiology

Hypothalamus produces a gonadotrophin releasing hormone which promotes the synthesis of follicle stimulating and luteinising hormone in the pituitary gland. Follicle stimulating hormone has an effect on spermatogenesis and stimulates the **production of testosterone and** other steroids. There is a negative feedback control of LH by testosterone and FSH by a non-adrogenic hormone called inhibin produced by the germinal epithelium. Testosterone is responsible for the sex characteristics of the adult male.

Clinical Problems

1. Infertility

This may result from selective damage to germinal epithelium or may be part of a more general disorder affecting Leydig cells as well.

2. Eunuchoidism

As a result of the failure of Leydig cell function there is failed development of the normal male secondary sex characteristics together with elongation of the limbs. The cause of the Leydig cell failure may be primarily gonadal, as in Klinefelter's syndrome, or secondary to gonadotrophin deficiency due to a pituitary or hypothalamic lesion.

3. Impotence

Whilst impotence may accompany eunuchoidism when it occurs in a virile man it is usually associated with a psycho-sexual disturbance.

Investigations

One may distinguish between primary pituitary and hypothalamic failure or primary gonadal failure by measurement of blood FSH, LH and testosterone levels. Stimulation tests with exogenous HCG (LH) **GnRH and Clomiphene may provide additional information. Seminal analysis and testicular biopsy are useful in evaluating infertility.** In general serum LH reflects Leydig cell function and serum FSH reflects both the function of germinal epithelium and also the function of Leydig cells.

Treatment

Infertility can be treated most successfully if it is due to a varicocole. Eunuchoidism will respond to androgen therapy, chorionic gonadotrophin (LH) or gonadotrophin releasing hormone depending on whether the disease is primarily gonadal or secondary to gonadotrophin deficiency. Impotence occurring on its own responds only to *psychotherapy*.

Risk factors for coronary heart disease (CHD):

Modifiable:

- Hypercholesterolaemia
- Hypertension
- Smoking
- Diabetes mellitus
- Low HDL-cholesterol
- Hypertriglyceridaemia
- obesity
- Lack of exercise

Unmodifiable:

- Age and sex
- Family history of atherosclerosis

Cholesterol: Strong relationship between plasma cholesterol concentration and CHD. Trials show that reducing the cholesterol level reduces the incidence of M.I. Ideally aim for plasma cholesterol <5.2 mmol/l.

Triglyceride: The relationship between hypertriglyceridaemia and CHD is less close than with cholesterol but some triglyceride-rich lipoproteins do appear to be atherogenic, e.g. in familial combined hyperlipidaemia and remnant hyperlipidaemia. Normal fasting plasma triglyceride level is <1.7 mmol/l. Levels >11 mmol/l may cause pancreatitis.

HDL Cholesterol: Many studies show an inverse relationship between HDL-cholesterol and CHD risk. Redundant surface components from chylomicrons and VLDL produced by the action of lipoprotein lipase are taken up by HDL.

The Lipoproteins

Transport of triglyceride from around the body is carried out by macromolecules known as lipoproteins because triglyceride is insoluble in plasma. Lipoproteins are composed of triglyceride, cholesterol, phospholipid and protein. The protein is known as apolipoprotein and there are several different proteins - AI, AII, B, C, E. Classification of lipoproteins was previously carried out by electrophoresis but now more so by ultracentrifugation into the classes below:

<u>Lipoprotein</u>	<u>Main constituent</u>	<u>Apoprotein</u>
Chylomicrons	Triglyceride	B48, C, E
VLDL	Triglyceride	B100, C, E
LDL	Cholesterol	B100
HDL	Cholesterol	AI, AII, C, E
VLDL Remnants (IDL)	Cholesterol	B100, E

The apoproteins control the metabolism of lipoproteins through interaction with enzymes and/or receptors.

Chylomicrons: largest of the lipoproteins, produced by the intestinal epithelium during absorption of dietary fat. They enter the circulation via the thoracic duct and are degraded by lipoprotein lipase which lines the capillary endothelium, especially in muscle and adipose tissue. Chylomicron remnants are produced which are rapidly taken up by **the liver**.

Very Low Density Lipoprotein (VLDL) containing endogenous triglyceride produced by **the liver is also degraded peripherally by lipoprotein lipase producing VLDL remnants (intermediate density lipoproteins - IDL)**. IDL is metabolised by the liver to low density lipoprotein (LDL).

LDL contains 60-70% of plasma cholesterol. LDL and probably IDL are the major source of cholesterol that accumulates in atherosclerotic plaques. Overproduction or decreased catabolism of LDL is of great importance in relation to atherosclerosis. Uptake is via the LDL receptor which is influenced by hormones, drugs and diet and is genetically defective in familial hypercholesterolaemia.

High density lipoproteins (HDL) contain 20-30% of plasma cholesterol. Mild hypercholesterolaemia can therefore be due to increased HDL alone. This requires no treatment because the role of HDL appears to be the removal of cholesterol from peripheral tissues including the arterial wall.

Classification of hyperlipidaemia

It is often difficult to definitively classify hyperlipidaemic patients because lipoprotein electrophoresis or ultracentrifugation are usually not done (they **are not needed to decide on treatment**) and a number of factors, **primary and secondary, are often operative (e.g. genetic susceptibility, high fat diet, obesity, alcohol, diabetes)**.

Frederickson's classification:

- is based on lipoprotein electrophoresis (modern ultracentrifugation gives the same result). Not all types correspond to a well defined pathological mechanism. Different diseases can produce the same lipoprotein pattern. In addition to the measurement of plasma cholesterol and triglycerides classification can be taken further by the inspection of plasma refrigerated at 40C overnight: **chylomicrons have a creamy appearance, VLDL makes the plasma turbid, increased LDL does not affect the appearance of the plasma.**

Type I	Chylomicronaemia syndrome
IIa	LDL increased
IIb	LDL + VLDL increased
III	increased IDL (VLDL remnants) <i>probable disease</i>
IV	VLDL increased
V	VLDL and chylomicrons increased

Clinical classification:

Common ('polygenic') hypercholesterolaemia: most common cause of plasma cholesterol >5.2 mmol/l, reflects an interaction between genetic and environmental factors. More than one metabolic basis, corresponds to Frederickson IIb or IV. Hypercholesterolaemia tends to be mild to moderate, xanthomas do not occur but **patients may have corneal arcus, xanthelasmas, positive family history of CHD, and may be obese.**

Familial hypercholesterolaemia: **raised LDL levels (i.e. Frederickson IIa) occur due to impaired function of LDL receptors.** Inherited as an autosomal dominant 1 in 500 of the populations are heterozygotes. CHD may present in the fourth or even third decade of life. The condition is present in 1 out of 25 patients presenting with M.I. before age 60. Tendrpp xanthomata are pathognomic. Plasma total cholesterol >7.8 mmol/l (or >6.7 before age 16), LDL cholesterol >4.9 mmol/l. Triglyceride is normal or slightly elevated. Polyarthrititis may occur.

Homozygous FH affects 1 per million and results in CHD in childhood with a life expectancy of about 20 years.

Remnant hyperlipidaemia: Raised IDL (Frederickson type III). Uncommon. Marked elevation of cholesterol and triglyceride result in premature atherosclerosis. Patients have characteristic phenotype of apo E, apo E2/2. The condition is usually found in rouno to **middle aged adults who are obese, often diabetic and have palmer crease striite xant omas, tuberqus or eruptive xanthomas.**

Familial combined hyperlipidaemia: Autosomal dominant, common condition. Moderate increase in cholesterol (7-9 mmol/l) and triglyceride (3-6 mmol/l) or either. Strong family history of CHD is **usually found but diversity** of pattern of hyperlipidaemia within a family is characteristic. Xanthomas do not occur. Production of apo B, the structural protein of VLDL and LDL is increased (useful in diagnosis); levels of both lipoproteins or either alone are elevated. The condition therefore corresponds to Frederickson's IIa, IIb or IV.

Chylomicronaemia syndrome: Severe hypertriglyceridaemia results from **impaired clearance of chylomicrons due to deficiency of lipoprotein lipase or the protein which activates it, apo C-II.** The primary form of chylomicronaemia (Frederickson type I) is a rare autosomal recessive disorder presenting in childhood or early adult life with acute pancreatit,,i5, episodes of abdominal pain dating back to childhood, eruptive xan **Womii,~lipaemia retinalis and hepatosplenomegaly.** No excess risk of CHD.

Familial hypertriglyceridaemia: Increased VLDL synthesis (Frederickson type IV) with chylomicronaemia if severe (Frederickson type V) due to impaired lipoprotein lipase activity as above. HDL **cholesterol levels** tend to be low. Metabolic defect unknown. Patients are usually obese, often diabetic with CHD. Pancreatitis occurs in severe cases.

Elevated HDL cholesterol: Mild hypercholesterolaemia may be due to unusually high levels of HDL-cholesterol e.g. 2-3 mmol/l. A benign abnormality.

Secondary hyperlipidaemia: Common causes are diabetes mellitus, alcohol abuse, therapeutic drugs (thiazides, oral contraceptives, tinoids and corticostbroidgj, hypothyroidism, chronic renal failure, nephrotic syndrome, cholestasis, bulimia. -----

Common hyperlipidaemias
caused by
hypertriglyceridaemia.

Treatment

Seek and treat or advise on all modifiable risk factors. Identify and treat causes of secondary hyperlipidaemia. Explain the goal of reducing CHD risk. Assess whether CHD is already present and consider investigation. Institute dietary treatment by involving the dietitian. Monitor the result and encourage compliance. Encourage exercise.

Dietary regimen: 1000-1200 Kcal per day depending on the patients activity. 800 Kcal/day if no response or for the very sedentary patient. Little or no alcohol. Reduce total fat to (30% of total dietary energy intake, saturated fat to (10%. Reduce cholesterol intake to (300 mg/day. Increase intake of complex carbohydrates and fibre. Use polyunsaturated fat. Moderate salt intake.

