School of Medicine

Year 1, 2012/13

## Endocrinology

Spring term course guide



The Dwarf Francisco Lezcano, called "El Nino de Vallecas" by Diego*Velazquez*

Course Leaders:

**Dr Niamh Martin** and **Professor Karim Meeran**

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https://education.med.imperial.ac.uk

ENDOCRINOLOGY

**Year 1 Spring term course guide**

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**SOLE FEEDBACK – year 1 Endocrinology**

The following pages provide you with templates on which you can record your thoughts as the course proceeds. At the end of the course you can enter your views onto SOLE.

**Please answer all questions by selecting the response which best reflects your view.**

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|  | Strongly Agree | Agree | Neutral | Disagree | Strongly Disagree |
| The content of this module is useful. |  |  |  |  |  |
| The support materials available for this module (e.g. handouts, web pages, problem sheets) are helpful. |  |  |  |  |  |
| I receive sufficient feedback and guidance. |  |  |  |  |  |
| Overall, I am satisfied with this module. |  |  |  |  |  |

Please use this box for constructive feedback and suggestions for improvement.

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**SOLE FEEDBACK - INDIVIDUAL LECTURERS**

Please note that for SOLE, a Lecturer’s name will only appear once. This template gives you the opportunity to record your comments about each lecture in the order of delivery.

**On the following section, you have an opportunity to record any comments and constructive feedback you have for each lecturer.**

|  | **The lecture(s) are well structured** | | | | | **The lecturer explains concepts clearly** | | | | | **The lecturer engages well with the students** | | | | |
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| **Lecturer and Lecture Title** | Strongly Agree | Agree | Neutral | Disagree | Strongly Disagree | Strongly Agree | Agree | Neutral | Disagree | Strongly Disagree | Strongly Agree | Agree | Neutral | Disagree | Strongly Disagree |
| <Prof. Karim Meeran>  <Thyroid Disorders> |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| <Lecturer>  <Lecture B> |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
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| **Lecturer and Lecture Title** | **Please use this box for additional constructive feedback.** |
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Endocrinology

**INTRODUCTION**

The Endocrinology course is taught in the Spring Term of year 1 and the Autumn/Spring terms of year 2.

Endocrinology is the study of endocrine glands and their chemical products, called hormones, which are released directly into the bloodstream. It is one of the body’s two principal communication systems (the other being the nervous system).

The endocrinology system course runs across the first two years of the undergraduate medicine curriculum. In the first year (second term) there are six sessions which cover basic scientific aspects of important components of the endocrine system and relate them to important clinical disorders which can result from specific endocrine defects.

The endocrine glands to be considered include the hypothalamo-pituitary axis, the pancreatic Islets of Langerhans (the source of insulin) and the most common of all endocrine disorders diabetes mellitus, the thyroid, the adrenals, the gonads and the parathyroid glands. During the second year (first term) the focus is more on the clinical disorders associated with these endocrine glands, and includes methods of diagnosis and broad consideration of treatments currently available (particularly pharmacological and drug therapeutics aspects).

The structure of most sessions will be lecture presentations (many of them multi-teacher) and tutorials. The tutorials will provide an opportunity to go over specific aspects of the lectures maybe requiring clarification and expansion, and to consider case histories. An opportunity for self-assessment will also generally be included in many sessions, with examples of true/false questions provided. These will also be available on the intranet.

All sessions will include tutorials run in sequence. The two tutorial groups (groups 1 and 2) will follow each other as indicated in the tutorial timetable, each tutorial running for approximately 30 min.

There will also be further opportunity to study endocrinology during clinical rotations and specialties as well as more in-depth study during the BSc. Endocrinology Pathway that will offer various endocrinology modules.

**COURSE STRUCTURE**

There are 12 lectures and 6 tutorials.

**ASSESSMENT**

**Formative Assessments**

Endocrinology will be assessed formatively in a peer-marked short answer (PMSA) question session. SBA questions can be assessed online.

**Summative Assessment**

The course will be examined in a single examination: Endocrinology Paper 3 LCRS (90 min) in June 2013. The questions will be SBA/ SAQ/EMQ

Further details about examinations are provided on the Intranet.

**Niamh Martin and Karim Meeran August 2012**

**BLACKBOARD**

We are also including the guidebook MCQs as quizzes to help you with your revision and understanding on Blackboard. This will enable you to look at questions at your leisure and obtain the answers directly. Instructions as to how to use Blackboard are given below.