Drug treatment:	Indication
Bile acid sequestrants (cholestyramine, colestipol)	Hypercholesterolaemia
Nicotinic acid, fibrates (bezafibrate, gemfibrozil)	Hypertriglyceridaemia or combined hyperlipidaemia
HMG CoA reductase inhibitors	Hypercholesterolaemia, but also reduce triglycerides to a lesser extent.

Amenorrhoea: The **failure of menstruation to occur at the appropriate time**. May be: Primary: Menstruation never established. Secondary: menstruation established then ceases.

Cryptomenorrhoea: Menstruation occurring but not evident due to obstruction to menstrual outflow, e.g. imperforated hymen.

Causes of Amenorrhoea:

1. Physiological: pregnancy, menopause.
2. Dysfunctional: **hypothalamic-pituitary-ovarian-endometrial axis intact, but function disturbed.**
 - a) Hypothalamic: cortical influences - stress, change in way of life etc. change in body weight, anorexia nervosa. **Post pill amenorrhoea.** Hyperprolactinaemia.
 - b) Hypothalamic-pituitary-ovarian: polycystic ovary syndrome (Stein-Leventhal syndrome).
 - c) Excessive androgen production: Adrenal lesion - congenital adrenal hyperplasia, adrenal tumour. Virilising ovarian tumour.
3. **Pathological**: Destructive lesion or development defects
 - a) Hypothalamic Kallman's syndrome.
 - b) Pituitary: Pituitary tumour hyperprolactinaemia: Sheehan's syndrome.
 - c) Ovary: Gonadal dysgenesis - Turner's syndrome.
 - d) Uterus: Failure of Mullerian development. Intra-uterine adhesions - Asherman's syndrome.

POLYCYSTIC OVARY SYNDROME

Example of hypothalamic-pituitary-ovarian dysfunction characterised by amenorrhoea, infertility and enlarged ovaries with thickened perilymphatic capsules (tunica) which on sectioning exhibit multiple follicular cysts. Sometimes associated with hirsutism and obesity.

Underlying disorder probably ovarian enzymatic defect in pathway of conversion of androgens to oestrogens. The results in elevated androgen levels which result in disturbance of gonadotrophin secretion; characteristically low- normal FSH and elevated LH levels.

HIRSUTISM IN FEMALES

Abnormal development of facial and body hair. Associated with elevated androgen production of abnormal sensitivity to normal levels of circulating androgens; may be:-

1. idiopathic;
2. iatrogenic, testosterone, anabolic steroids, epanutin;
3. adrenal; congenital adrenal hyperplasia, Cushing's syndrome, adrenal tumour;
4. ovarian; Stein-Leventhal syndrome, Virilising ovarian tumour.

where associated with virilisation - clitoromegaly, deepening of the voice, amenorrhoea and male pattern baldness - patient obviously exposed to strong androgenic influences.

OVULATION INDUCTION THERAPY

Mainly indicated in the treatment of infertility due solely to ovulation failure.

Types of therapy available

1. Clomiphene: hypothalamic-pituitary-ovarian dysfunction.
2. Human gonadotrophins. Pituitary gonadotrophin failure.
3. FSH/LH releasing hormone.
4. Bromocriptine: hyperprolactinaemia.

The menopause marks the end of menstruation and is due to cessation of ovarian hormone production. This can result from natural involution or surgical removal of the ovaries. The median age of natural menopause is 49 years although there is considerable variation. Prior to **the final cessation of menses, there may be a peri-menopausal period of declining ovarian function when menstruation becomes less regular and symptoms of oestrogen deficiency more common.**

The major biochemical change at the menopause is a large fall in plasma oestradiol which is replaced as the main circulating oestrogen by oestone which is derived from adrenal androgens by peripheral conversion. This takes place in adipose tissue and oestrone levels are higher in obese women. Associated with the decline in **oestrogen activity there is a rise in gonadotrophins, a raised FSH being the best biochemical marker of the menopause.**

Oestrogen deficiency has several effects on other tissues. **There is atrophy of the genitalia and breasts.** Calcium metabolism is also involved with an increase in bone resorption. This leads to a loss of bone at a rate of about 1% **per year for the rest of life and with this an increased risk of fracture.** Biochemically the changes in calcium metabolism are reflected in **increased plasma and urinary calcium together with raised plasma alkaline phosphate and urinary hydroxyproline excretion.**

The major symptom of **the menopause is the hot flush or sweat.** These are very variable *although* there is a tendency to decline with age. The next most important symptoms relate to sexual function and include loss of libido, vaginal dryness and dyspareunia. **Other symptoms are less specific and include changes in mental state and sleep pattern and muscle and joint pains.**

Oestrogen therapy leads to correction of the biochemical abnormalities and will usually relieve hot flushes. Relief of other symptoms is frequent but less predictable. Oestrogens will also reduce the rate of bone loss and with that the fracture rate. Such therapy is contraindicated in the presence of a history of thromboembolic disease, breast or gynaecological cancer, liver disease and severe varicose veins. In patients in *which* oestrogens are contraindicated, the progestogen norethisterone may be useful.

Transdermal oestradiol 'patches' became available in 1987. Oestradiol given this way avoids the 'first-pass' effect on the liver and thus does not **affect the liver enzymes which may be implicated in clotting and hypertension.**

The Climacteric and Postmenopause

The climacteric is the 2-3 year transitional phase during which reproductive function ceases. It is due to the decline in ovarian production of oestrogens, especially oestradiol, which occurs in the late 40s or early 50s. Progressive ovarian failure eventually results in amenorrhoea and the menopause is simply the last menstrual bleed. It is the only constant feature of the climacteric.

The postmenopausal woman is not totally lacking in oestrogens because adrenal androstendione is peripherally converted to oestrone, particularly in adipose tissue.

Signs and Symptoms (Figure 1)

Vasomotor symptoms: hot flushes and night sweats are the most common acute symptoms. They may first be experienced early in the climacteric when menstruation, albeit irregular, is still occurring. They are self limiting but continue to occur for more than 5 years in approximately 25% of women who experience them.

Vasomotor symptoms are believed to result from central, possibly hypothalamic, disturbances and are associated with profound changes in pulse rate, skin impedance, and central and peripheral body temperatures. They are also an important cause of insomnia.

Psychological symptoms increase in incidence during the climacteric, but the importance of oestrogen deficiency in their aetiology remains controversial. Classical, severe anxiety and/or depression neuroses seldom, if ever, result from ovarian failure. Minor degree of psychological retardation, such as impairment of memory and concentration, inappropriate mood swings, anxiety and irritability may be due to oestrogen deficiency but can also be the result of coincidental domestic, social and economic crises.

Lower genital tract: oestrogen deficiency can result in atrophy of the vulva, vagina and urethra. Symptomatic sequelae, which are not self limiting, include dyspareunia, apareunia and recurrent bacterial infections. Loss of more likely (unproven) to be mediated via these effects than through a central mechanism. Eventually fibrosis may develop in the urethra, causing the 'distal urethral syndrome'.

Osteoporosis is a long-term sequela of oestrogen deficiency. The climacteric is associated with a reduction of bone mass relative to bone volume which eventually results in osteopenia and an increase in the risk of certain types of fractures. Bone loss greatest in first few years. Skeleton is at risk after 10 or 15 years.

Plasma lipids and lipoproteins: the plasma concentrations of cholesterol, triglycerides and low and very low density lipoproteins may increase by as much as 20% during the climacteric. The protection enjoyed by premenopausal women against coronary heart disease is reduced, with mortality rates from myocardial infarction rising during the postmenopause until they eventually approximate those found in men.

Incidence Rates

The following incidence rates apply to most developed countries. No data are available for developing countries.

Hot flushes and night sweats are experienced by 75% of **climacteric and immediately postmenopausal women** but only 25% are sufficiently disturbed to seek medical advice. Some 40% of these (10% of total) require only explanation and reassurance, whereas the physical discomfort experienced by the remainder (15% of total) necessitates more active treatment. Symptoms due to lower genital tract atrophy are the presenting complaint in 10% of those seeking advice.

Caucasian postmenopausal women over the age of 60 years, who comprise 13% of the total population, are most at risk from osteoporosis and related fractures. The wrist fracture rate rises approximately tenfold during the postmenopause reaching 65/10,000 by the age of 80 years, and at least 25% of postmenopausal women over the age of 60 years have radiological evidence of vertebral compression fractures. The incidence of femoral neck fractures doubles every 7 years to reach 25% by 90 years. Negroes, however, for reasons incompletely understood, are less susceptible to osteoporosis.

In many developed countries the total cost of treating osteoporosis and related fractures is very high. For **example, there are 6.4 million postmenopausal women aged over 60 years in the UK and the financial consequences of fractures of the neck of the femur alone are, in this group, at least £100 million/year. In the USA this figure exceeds \$1 billion/year.**

Osteoporotic Fractures

1. Colles (wrist)
2. Vertebral crush
3. Neck of femur

Chances of OP

Women in 50's < 5%
Women in 60's 25%
Women in 70's 50%

Diagnosis

The typical nature and temporal association of acute vasomotor symptoms with oligomenorrhoea or amenorrhoea makes their misdiagnosis unlikely. Other conditions associated with flushing, sweating and palpitations (e.g. phaeochromocytoma, carcinoid disease and thyroid disease) have additional symptoms which should make the true diagnosis obvious. As plasma gonadotrophic and oestrogen concentrations fluctuate widely during the climacteric detailed biochemical investigations are often of little value in diagnosis and symptoms are always the best guide. Endocrine investigations cannot accurately predict the eventual severity and duration of symptoms nor the response to therapy.

The greatest challenge to the clinician is establishing whether psychological disturbances result from domestic crises or are due to oestrogen deficiency. Accurate diagnosis is essential because symptoms resulting from breakdowns in family relationships are best treated by psychiatrists, marriage guidance counsellors and social workers - not by oestrogens. When diagnosis proves difficult biochemical investigations may be of value as high plasma oestrogen concentrations exclude ovarian failure, though the converse does not necessarily apply - but some HRT can always be tried and stopped if it isn't helpful.

Therapy

hypnotics and sedatives, although widely prescribed, have not been shown capable of relieving symptoms of oestrogen deficiency, and the available evidence indicates that the benefits of clonidine on vasomotor instability are minimal.

Oestrogen therapy

indications - at present, oestrogens are prescribed mainly in cases of vasomotor instability or lower genital tract atrophy. Failure to relieve the symptoms (e.g. hot flushes, night sweats, dyspareunia) casts doubt on the diagnosis. Very occasionally, however, therapy fails due to lack of absorption of oestrogens from the gastrointestinal tract. Thus subcutaneous or vaginal administration may sometimes be necessary (or implant or transdermal).

Other indications include short-term trial therapy (approximately 3 months) to establish whether psychological symptoms are due to oestrogen deficiency, if this cannot be determined from the history. Oestrogens are effective in relieving those psychological symptoms which are caused by oestrogen deficiency, an effect which is **in part indirect and due to relief of** flushes, sweats and insomnia. However, oestrogens also exert a direct 'mental tonic' effect which is **independent of the relief of vasomotor** instability. **If the patient says she feels better the HRT may be continued.**

Oestrogen therapy may also be indicated to prevent loss of bone mass. This requires long-term treatment which may only be effective for as long as therapy is prescribed and, following cessation of treatment, * bone may be lost at an increased rate.* Maintenance of bone mass may therefore require continuous treatment for over 10 years. Such treatment is widely used in the USA where the incidence rates of major fractures have been reported to have halved as a result. Thus it is very cost effective.

* NO since disproved, bone continues to be lost t 'normal' rate.

Oestrogen therapy should always be considered when there is a strong premature menopause or early castration which significantly increase the risk of the early development of osteoporosis and coronary artery disease.

There is no compelling evidence that oestrogens delay ageing and prevent development of facial wrinkles and sagging breasts. But oestrogen does restore skin thickness.

Side-effects - the commonest side-effects which occur **in approximately 5-10% of patients include nausea, breast tenderness (usually both self-limiting), physiological vaginal discharge and leg cramps**. Leg cramps are dose dependent

and are not related to thromboembolic disease. Maximal weight increases are usually less than 1.5 kg. Thus the **side-effects are not usually serious.**

Very occasionally, marked increases in blood Pressure and renin substrate do occur and pre-existing hypertension should be controlled before therapy is prescribed. Not with transdermal systems.

Potential hazards of exogenous oestrogens - consideration of the two major hazards of exogenous oestrogens (endometrial carcinoma and thromboembolism) raises two questions.

Should oestrogens be prescribed alone in an unopposed manner or in combination with a progestogen?

Should 'natural' or 'synthetic' oestrogens be used in postmenopausal women?

The incidence of endometrial adenocarcinoma in untreated postmenopausal populations is approximately 1/1000 women years and is increased by unopposed oestrogen therapy to 5/1000 women years.

Prospective studies have shown that the **addition of progestogens to the oestrogen therapy reduces the incidence of endometrial hyperplasia which is a precursor of cancer. This effect is duration-dependent and optimal responses are obtained with *12 days* of progestogens each month.**

* 0.7 mg is enough (see over)

Oral **contraceptive** use has been associated with an increased risk of both arterial and venous thromboembolism, positively correlated with increasing age, weight and smoking. Although such data have been applied to oestrogen-exposed postmenopausal women, the extrapolation and comparisons of risks is **not valid** for two reasons. Firstly, premenopausal and postmenopausal women have quite dissimilar endocrine environments. Secondly, the synthetic oestrogens prescribed in oral contraceptives are, on a weight-for-weight basis 70-100 times more potent than the natural oestrogens usually given to postmenopausal women. **This greater potency probably accounts for the ore profound and adverse changes in blood clotting factors and lipid concentrations observed with oral contraceptive therapy.** Preliminary studies have shown no **increase in thromboembolic disease following natural** oestrogen administration in the postmenopause.

Contraindications (Figure 2) - very occasionally, oestrogens may be administered in the presence of an absolute contraindication if symptoms are very severe, but such a decision should only be made following specialist advice. Otherwise norethisterone 5 mg daily may prove useful in partially relieving severe vasomotor instability. (or Provera 10 mgm)

The majority of **relative contraindications** have not been conclusively shown to increase the hazards of oestrogen administration but are included because of a putative risk. Again, specialist advice should be sought before therapy is prescribed. If this is unobtainable and symptoms are severe small doses of an **oestrogen** plus progestogen regimens should be prescribed, and scrupulous surveillance of the vulnerable end-organ or system must be maintained.

Heavy smokers, and obese and hypertensive patients should be warned that they may be at an increased risk of complications.

Patient management - oestrogens should be prescribed only when the clinician is reasonably certain that symptoms are due to oestrogen and deficiency* and after the patient has been fully informed of all benefits and risks. The pretreatment assessment should include measurements of weight and blood pressure and breast and pelvic examination. Cervical smears should be repeated every 3-5 years. When risk factors are present additional investigations should include mammography for breast dysplasia and a lipid profile when there is a strong family history of arterial disease. Gross varicose veins should be treated appropriately. Vaginal bleeding is likely to recur during therapy but fertility will not be restored. If the patient already has abnormal vaginal bleeding oestrogens must never be prescribed until the condition has been fully investigated.

* or fluctuations (i.e. in the peri-menopause). A therapeutic trial is often justified.

The optimal oestrogen dose is that which just controls symptoms adequately. It can be determined by starting with low doses and increasing until symptoms disappear or vice versa. Weight and blood pressure should be checked at 6 monthly intervals and breast and pelvic examinations should be repeated annually. If oestrogens are Prescribed alone an endometrial biopsy should be performed annually irrespective of the bleeding pattern, as endometrial hyperplasia has been found with regular withdrawal bleeding, breakthrough bleeding or even when no bleeding has occurred. With combined oestrogen and progestogen therapy endometrial biopsy is required following unscheduled bleeding. Withdrawal bleeding, however, is almost always associated with a normal endometrium and therefore does not require routine biopsy.

Duration of therapy is dictated more by the type than the severity of symptoms. Thus, most patients with vasomotor instability can (but no need to) be successfully weaned off treatment after 18-24 months, whereas those with end-organ atrophy, who are often using oestrogen creams, may require continuous long-term therapy. Management of patients using topical cream is identical to those using oral therapy.

Lipid profiles should be repeated every 2-3 years when long-term therapy is prescribed for relief of symptoms or following premature menopause. Measurements of bone density are invaluable in determining the need for oestrogens when prophylactic use is contemplated for combating osteoporosis.

Abrupt cessation of treatment invariably results in **an acute exacerbation of symptoms and therefore the oestrogen dosage should be gradually** reduced over a 2-3 month period.

Prescribed sensibly, oestrogens carry minimal risk but indiscriminate use, gross overdosage or lack of adequate patients surveillance may result in serious adverse effects. Oestrogens per se are not dangerous but the manner in which they are used can be.

FIGURE 1

Symptoms associated with the rZinacteric and postseaopausal years

Acute

Vasomotor symptoms

Hot flushes
Sweats
Insomnia
Palpitations

Psychological symptoms

mood changes
Anxiety
Loss of memory
Loss of concentration
Irritability

Reproductive tract symptoms

Genital-tract atrophy
Loss of libido
Dyspareunia

Urinary symptoms

Urethral syndrome

Skeletal disease

• Osteoporosis

Cardiovascular diseases

• Coronary heart disease

Chronic

Thrombosis

FIGURE 2

Absolute and relative contraindications to exogenous oestrogen therapy

Absolute

Breast carcinoma
Endometrial carcinoma
Endometrial hyperplasia

Relative

myocardial infarction	1989
Cerebrovascular accident	Estraderm patches
Thromboembolic disease	may be tried in
Abnormal lipid profile	nearly all
Active or oestrogen-related liver disease	these cases
Breast dysplasia	
Hypertension	
Obesity	
Heavy smoking - but this increases risk of osteoporosis	

- **PRACTICE POINT**

Although vasomotor symptoms in the menopausal patient are self-limiting the symptoms of vaginal and urethral atrophy are not.

- **PRACTICE POINT**

Endocrine investigations in the menopausal patient cannot accurately predict the eventual severity and duration of symptoms nor the response to therapy.

- **PRACTICE POINT**

The greatest challenge to the physician is to establish whether psychological disturbances in the menopausal patient are a result of domestic crises or oestrogen deficiency.

- **PRACTICE POINT**

Oestrogen therapy should always be considered when there is a strong family history of osteoporosis and must be given following premature menopause or early castration.

- **PRACTICE POINT**

in the treatment of menopause patients the addition of progestogens - 10 -12 days/month - to the oestrogen therapy reduces the incidence of endometrial hyperplasia which is a precursor of cancer.

- **PRACTICE POINT**

If the menopausal patient has had any abnormal vaginal bleeding never prescribe oestrogens until the condition has been fully investigated.

- **PRACTICE POINT**

Oestrogen therapy in the menopausal patient should not be stopped abruptly.