Click on the Blackboard icon, or <https://bb.imperial.ac.uk>

* Put in your username and password (i.e. your normal username and password).
* Click on year Discussion Boards (Year 2 - 2012-2013).
* Click on the icon “Assessments” in the left hand column.
* A list of quizzes will appear.
* Click on the title of the quiz to run it.
* Read the instructions which will tell you how long you have for the quiz.
* Turn off any popup blocking software.
* Press “begin assessment”.
* Answer each question.
* Click on Save and view next

You can answer the questions in any order, and when you do the last one, it will go back to question 1 to give you another chance to change your answer.

* Click on Finish when you have finished.
* Click on OK.

You can view your answers and the correct answers.

**Discussion board:**

Once logged in, click on “Discussions” to ask or answer a query. This is a really good way to learn. Niamh Martin and I will regularly check this during the course, but it is hoped that queries will be answered by students as well.

*Karim Meeran*

August 2012

Learning objectives – Year 1 (2012/13) Spring term

These session objectives may include tasks you should be able to carry out after you have completed the relevant activity. They provide you with a way to assess how well you are keeping up with the material. Note that they are also provided to the external examiners as a guide to what you should know at the end of the course.

**Lecture 1 Introduction to endocrinology (Dr. Chris John)**

* Define the terms hormone, endocrine gland, neurotransmitter and neurosecretion.
* Identify the features which distinguish endocrine from paracrine and autocrine systems.
* State that most hormones can be classified either as protein (and polypeptide) or steroid hormones, but that a few do not fall easily into either of these two groups and therefore form a third group.
* Describe the principal stages of protein/polypeptide hormone synthesis, how they are stored and the mechanism of their secretion into the circulation.
* Describe the different types of membrane receptor and the intracellular mechanisms of action induced by hormones.
* Explain how steroid hormones are synthesised and released into the circulation.
* Describe the receptors and mechanisms of action of steroid hormones.
* Define the terms negative and positive feedback and explain how any individual hormone system is controlled.

**Lecture 2 Hypothalamo-adenohypophysial axis (Prof. John Laycock)**

* Draw a labelled diagram showing how hypothalamic hormones reach their target cells in the adenohypophysis (anterior pituitary) using the terms hypothalamic nuclei, neurosecretions and hypothalamo-hypophysial portal system.
* Identify the six chief adenohypophysial hormones and relate them to the hypothalamic hormones which control them, indicating whether the latter hormones stimulate or inhibit their production.
* Describe the general features of synthesis, storage and release of the adenohypophysial hormones, including the pre-prohormone and prohormone stages when relevant.
* Describe the principal physiological actions of corticotrophin (ACTH), thyrotrophin (TSH) and the two gonadotrophins (LH and FSH).
* Draw a diagram illustrating direct, indirect and short negative feedback loops, using the hypothalamo-adenohypophysial-thyroidal axis for your example.
* Describe the growth promoting and metabolic actions of somatotrophin (growth hormone).
* Draw a labelled diagram illustrating the various controlling influences on somatotrophin release.
* List the various actions of prolactin indicating which one is its principal physiological effect.
* Draw a labelled diagram illustrating how prolactin release is controlled, using the term neuroendocrine reflex arc.
* Explain why hyperprolactinaemia is associated with a contraceptive effect on the reproductive system

Lecture 3 The hypothalamo-neurohypophysial system (Prof. John Laycock)

* Draw a simple labelled diagram identifying the principal features of the neurohypophysial system.
* Name the two neurohypophysial hormones and indicate how their chemical structures differ.
* Describe the principal steps involved in the synthesis, storage and release of the neurohypophysial hormones.
* Name the receptors for vasopressin and the major intracellular pathway activated through each receptor.
* Name target cells for each of the vasopressin receptors.
* List the principal physiological actions of the neurohypophysial hormones.
* Relate the actions of the hormones to their receptor types.
* Draw a labelled diagram illustrating the principal physiological action of vasopressin on renal water reabsorption.
* Describe the control systems involved in the production of the neorhypophysial hormones
* Draw a simple diagram illustrating the neuroendocrine reflex arc for oxytocin.

**Lecture 4 Insulin secretion and intermediary metabolism (Dr. Stephen Robinson)**

* Explain why the blood glucose concentration is closely regulated and list the hormones that control it.
* Draw a labelled diagram illustrating the relationship between the different types of cell in the islets of Langerhans.escribe the endocrine pancreas.
* Give an overview of the principal metabolic pathways for carbohydrates, proteins and fats, and the hormones that regulate these pathways.
* Describe the structure of a typical islet of Langerhans, identifying the different cellular components and their principal endocrine secretions.
* Describe the main features of insulin synthesis, storage and secretion.
* List and describe the principal actions of insulin
* Discuss the insulin receptor and its function.
* Draw a labelled diagram illustrating the factors which regulate the release of insulin.
* Describe the synthesis, storage and secretion of glucagon.
* List and describe the principal actions of glucagon.
* Draw a labelled diagram illustrating the factors which regulate the release of glucagon.
* Describe in your own words what the diagnosis of diabetes means to patients (video)
* Describe the beta-cell sensing mechanism of glucose
* Describe the endocrine regulation of intermediary metabolism