APPROXIMATE COSTS FOR 3 MONTHS AND 1 MONTH ORAL TREATMENT AT LOWEST DOSAGE

		3 MONTHS £	1 MONTH £
OESTROGEN + P <u>ROGESTOGEN</u>			
Estraderm patches + Norethisterone acetate p.Us = Estrapak			8.00
<u>continuous</u>			
<u>- natural oestrogen</u>			
conjugated equine oestrogen 625 µg/1.25 mg + norgestrel 150 µg (12 days)	Prepak-C	11.50	4.00
oestradiol 1 mg/2mg + oestradiol 500 µg/1mg + norethisterone acetate 1 mg (10 days)	Trisequens	10.00	3.30
<u>- synthetic oestrogen</u>			
mestranol (dose varies) + norethisterone 1 mg (13 days)	Menophase	8.00	2.80
<u>cyclical - natural oestrogen</u>			
oestradiol valerate 1mg/2 + norgestrel 500 µg (10 days)	Cyclo-Progynova	8.50	3.00
OESTROGEN ALONE			
<u>natural</u>			
Oestradiol patches	Estraderm		7.00
oestriol 270 µg + oestradiol 600 µg + oestrone 1.4 mg	Hormonin	4.70	1.60
oestradiol valerate 1mg/2mg	Progynova	6.00	2.00
Oestriol 250 µg	Ovestin	2.00	
conjugated equine oestrogens 625 µg 1.25 mg	Premarin "	3.80 6.15	1.30 2.05
<u>synthetic</u>			
piperazine oestrone sulphate 1.5 mg	Harmogen	7.00	2.30
ethinyloestradiol 10 µg		1.25	0.40

Effective doses

Progestagens 12 day course

Micronor 2 x 0.35 mg 48p.

Provera 10 mg £3.12

Duphaston 10 mg £2.01

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PARATHYROID HORMONE SECRETION AND VITAMIN D METABOLISM AND THEIR DISEASES

DR. P. BELCHETZ

PARATHYROID HORMONE

Biochemistry: parathyroid hormone is a polypeptide secreted by the parathyroid glands. The secretion rate is controlled by plasma calcium; hypercalcaemia suppresses, hypocalcaemia stimulates.

Biological action: The main target hormones for parathyroid hormone are the kidney and bone. In the kidney parathyroid hormone increases tubular reabsorption of calcium; decreases tubular reabsorption of phosphate and stimulates the conversion of 25OH vitamin D to 1,25(OH)₂ vitamin D. In bone it stimulates metabolism by a direct action on osteoclastic resorption. Target organs contain cell membrane receptors which act via adenylcyclase.

VITAMIN D

Biochemistry: Vitamin D is a sterol produced in the skin (D₃) by UV radiation or absorbed from the diet (D₂ and D₃).

Metabolism: Vitamin D undergoes metabolism in the liver to form 25OH vitamin D; the main circulating metabolite. In the kidney 25OH vitamin D is metabolised to 1,25(OH)₂ vitamin D; the most potent metabolite of vitamin D. The production of 1,25(OH)₂ vitamin D is under endocrine control by plasma parathyroid hormone, calcium, phosphate, growth hormone, prolactin and sex steroid concentration.

Biological action: The main target organs for vitamin D are the gut and bone. It stimulates calcium and phosphorus absorption, bone resorption and promotes the calcification of osteomalacic bone. It heals the myopathy of vitamin D deficiency. Like other steroid hormones it is transported in plasma by a specific binding protein and in target organs the cells possess a specific binding protein which translocates vitamin D to the nucleus where it stimulates protein synthesis.

CALCITONIN

Biochemistry: Calcitonin is a polypeptide produced from the C-cells of the thyroid. Its secretion is stimulated by hypercalcaemia and the gastrointestinal hormones.

Biological action: The target organs for calcitonin are bone and kidney. It inhibits osteoclastic bone resorption and decreases tubular reabsorption of calcium. Specific cell membrane receptors are present in the target organs which act via adenyl cyclase.

ENDOCRINE CONTROL OF CALCIUM HOMEOSTASIS

Plasma calcium is controlled in humans by parathyroid hormone and vitamin D. Calcitonin plays a minor role. Sex steroids, growth hormone, cortisol and thyroxine have important regulatory functions but unlike parathyroid hormone and vitamin D there is no feed back control on their secretion by plasma calcium concentration.

PARATHYROID DISEASES

Primary hyperparathyroidism: Due to an autonomous over-secretion of parathyroid hormone; plasma calcium and parathyroid hormone are high and plasma phosphate low. It is a common disease particularly in postmenopausal women. Patients present with renal stone disease, bone disease or symptomatic hypercalcaemia. A substantial number of patients now present with asymptomatic hypercalcaemia found on biochemical screening.

Secondary hyperparathyroidism: Present in vitamin D deficient osteomalacia or renal failure. Plasma calcium is low and plasma parathyroid hormone high. Patients present with signs and symptoms of the underlying disease.

Tertiary hyperparathyroidism: Autonomous over-secretion of parathyroid hormone occurs in patients with prolonged secondary hyperparathyroidism. Most commonly seen in patients with chronic renal failure.

Hypoparathyroidism: Due to a deficiency of parathyroid hormone (usually surgical but can be idiopathic) or to a failure of parathyroid hormone to act on its target organs (pseudo-hypoparathyroidism). The plasma calcium is low and plasma phosphate high. Patients usually present with tetany or fits.

VITAMIN D DISEASES

Osteomalacia and rickets: Due to a deficiency in vitamin D (from sunlight exposure) or absorption (malabsorption) or a failure in metabolism (renal failure). Plasma calcium, phosphate and vitamin D metabolites are low and there is secondary hyperparathyroidism and increased plasma alkaline phosphate levels. Patients present with bone disease and myopathy.

Vitamin D intoxication: Iatrogenic except in sarcoidosis where there is over production of 1,25(OH) 2 vitamin D. Plasma calcium, phosphate and the vitamin D metabolite levels are high and there is secondary hypoparathyroidism. The patient presents with symptomatic hypercalcaemia.

CALCITONIN DISEASES

Medullary carcinoma of the thyroid: Due to autonomous over-secretion of calcitonin from C cells which have become malignant. There are various clinical stigmata but no abnormality in calcium metabolism. Patients present with thyroid enlargement.

HYPERCALCAEMIA

CAUSES

common

malignancy

hyperparathyroidism%

uncommon

thyrotoxicosis
vitamin D poisoning
sarcoidosis
hypocalciuric hypercalcaemia-

rare

Addison's disease
milk alkali syndrome '
acute renal failure
thiazides
Paget's disease
immobilisation -
APUDomas
idiopathic hypercalcaemia of infancy

SYMPTOMS OF HYPERCALCAEMIA

tiredness and lethargy
polyuria, nocturia and polydipsia
anorexia, nausea, vomiting
abdominal pain, constipation
proximal muscle weakness
drowsiness, psychosis and coma

CAUSES OF OSTEOPOROSIS

Generalised

postmenopausal women
hypo-oestrogenic states, e.g. Turner's syndrome
corticosteroid excess
thyrotoxicosis
hypogonadism

Localised

immobilisation, e.g. fracture
inflammatory disease, e.g. rheumatoid arthritis

A. NORMAL GROWTH

1. Pattern of normal growth and spectrum of normality Linear and Velocity percentiles.
2. Influences on growth pattern - (and requirements for normal growth).
 - a) Health or Disease
 - b) **Food intake, digestion and absorption**
 - c) **Prenatal effects (reflected by birth weight and length)**
 - d) **Genetics and hereditary (familial and racial)**
 - e) **Environmental and psychological**
 - f) **Exercise**
 - g) **Hormonal - notably thyroid, growth hormone, adrogens and oestrogens, corticosteroids and insulin.**
3. **Indications for concern about growth abnormalities**
 - a) **Extreme positions on percentile charts**
 - b) **Exceptional positions within a family position**
 - c) **Gross deficiency between height and weight percentile positions**
 - d) **Lack of pallelism of longitudinal growth to percentile lines**
 - e) **Gross physical disproportion**
 - f) **Other physical abnormalities or mental retardation**

B. PUBERTY

1. Sequence of events and spectrum of normality.
2. Significance of pubertal growth spurt. This is of great importance in contributing about 20% of ultimate height, **occurring relatively early in the sequence of pubertal changes in girls, but later in boys (at least 2 years later than girls).**
3. **Factors influencing the timing and pattern of puberty.**
 - a) Health or **disease**
 - b) **Nutrition**
 - c) **Genetic and hereditary (familial and racial)**
 - d) **Environmental and psychological**
 - e) **Climate, temperature and light**
 - f) **Hormonal (gonadotrophins and gonadal hormones but also thyroid and growth hormone).**
4. Indications for concern about pubertal abnormalities. True precocious puberty (as **distinct from sexual precocity**) is associated with **gonadal enlargement and activity, and is rather arbitrarily defined as first changes before 8 1/2 years in girls and 9 1/2 years in boys.** Though usually idiopathic, a much higher percentage have an underlying pathology in boys. **Delayed puberty is usually a variant of normal and does not warrant investigations before 14 in girls or 16 in boys (unless psychological stress dictates).** Abnormal timing of puberty greatly affects the growth pattern by variation in the age of pubertal growth spurt which precedes bone fusion and ultimate cessation of growth.

3r.-.

Diabetes is a syndrome of chronic hyperglycaemia for which there is a variety of causes. Easily-understood causes of diabetes due to pancreatic disease are rare. The majority of cases have an unknown cause.

Genetic factors

Both IDDM and NIDDM run in families and so genetic factors have a role to play. They are stronger in NIDDM with identical twin concordance of almost 100% although the hereditary mechanism is unknown. Genetic factors are less strong in IDDM with identical twin concordance of ~50%, but are better understood. Childhood IDDM is associated with genes on the short arm of chromosome 6 in the major histocompatibility locus. The HLA **antigens DR3 and D1W** are strongly associated with IDDM and inheriting **both** these antigens carries high risk for the condition.

Environmental agents: NIDDM

The major risk factor seems obesity. **Not all overweight people are diabetic and** not all NIDDM subjects are fat, but being overweight seems a contributory factor in many cases of NIDDM. How obesity causes chronic hyperglycaemia is unknown, but either obesity causes resistance to the action of insulin or there is relative insulin deficiency relative to body weight.

Environmental agents: IDDM

What turns the predisposed 'at-risk' person into a diabetic subject? It may be that inheriting the risky HLA types make the individual react to environmental agents in an abnormal way and so viruses or toxic substances may lead to chronic islet damage.

Pathology

NIDDM has an interesting pathology with the islets containing some amyloid material. This amyloid may be the result of islet 'exhaustion' or as recent studies suggest, possibly a primary damaging factor.

IDDM islets feature an infiltration with lymphocytes and polymorphs, termed 'insulinitis'. This inflammatory reaction is thought to represent an 'autoimmune reaction' and may be initiated by an environmental agent, e.g. a viral infection.

What is Diabetes?

Diabetes is a condition in which there is too much sugar (glucose) in the blood. **The body uses glucose as a fuel and normally** the amount present is very strictly controlled in the range of about 2-6 mmol/l. The level is lowest on rising, before breakfast and highest after meals. No matter what is eaten or drunk, **a normal person will not push the glucose level past about 6 mmol/l**. This is because insulin, a polypeptide hormone made in **the pancreatic islets, stops the glucose level from going** too high. If the glucose level is chronically raised past about 7 mmol/l, then DIABETES MELLITUS or 'DIABETES' is present.

(Diabetes insipidus is a rare condition due to lack of **anti-diuretic hormone and the term 'diabetes' usually refers to chronic hyperglycaemia**).

HYPERGLYCAEMIA = a high blood glucose level

HYPOGLYCAEMIA = a low blood glucose level

Classification of diabetes

1. Type I - IDDM = insulin-dependent diabetes mellitus
2. Type II - NIDDM = non-insulin-dependent diabetes mellitus
3. Pancreatic diseases, e.g. chronic pancreatitis, pancreatectomy.
4. Genetic syndromes, e.g. dystrophia myotonica, Friedreich's ataxia.

Drug-induced: thiazides, steroids

Endocrine diseases: Cushing's syndrome; acromegaly, pheochromocytoma.

7. MRDM: malnutrition-related diabetes mellitus: protein restriction, cassava toxicity

Diagnosis

In a patient with typical symptoms and a high blood glucose level of 11 or 12 mmol/l or more, the diagnosis is obvious and certain. No further diagnostic test is required and treatment can be started. In the absence of typical symptoms or a borderline glucose value, e.g. 8 mmol/l, then an oral glucose tolerance test may be helpful (OGTT).

The patient attends in the morning, having fasted overnight and is given an oral load of 75g of glucose. Blood samples are taken immediately before the load and at 30, 60, 90 and 120 minutes for glucose values. **The World Health Organisation (WHO) has set criteria for the diagnosis of diabetes for the OGTT. For borderline cases, the category of 'impaired glucose tolerance' or IGT was introduced.** Interpretation of the values depends on whether the samples are venous or capillary blood or are whole blood or plasma.

Presentations of diabetes

- a) 'Classical' - chronic hyperglycaemia leads to an osmotic diuresis and the patient complains of thirst, polyuria and weight loss. Other symptoms are tiredness blurred vision and muscle cramps.
- b) Hyperglycaemic coma - DKA
- HONKC
- c) Infections - monilia - pruritus vulvae, balanitis -- *suspect in occurrence*
- bacterial, skin infections *males*
- d) Chronic complications - e.g. macrovascular - IHD
CVD
PVD

microvascular - retinopathy
- nephropathy

neuropathy
- e) Associated conditions - obesity, hypertension
- f) asymptomatic - chance finding

Factors helpful in distinguishing IDDM/NIDDM

I D D M

N I D D M

Age at presentation

Often children, teenagers
or young adults: may occur
at any age

Usually middle-aged or
elderly: may occur at
any age

Physique at
presentation

Often thin

Often overweight

Clinical history

Often short - days or weeks

Often months

Biochemistry

Ketosis-prone and risk of
ketoacidosis due to insulin
deficiency

Rarely ketosis-prone,
except under extreme
stress, e.g. severe
infection

Aims of treatment

1. Save life
2. Freedom from symptoms
3. Achieve and maintain ideal body weight
4. **Prevention of long term complications through the normalisation of blood glucose and HbA1c levels**

What is control?

1. **Removal of symptoms and attainment** of ideal body weight
2. No glycosuria
3. **Pre-meal blood glucose (BM Stix) 4-7 mmol/l and HbA1 \leq 8% (normal range 4-6%)**

Self Monitoring of Control

1. Urine testing using diastix or clinitest tablets for glucose and ketostix or acetest tablets for ketones.
2. **Blood testing using reagent strips with or without reflectance meters, e.g. BM stix, glucostix, exactech.** Good technique is imperative or results are meaningless.
3. Record results in a diary and bring to clinic.

Education

Patients must understand the reasons for attempting to obtain good control (otherwise there will be no incentive to comply). Liaison nurses play a **key role in teaching monitoring techniques, injection techniques, managing insulin and reinforcing the principles of diet treatment.**

Diet

The diet is the cornerstone of diabetic treatment both for **IDDs and NIDDs and needs to be tailored to the patients age, weight, type of work and activity, race and creed.**

For **NIDDs, diets should aim to eliminate all forms of sugar and restrict total energy intake. Reduce calorie and fat intake, increase (complex) carbohydrate content and fibre.** Encourage use of polyunsaturated fats and moderation of protein. In the elderly, simple sugar restriction is often all that is required.

Remember that the commonest cause for failure of a diet to control blood sugar is poor dietary compliance, in **this instance adding tablets or insulin will merely cause weight gain!**

For **IDDs simple sugars** must be avoided but carbohydrate restriction is not necessarily required. The main principle is of a steady, regular daily intake of carbohydrate. **The total amount of carbohydrate varies between 100-250g** depending on age, build and activity. The form the carbohydrate takes will also vary according to individual preference and requirements.

For convenience the carbohydrate is normally taken in three main meals and three snacks, which should not be missed. By understanding the principles of 10g 'portions' of carbohydrate, patients may interchange types of carbohydrate and thus avoid boredom in their diet. At times of increased activity, extra carbohydrate may be taken to avoid hypoglycaemia.

INSULIN

Insulin preparations

With the advent of human insulins, manufactured by conversion of porcine insulin (NOVO) or by bioengineering (Lilly), insulin manufacturers are progressively phasing out older insulins of beef and pork origin. The commonly used human insulins are listed below. The time of maximum action and duration of activity are influenced by several factors and so should be used only as a rough guide. All insulins in UK are supplied in U100 vials and patients use disposable syringes marked in units (0-50 or 0-100).

<u>Short Acting</u>	Time max	Duration
Actrapid		
Humulin S	2-3 hrs	6-8 hrs
Velosulin		

<u>Intermediate Acting</u>	Time max	Duration
Humulin I)		
Insulatard) Isophane		
Protaphane) insulins	4-12 hrs	upto 24 hrs
Monotard Insulin Zinc Suspension)		

Mixtures of Short and Intermediate Insulins

Humulin MI	(10% Humulin S, 90% Humulin I)
Humulin M2	(20% Humulin S, 80% Humulin I)
Humulin M3	(30% Humulin S, 70% Humulin I)
Humulin M4	(40% Humulin S, 60% Humulin I)
Mixtard)	30% short acting, 70% isophane - intermediate acting
Actraphane)	
Initard	50% short acting, 50% isophane - intermediate acting

Long Acting

Humulin Zn	6-14 hrs	20-28 hrs
Ultratard M.C.	10-30 hrs	30-36 hrs

It is now accepted that all new insulin-requiring diabetic patients should commence therapy on 'human' insulins.

Non-human insulins

Some diabetic patients are long-established on older non-human insulins, e.g. **Rapitard, a biphasic intermediate acting insulin of mixed beef/pork origin, and Protamine Zinc Insulin, a long acting beef insulin, etc.** While these insulins are available there is no indication to change the type of insulin prescribed. A few patients may lose their normal hypoglycaemic symptoms with human insulin, and these may be changed to animal insulin, this is very rare.

Treatment Guidelines

Give insulin if there are signs of insulin deficiency, i.e. ketosis, weight loss. Some maturity onset diabetics with weight loss can be treated with sulphonylureas provided they do not have ketonuria.

If the patient has some endogenous insulin production; use once (or twice) daily intermediate insulin.

If the patient has no endogenous insulin production use twice daily mixture of short and intermediate acting insulins. Alternatively a long acting insulin (e.g. ultratard) may be given to provide steady basal insulin level supplemented by injection of short acting insulin before the three main meals, which can be given by a specially designed portable syringe (the Novopen).

Side effects of insulin

1. Hypoglycaemia
2. Fatty lumps
3. **Insulin allergy (local inflammation) and subcutaneous fat atrophy, - rare with highly purified animal and human insulins**

Li po dystrophy

ORAL HYPOGLYCAEMIC AGENTS

Indications for oral hypoglycaemic agents

Type II, Non Insulin Dependent (NIDDM) diabetes where diet and attainment of ideal body weight has failed to control diabetes; provided there is no ketoacidosis. If not overweight use sulphonylurea. If **obese, use biguanide if renal and liver function is normal and no cardiac failure.**

- | 1. Sulphonylureas | Dose |
|-------------------|--|
| a) Commonly used | |
| Tolbutamide | 0.5-1 g T.D.S. (short action useful in elderly) |
| Glibenclamide | 2.5-30 mg once daily (high dose divided) |
| Chlorpropamide | 100-500 mg once daily (long acting - avoid in elderly) |

b) Less commonly used

Acetohexamide	0.25-1.5 g	
Glibornuride	12.5-75 mg daily	
Gliclazide	40-80 mg daily	
Glipizide	2.5-30 mg daily	
Gliquidone	45-180 mg daily	hepatic metabolis - can be used in renal failure
Tolazamide	100 mg-1 g daily	flushing with alcohol does not occur

2. Sulphapyrimidine

Glymidine 0.5-2 g daily

Rarely used except in sulphonylurea sensitivity. Properties and side effects similar to sulphonylureas.

3. Biguanide

Metformin 500mg daily - 850 mg BD

Side effects

Sulphonylureas

Biguanides

Weight gain
Hypoglycaemia
Facial flushing with alcohol
(esp. chlorpropamide)
Anorexia
Nausea
Vomiting
Epigastric discomfort
Hyponatraemia (chlorpropamide)
Paraesthesiae)
Skin rashes)
Jaundice) uncommon
Eosinophilia)
Thrombocytopaenia)
Leucopaenia)

Lactic Acidosis
Anorexia
Nausea
Vomiting
Diarrhoea
Metallic taste
Weakness
Drowsiness
B₁₂ malabsorption

Screening for complications

Good treatment involves screening for early signs of diabetic complications including BP and proteinuria checks, fundoscopy (through dilated pupils) and examining feet.

A most important factor in diabetic control is that the patient controls his therapy day by day. The medical staff have an advisory role pointing out the pitfalls and advantages of treatment, however patients should be conscious that long term poor blood glucose control is invariably associated with severe, unremitting and eventually lethal complications of diabetes. Many other factors, ranging from psychological to medical, make great impact on control and thus the doctor cannot afford to ignore these other factors, e.g. adolescence, pregnancy, work pressures, etc. It is this which gives rise to the importance of the education of the diabetic patient and the translation of education into compliance -which at present seems the doctors 'art' rather 'science'.

Despite advances in management, the life expectancy of diabetics has not improved significantly in the past 30 years. The excess mortality is mainly due to macrovascular disease, to a greater extent, microvascular disease. The frequency of complications increases with duration of diabetes. There is some evidence that optimal control of blood sugar (though it **is rarely possible to achieve non-diabetic levels**) **reduces the risk of microvascular disease, though even in apparently well-controlled diabetics complications occur**.

The prevalence of microvascular and macrovascular disease shows a marked geographical variation, suggesting that genetic and/or environment factors may be involved.

1. MICROANGIOPATHY

Characterised by sclerosis of the walls of arterioles, venules and capillaries, it affects most tissue in the body but the retina and kidney show the effects most markedly. Generally clinical complications develop after 10-15 years of diabetes and are rare within the first 10 years. However with non-insulin dependent diabetes it is rarely possible accurately to estimate the date of onset.

i) Diabetic Retinopathy

Commonest cause of blindness in the adult population under 65 in the U.K. Changes include:

- a) venous dilatation
- b) capillary microaneurysms - due to loss of epithelial cells and pericytes. Seen as pinpoint 'dots'.
- c) Exudates - characteristically 'hard' but also occasionally 'cotton wool'. May lead to oedema and loss of vision if around the macula.
- d) Haemorrhages - initially 'dot and blot', but may become flame-shaped or subhyaloid.
- e) **Proliferative changes - progressive new vessel and glial formation anterior to preretinal membrane, usually in eyes with extensive background (a, b, c, d) changes.**

Loss of vision may be due to macular haemorrhage, macular oedema, haemorrhagic glaucoma, or retinal detachment.

Treatment:

Laser photocoagulation - either xenon beam or the more localised argon beam has been used successfully in both neovascularisation and maculopathy.

Clofibrate - though reducing the number of hard exudates, no effect on visual acuity.

Hypophysectomy - in rare instances dramatic remission of neovascularisation has been reported but in view of high morbidity rarely used.

Improved blood glucose control - conflicting results; apparent early deterioration followed by long-term improvement in retinopathy.

(ii) Diabetic nephropathy - commonest cause of death in young diabetics. Due to arteriosclerosis and glomerulosclerosis, the former occurring mainly in the afferent glomerular arterioles. Glomerulosclerosis may be diffuse (not confined to diabetes) or nodular (Kimmelstiel - Wilson lesion).

Clinically the onset is insidious, the first sign often being an on-selective intermittent proteinuria (a burst) usually occurring after 10 years of diabetes. Microproteinuria (>30 ug/min) may prove to be an early indicator of diabetic nephropathy.

Proteinuria becomes persistent leading to hypertension, and/or nephrotic syndrome, chronic renal failure and death.

Progress may be slow or rapid but relentless once proteinuria develops. Diabetics are also prone to DTI's.

Treatment:

No method of prevention is known and treatment of the renal disease is medical with BP control, reduced protein intake, etc. Diabetic control may become erratic if **the patient is on insulin therapy**. Occasional units will offer chronic dialysis (including chronic ambulatory peritoneal dialysis) or more successfully renal transplantation.

2. MACROANGIOPATHY

Atherosclerosis is more widespread and develops prematurely in the diabetic. The pathology is no different from that of the non-diabetic. **Medial calcification of medium-sized arteries** also frequently occurs but is probably clinically insignificant and not related to atherosclerosis.

In western cultures the incidence of coronary artery disease (no sex difference), stroke and peripheral vascular disease (which may result in gangrene and amputation) is 2-4 x more frequent in diabetics than in the general population.

Treatment:

As in non-diabetic arterial disease, i.e. avoid smoking, obesity, hypertension and, possibly, modification of fat intake.

3. NEUROPATHY

Aetiology unknown but metabolic and possibly also vascular factors involved. A number of syndromes have been described and have been broadly divided into **symmetrical polyneuropathies, with a predominance of sensory and autonomic abnormalities, an asymmetrical syndromes comprising a variety of mononeuropathies, multiple mononeuropathies and radiculopathies**.

a) Symmetrical sensory polyneuropathy

Often no symptoms - **loss of vibration sense and ankle jerks**. May be paraesthesiae in feet and less often in hands. Painful stabbing or burning pain, especially in feet may occur. With severe distal sensory neuropathy, Charcot's arthropathy may occur and, in association with impaired circulation, neuropathic ulcers may develop. Phenytoin, carbamazepine and motival may be of use in treatment of painful neuropathy.

b) Autonomic neuropathy

Signs of autonomic neuropathy are not uncommon but symptoms are very rare. Pupillary responses may be sluggish (rarely Argyll Robertson), postural hypotension, abnormal sweating, gastrointestinal larr oea and constipation, loss of temperature sensation, impotence and lack of awareness of hypoglycaemia can occur. May respond to improved diabetic control but also may resolve spontaneously. **Otherwise treatment is symptomatic.**

c) Mononeuropathies

— . 1 C. K

Isolated cranial nerve palsies - especially III, IV and VI. Occasionally affects sites of nerve entrapment e.g. ulnar, median or radial nerves. Often spontaneous recovery. Diabetic amyotrophy causing weakness of hip muscles, often with extensor plantar response and raised CSF protein. Usually responds to good control of diabetes.

4. SKIN CHANGES

- a) Pyogenic infections - carbuncles
- b) Candidiasis - oral, vaginal, paronychia
- c) Necrobiosis lipoidica
- d) Xanthomata

5. DIABETIC ULCERS

Seen in feet. Either due to neuropathy and/or macrovascular disease. Major cause of morbidity which, in neuropathic feet, is potentially avoidable. Diabetic patients need regular chiropody. Foot disease is the commonest cause of hospital admission among diabetic patients. Diabetes remains the major cause of lower limb amputation in U.K.

Diabetes under 2 years of age is rare, but peaks of incidence occur at 5 and 11 years. By **age 16 years, about 0.2% (2 per 1,000)** children are diabetic.

Presentations in children

Ketoacidosis
Bed wetting
Weight loss, thirst, polyuria

Management

Team approach: paediatrician/diabetic specialist, nurse specialist/health visitor, dietitian, psychologist.

Diet: **adapted to activities, daily routine, acceptability and growth.**

Insulin: 0.5-0.75 units/Kg body weight. Often given once daily in early childhood.

Monitoring: Diary of BM tests at home. HbA_{1c}. Height and weight charts.

Particular problems: children do not like needles or diet. Illness and clinic visits = missed school. Diabetic control: hyper and hypoglycaemia. Psychological difficulties: the over-protected child. Manipulative behaviour. Puberty. **The chronic complications of diabetes are not seen in childhood.**

A View of Diabetes in Adolescence

The discovery of insulin in 1922 changed juvenile diabetes from an inevitably fatal disease into a chronic treatable condition accompanied by the development of a wide variety of degenerative complications.

Whether the control of blood glucose was related to the development of chronic complications was debated over the ensuing decades. Resolution of this problem was hampered by the retrospective nature of most studies, the lack of any suitable measurement of glycaemia and the inability to normalise blood glucose long-term. As these difficulties were overcome, it became increasingly recognised that the two main risk factors for the development of diabetic complications are long duration of disease and chronic hyperglycaemia. This awareness of the importance of glycaemic control led the quest for its attainment to be one of the central themes of diabetes management.

From a simple standpoint, the blood glucose level is dependent on diet, insulin treatment (particularly 'insulinisation' of the liver) and exercise. Current fashion recommends a diet rich in carbohydrate of an unrefined nature and it may be helpful for all family members, rather than the patient alone, to adopt this policy. In general, glycaemic control is progressively improved by an increasing number of daily insulin injections, the ultimate example of this is the normoglycaemic state obtained by continuous subcutaneous insulin infusion (CSII) using pump treatment. However, most young children may obtain reasonable control on one daily injection. After age 6-8 years two injections per day are preferable.

Further refinement may be obtained using multiple daily injections for which a pen injector may be suitable. The use of pens and pumps may lead to practical problems, if used at school. Modern injection treatment is easy to use, unobtrusive and disposable. The eventual choice of an insulin regimen for any individual patient is based on trial and error and has an empirical basis.

Exercise is a feature of childhood. Management of diabetes depends on whether it is anticipated or not. **Hypoglycaemia can be prevented by extra (unrefined) carbohydrate prior to planned exercise and a reduction in the preceding soluble insulin dose.** Individual experiment is necessary. The patient/parent needs to understand the causes of hypoglycaemia (too much insulin, missed meal, exercise) and anticipate it.

The adolescent diabetic patient will require advice on the hypoglycaemic effect of alcohol in conjunction with insulin, avoidance of smoking and, for girls, on contraception.

Major problems in management may arise during the adolescent period. The rigidity and life-long nature of the regimen involving continued attention to diet, frequent finger-prick blood glucose tests and daily insulin injections may become too demanding for many patients. In addition, the authoritative nature of the clinic or doctor may be resented. 'Brittle diabetes' may result. This is a concept in which the diabetic condition is inexplicably unstable and attention and blame are given to this inherent 'instability' rather than to the patient's behaviour. The latter is often **manipulative and the diabetes may be used to avoid situations unpleasant to the patient,** such as school or unfavourable home circumstances.

Much of the management of diabetes depends on organisation and the logistics of the service provided. It is my personal view that specialist clinics for diabetic children are helpful (though not mandatory) for the concentration of all the ancillary services that may be needed, including liaison nurses, dietitians and educational aids. **Co-operation between 'adult diabetologist' and interested paediatrician should help to increase the awareness of aspects of each others practices and aspirations, lead to an exchange of ideas, smooth the progress of patients** from the children's to the adult clinic and, above all, reduce default rate during the adolescent handover period.

The management of the adolescent diabetic child hinges on the practical application of theoretical knowledge and a judicious balance between optimism and pragmatic reality. Despite all the effort expended, using glycated haemoglobin as a measure of glycaemic control, most diabetic children obtain a **mediocre degree of control; while some achieve an appallingly poor degree of control.** Excellent control is usually only evident in the first year or two after diagnosis and this may be related to some remnant endogenous insulin secretion.

Children with diabetes remain a difficult management problem, and it should not be forgotten that after graduation from the **paediatric department, they must continue to struggle with their chronic condition hopefully avoiding the chronic complications with which many of them will be inevitably faced.**

DIABETES - ACUTE COMPLICATONS

DR. P.G. WILES

HYPOGLYCAEMIA : Very common
DIABETIC KETOACIDOSIS : Common
HYPEROSMOLAR NON-KETOTIC COMA : Rare
LACTIC ACIDOSIS : Extremely rare

Emergency distinction of the unconscious coma patient

Hypoglycaemia	DKA
Cold, clammy skin	Warm, dehydrated
tachycardia	Increased respiration
	If conscious level impaired, patient is very ill.

Check B.G. with a stick or meter

If unsure: GIVE DEXTROSE OR SUGAR

NEVER GIVE INSULIN

HYPOGLYCAEMIA

Causes: *Insulin:*

- 1) given without food or with meal delayed.
- 2) Extra *insulin* (overdose) usually accidental, sometimes deliberate.

Sulphonylureas (especially chlorpropamide and glibenclamide)

Exercise

Alcohol

Variation in absorption eg hot bath, sauna, exercise

Variation in injection site

Variation in insulin/mixing/brand

Symptoms Paraesthesiae
Blurred vision, diplopia
Altered conscious level, seizures

Signs: Pallor, tachycardia, sweating, cold skin, impaired
conscious level and *coordination*.
May appear drunk

Treatment

Patient can swallow: Oral dextrose, sugar (rapidly absorbed
carbohydrate) followed by longer acting carbohydrate.

Patient *cannot* swallow: IV Dextrose
SC/IM glucagon

Insulin taking patients may be discharged home once fully conscious with
stable blood glucose, sulphonylurea patients require overnight admission.

DIABETIC KETOACIDOSIS - DKA

Medical emergency which demands treatment in hospital. Mortality rate still 3-10% which increases with age and delayed treatment.

Precipitating factors:

Infection
Myocardial infarction
Trauma
Errors in insulin dose
Surgery
Deliberate mismanagement

Symptoms

Vomiting	Dehydration
Thirst	Tachycardia
Weakness	Dry skin
Weight Loss	Hyperventilation
Abdominal pain	Abdominal pain
Visual disturbances	Acetone on breath
Leg cramps	Reduced conscious level

Diagnosis

History and examination
Hyperglycaemia
Ketonuria
Acidosis

Laboratory findings-:

Hyperglycaemia
Dehydration
Metabolic acidosis

Plasma	glucose	high
	bicarbonate	low
	potassium	normal or high initially
	sodium	high
	urea	high
arterial	pH	low
	P02	usually normal
	PC02	base deficit
venous	PCV	- high
	WBC	- high

Management

1. Brief history and examination
2. Insert airway if unconscious
3. Start i.v. infusion of 0.9% NaCl (see below)
4. Remove blood for FBC, glucose, urea and electrolytes, blood culture and arterial blood gases.
5. Start insulin treatment (see below)
6. N/G tube if vomiting
7. Monitor urine output and send MSU when available
8. ECG monitor

9. Consider use of antibiotics
10. ECG + CXR
11. Consider low dose heparin
12. oxygen if hypoxaemic

Rehydration and correction of electrolyte losses

0.9% NaCl

First hour 1-2 litres

Second hour 1 litre

Third-sixth hour continue 0.9% NaCl

When BG falls to about 12 mmol/l, change to 5% or 10% dextrose

Reduce infusion rate if risk of heart failure, consider CVP line

Potassium

NOT straight away,

Add 20 mmol/l (1.5G KCL) to third and subsequent bags of 0.9% NaCl

Monitor serum K and ECG

Bicarbonate

Rarely required

2. Insulin Therapy

Actrapid MC (Adults i.v. infusion 4-6 u./hr

or other (or 1m 10 u. stat., 6 u./hr

Short-acting

insulins (Children 1m 0.25 u./kg stat., 0.1 u./Kg/hr

(or infusion 0.1 u. /kg/hr

When plasma glucose <12 mmol/l, reduce insulin to 1-2 u/hour - but DO NOT STOP at any stage.

Continue i.v. insulin while ketonuria is present. May be required for 2-4 days.

HYPEROSOLAR NON-KETOTIC SYNDROME

More frequently in elderly and West Indians. Mortality may be high as 50%. Its features include hyperglycaemia, hypernatraemia and uraemia in the absence of plasma and urinary ketones and acidosis. Osmolality calculated by $2(\text{Na} + \text{K}) + \text{urea} + \text{glucose}$ (Normal = 280 mOsm/l) and hyperosmolar when greater than 350 mOsmol.

Management: fluid and insulin replacement as for ketoacidosis though consider use of 0.45% saline. Heparin infusion and prostacyclin may be needed for prevention or treatment of thrombosis or gangrene.

LACTIC ACIDOSIS

This is a rare complication associated with biguanide therapy in older patients. The normal plasma lactate is about 1mmol/l, but may rise to >5mmol/l with resultant acidosis with severe systemic upset e.g. infection, pancreatitis, renal or liver failure. Management involves reversing acidosis and treating the underlying cause. The outcome is often fatal.

Stop metformin in diabetic patients who have a myocardial infarction.

PREGNANCY

The outcome of diabetic pregnancy is one of the success stories of intensive blood glucose control. Maternal mortality is now the same as normal pregnancy. Perinatal foetal mortality is now <2% in the best centres.

Foetal morbidity and mortality (Effects of diabetes on the foetus)

Macrosomia: probably the result of maternal hyperglycaemia and foetal hyperinsulinaemia, probably most often seen in unrecognised gestational diabetes.

Respiratory distress syndrome (RDS): a feature of 'immaturity'.

Hypoglycaemia: the result of fetal islet hyperplasia and excess insulin production, i.e. poor control of maternal diabetes in the late stages of pregnancy and labour.

Hyperbilirubinaemia: immature liver enzymes

Hypocalcaemia: mechanism unknown

Congenital malformations: Now account for 40% of perinatal mortality. Cardiac and neural tube defects are particularly common (3x more than normal). Sacral agenesis is rare but typical of diabetic pregnancy. Prevention of anomalies requires good control in the weeks immediately before and after conception. Hence the need for preconception counselling to improve diabetic control (normalise blood glucose).

Obstetric factors (Effects of diabetes on the pregnancy)

Pre-eclampsia: increased prevalence in diabetic pregnancy.

Polyhydramnios: increased prevalence. May cause premature labour.

stillbirth/intrauterine death: Classical diabetic complication occurring in last weeks of pregnancy.

Placental dysfunction: caused by microvascular changes. Monitored by sequential urinary oestriol measurements. Causes poor foetal growth and may require urgent delivery.

Difficult labour/disproportion/abnormal presentation: can occur as a result of macrosomia.

Pyelonephritis: may cause ketoacidosis. Pyelonephritis adversely affects perinatal mortality.

Effects of Pregnancy on established maternal diabetes

Renal glycosuria: tends to occur in all women in first trimester.

Increased insulin requirements: during second and third trimester up to 34/36 weeks. Then may decline. These changes reflect placental steroid output.

Retinopathy and nephropathy may worsen: screen for treatable retinopathy. Renal failure may require early delivery. Diabetic renal disease is still a relative contraindication to pregnancy.

Retoacidosis: causes foetal death.

Gestational diabetes mellitus (GDM)

Diabetes present only during pregnancy. GDM is common. Incidence rises after 16 weeks, steeply after 24 weeks. Diagnosis is by 75g oral glucose tolerance test (GTT) but the precise diagnostic criteria are the subject of debate. During pregnancy 'impaired glucose tolerance' should be regarded and treated as diabetes.

GTT is indicated for:

- Glycosuria
- GDM in previous pregnancy
- Obesity
- Previous stillbirth/perinatal death
- Previous baby > 4 kg
- Polyhydramnios
- Strong family history of diabetes

Some cases of GDM are missed on **these criteria.**

Treatment: Dietary restriction alone achieves normoglycaemia in a few but most need insulin. Give insulin if blood glucose persistently >4.5 mmol/L. Avoid oral hypoglycemic drugs because of their teratogenic effects.

Untreated GDM results in the same foetal problems as established diabetes.

Perform GTT at post-natal visit (6 weeks post-partum) to be sure that diabetes was gestational. GDM increases the likelihood of developing type II diabetes in later life.

Plan of management

Regular frequent antenatal monitoring. A combined obstetric/diabetic clinic (as at LGI) is best. Patients should do BM tests (finger-prick blood sugar measurement by glucose oxidase strip) at home 3-4 x daily and record a diary of results. Aim for blood glucose 4.5 mmol/L pre-prandially, and normal glycosylated haemoglobin (HbA1c). Anticipate rising insulin requirement in 2nd and 3rd trimester (may double) but insulin dose may fall in the last few weeks. Ensure healthy diet. Allow spontaneous labour at term if no specific obstetric/diabetic indication for earlier delivery. Diabetes alone is no longer an *indication* for early delivery.

During labour: tight blood sugar control by insulin infusion pump. Insulin requirements fall to pre-pregnancy levels at delivery (GDM patients stop insulin). Breast feeding encouraged. Diabetes with vascular/renal problems are higher risk pregnancies.

GP management: Diabetics are not good candidates for shared care. GPs need to refer diabetics early for pre-conceptual counselling. In patients whose *ante-natal* care is shared, GPs need to watch out for GDM.

Management during surgery

A. Non-insulin dependent: diet alone

For minor surgery, if well-controlled (plasma glucose < 7 mmol/l) manage as non-diabetic. Avoid glucose infusions over operative period. **Check blood glucose regularly and if necessary give insulin as in C.**

B. Non-insulin dependent: oral hypoglycaemics

Stop oral agent (for at least 3 days if on chlorpropamide) and assess blood glucose control on diabetic diet. Management thereafter as in A for minor surgery. Use insulin for major surgery. Avoid biguanides (lactic acidosis).

C. Insulin-dependent:

Either:

- i) sc insulin and i.v. glucose (suitable for minor ops and uncomplicated surgery)

or

- ii) **i.v. glucose - insulin - potassium (suitable for all ops and treatment of choice for emergency surgery, or lengthy and complex surgery) but requires more cooperation from anaesthetists and surgeons.**

i) S.C. insulin and i.v. glucose

Preparation Switch to 2-3 x **daily short/medium acting insulin.** Usual diabetic diet. Control diabetes by blood glucose measurement.

Operation Start 5% or 10% glucose i.v. (1 litre/8 h) on morning of operation and continue until patient is eating normally. Give 1/2- 1/3 usual daily dose of insulin as actrapid M.C. at 0800 h on day of operation. Check plasma glucose

- a) before operation,
- b) during operation,
- c) at 0700, 1100, 1500, 2100 h until diabetes stable on oral intake.

ii) Glucose-insulin-potassium therapy

on day of operation, at 0800 h start i.v. infusion, one litre of 5% or 10% dextrose containing 8-16 i.u. Actrapid plus 13.5 mmol k + (1 g KCl). Infuse over 8 h. **Check blood glucose hourly if level is:-**

- a) **4-10 mmol/l continue as above**
- b) 2-4 mmol/l reduce insulin dose
- c) > 10 mmol/l increase insulin dose

An insulin infusion pump can be used, if available, and should be used for complex surgery (especially cardiac bypass surgery) or when post-op recovery is likely to be lengthy.

Monitor blood glucose and potassium regularly. When eating normally, revert to normal sc qds insulin. **Remember that prolonged infusion of dextrose will cause hyponatraemia.**

Contraception

Generally advice is as for non-diabetics. Combined low-dose oestrogen-progesterone or progesterone-only pill may be used (care with previously GDM patients). **All young diabetic girls should be warned of the need for adequate contraception and of the potential problems of unplanned pregnancies if their diabetes is not well controlled.**

Impotence

Affects 50% or more of male patients due to arteriosclerotic disease, autonomic neuropathy or both. There is no cure and testosterone levels are normal. Management is by counselling of patient and partner and use of either intracorporeal papaverine injections, vacuum-tumescence devices or implantable prostheses.

Driving

Insulin-taking diabetic patients must inform the DVLC and their insurance company that they are taking insulin. **Patients should be advised to avoid driving for the first month of insulin therapy.** Insulin taking diabetic patients may not hold an HGV or PSV licence. Patients should keep a supply of sugar or sweets readily available in the car.

Occupation

There are a few occupations which insulin-taking patients are denied. It is generally preferable for patients to tell their employers and colleagues of their diabetes as this avoids later problems.

Travel

Patients should travel with ample supplies of insulin and equipment (and a letter explaining the medical need for such items). Lengthy journies, especially with time shifts, may need supplementary doses of insulin. Insulin will keep for many months at room temperature but extreme heat and direct sunlight should be avoided, as should freezing (insulin must not be left in the luggage hold of aircrafts). Vaccinations may be given as for non-diabetics. Avoid hypoglycaemia during travel - it frightens all around!

Sport

Increased activity lowers blood glucose therefore insulin dose may be reduced or carbohydrate intake increased (or both) according to type and time of activity. Hypoglycaemia must be avoided during dangerous, isolated activities therefore diabetics are normally advised to avoid parachuting, diving, rockclimbing, etc.

CATECHOLAMINES

The biosynthesis distribution and metabolism of the three primary catecholamines; adrenaline, noradrenaline and dopamine will be reviewed briefly. The presentation, diagnosis and treatment of pheochromocytoma will be described. The role of endogenous dopamine as a vasodilator and natriuretic will also be discussed.

Reference

Pheochromocytoma by A. Goldfien in Clinics in Endocrinology and Metabolism, Volume 10. Number 3, November 1981. Pages 607-630

POSTERIOR PITUITARY HORMONES AND RELATED DISEASES

The two hormones secreted by the posterior pituitary are oxytocin and arginine vasopressin (AVP - the antidiuretic hormone in man). Both are nonapeptides differing in amino acid sequence at only 2 positions. Both hormones are synthesised within the supraoptic and paraventricular nuclei within the hypothalamus. They are transported from the hypothalamic nuclei to the posterior pituitary by axonal flow. Each hormone is transported bound to a specific carrier protein - the neurophysins. The hormones are released from the nerve terminals within the posterior pituitary into the circulation, together with the neurophysins. Neither hormone is significantly protein bound in the circulation.

Oxytocin MW 1007

Oxytocin in the female stimulates uterine contraction and promotes the ejection of milk from the breast ('let-down' reflex). The role of oxytocin in the male is obscure but may be concerned with sperm transport.

Pathophysiology

No syndrome of oxytocin deficiency has been described. Excessive secretion by tumours (oat-cell carcinoma of the lung) has been described but always in association with excess AVP secretion. Iatrogenic excess of oxytocin (syntocinon drip for induction of labour) may be complicated by water retention (homology with AVP).

Arginine Vasopressin (AVP) MW 1084

AVP increases the permeability of water to the renal collecting duct membrane, and hence luminal fluid is exposed to medullary hypertonicity. The principal stimuli to AVP secretion are increased extracellular osmolality and decreased extracellular volume; when in opposition volume is maintained at the expense of tonicity.

High pharmacological doses of AVP induce severe vasoconstriction and have been used therapeutically to control bleeding oesophageal varices. The measurement of AVP is difficult but bioassays and radioimmunoassays have been developed.

Pathophysiology

A. Diabetes insipidus (D.I.) Both AVP deficiency and resistance of the collecting duct membranes to the action of AVP will result in an inability to concentrate urine. The symptoms are therefore polyuria and polydypsia and the differential diagnosis includes diabetes mellitus, chronic renal failure and primary polydypsia.

Lack of AVP secretion (pituitary D.I.) may be familial (very rare) or secondary to hypothalamic or pituitary disease.

1. Trauma: surgery or following head injury
2. Granulomata: sarcoid, histiocytosis X
3. Infection: syphilis, TB
4. Tumours: primary e.g. craniopharyngioma; secondary e.g. carcinoma of the breast.

Failure of the kidney to respond to AVP (nephrogenic DI) may also be familial or secondary to:

1. Severe hypokalaemia
2. Hypercalcaemia
3. Relief of obstructive nephropathy
4. Drug induced (lithium and demeclocycline (a tetracycline antibiotic)).

Diagnosis - Water deprivation test

Free access to fluid before the test

Patients may eat solid food during the test but no fluids allowed.
No smoking, no drugs.

Urine samples

Pass hourly or as near to this frequency as possible. Measure volume and record. Save aliquot for osmolality measurement

Plasma samples

Collect plasma sample at the beginning and on completion of test For osmolality and electrolyte measurement.

Weight

Weight at the beginning of the test and following each voiding

Begin at 09.00 with baseline urine and plasma samples and patients weight.

If weight loss exceeds 5% of baseline weight stop this part of the test.

At 17.00 if urine concentration does not exceed 600 mosm/kg with plasma osmolality greater than 290 mosm/kg proceed to administer 4 ug I.M. desmopressin (long acting ADH) **Collect aliquots of all urine passed over next 16 hours for osmolality.** During this period patients allowed access to fluids.

Interpretation

Following desmopression, urine osmolality:-

exceeds 600 mosm/kg = pituitary DI
fails to exceed 600 mosm/kg = nephrogenic DI

It may prove difficult to differentiate primary polydypsia from nephrogenic DI, however the former often have an initial plasma osmolality less than 275 mosm/kg.

Treatment

Pituitary DI: = Desmopressin intranasally or by S.C. injection

Nephrogenic DI: = **Paradoxically thiazide diuretics may reduce polyuria by inhibiting the function of the diluting segment of the kidney.**

B. Water Overload and Intoxication

A wide variety of condtions may promote antidiuresis and hence, with continued fluid intake result in a water overloaded state and dilutional hyponatraemia. Main causes are:

1. Tumours secreting AVP - e.g. oat cell carcinoma of bronchus
2. CNS disorders - e.g. meningitis, brain abcess
3. Lung disease - e.g. pneumonia, lung abcess
4. Drugs - e.g. morphine, chlorpropamide, carbamazepine, syntocinon
5. Response to trauma. Antidiuresis is common following surgery.

The pathophysiology of water overload is poorly understood. Not all causes are associated with raised circulating levels of AVP. The diagnosis is dependent on the demonstration of hyponatraemia, plasma hypo-osmolality, failure to maximally dilute the urine or conserve sodium, and the absence of renal, adrenal, thyroid or **pituitary disease**. Symptoms are variable. Rapid onset (water intoxication) is associated with confusion, convulsions, coma and death. Chronic onset may be symptomless.

Treatment

Acute water intoxication requires immediate restriction of water intake and hypertonic saline infusion to restore plasma osmolality. Chronic hyponatraemia may be controlled with water restriction.