**Lecture 5 Diabetes mellitus (introduction) (Dr. Stephen Robinson)**

* List the principal signs and symptoms of diabetes mellitus, and relate them to the underlying pathophysiology.
* Distinguish between Diabetes Mellitus types 1 and 2.
* Explain the aetiology of type 1 diabetes mellitus.
* Define insulin resistance and explain how it is related to diabetes, dyslipidaemia, hypertension and ischaemic heart disease.
* Describe the consequences of insulin resistance on glucose, lipid and protein metabolism
* Describe the physiology and risks of obesity.
* Describe the pathophysiology of type 2 diabetes

**Lectures 6 and 7 The thyroid and iodothyronines (Prof. John Laycock) and thyroid disorders (Prof. Karim Meeran)**

* Describe the anatomy of the thyroid and the structure of the follicles.
* List the main hormones produced by the follicular and parafollicular cells of the thyroid.
* Describe by means of a labelled diagram the principal features of iodothyronine synthesis, storage and release.
* Describe the physiological actions of the iodothyronines.
* Explain the mechanism(s) of action of the iodothyronines.
* Describe the control mechanisms of iodothyronine production with particular reference to the hypothalamo-pituitary-thyroidal axis.
* Describe the principal clinical effects of excess circulating iodothyronines, and name the condition described.
* Describe the principal clinical effects associated with a deficiency in circulating iodothyronines, and name the condition described.
* Understand the principles of treatment issues in the individual patient.

**Lectures 8 and 9 The adrenals and their hormones (Prof. John Laycock)**

Describe the anatomy of the adrenal gland, identifying the medulla and the cortical zones.

List the main hormonal products from the adrenal medulla and the adrenal cortex.

Draw simple pathways identifying the main intermediates in the synthesis of the adrenal steroids.

State that the adrenal steroids exert their main effects via intracellular receptors and genomic mechanisms.

Identify the main mineralocorticoid in humans and describe its principal actions.

Describe the control mechanisms for meneralocorticoid hormones.

Identify the main glucocorticoid in humans and describe its principal actions.

State that cortisol plays an important role in the endocrine response to stress.

Describe the principal features of the hypothalamo-pituitary-adrenal axis.

State that adrenal androgen production in women can be clinically important in conditions of overproduction.

Describe the effects of excess and deficiency of cortisol.

* Understand the principles of treatment issues in the individual patient.

Recognise the necessity for adrenal steroids for survival.

**Lectures 10 and 11 The Gonads (1 and 2) (Dr. Pat Cover, Prof. John Laycock and Prof. Glenda Gillies)**

Describe the stages of gametogenesis and the process of steroidogenesis in male and female gonads.

Label diagrams illustrating the principal structures of the testes and ovaries.

Draw simple flow charts illustrating the synthesis of progesterone, 17b-oestradiol and testosterone.

Describe the principal ovarian and endometrial changes that occur during the menstrual cycle.

### Relate the synthesis of the major gonadal steroids in males and females to the relevant hormones of the hypothalamo-adenohypophysial axis.

Describe how the cyclic production of ovarian steroids is linked to the endometrial, cervical and other changes of the menstrual cycle.

Describe the actions of the gonadal steroids in males and females.

Identify the principal features of the control systems operating on the production of the gonadal steroids, with particular reference to negative and positive feedback loops, in males and females.

Define the terms primary and secondary amenorrhoea.

List the principal causes of infertility with particular references to endocrine causes.

Name the two major functions of the testes and, with the use of a simple diagram, describe how they are regulated by the hypothalamo-pituitary axis.

With the use of simple diagrams that distinguish between the follicular (early, mid, late) and luteal phases of the menstrual cycle, summarise the endocrine regulation of ovarian function.

**Lecture 12 The endocrine control of calcium metabolism (Prof. John Laycock)**

* List the functions of calcium in the body.
* Identify the principal organs involved in calcium metabolism.
* Identify the bone cells and their functions.
* List the principal hormones which regulate blood calcium ion concentration, and their sites of synthesis.
* Briefly describe how parathormone, 1,25-dihydroxycholecaciferol (calcitriol) and calcitonin are synthesized.
* Describe the principal effects of parathormone, 1,25-dihydroxycholecaciferol and calcitonin on bone, the kidneys and the intestinal tract.
* Describe the mechanisms of action of parathormone, 1,25-dihydroxycholecaciferol and calcitonin.
* Explain how parathormone, 1,25-dihydroxycholecaciferol and calcitonin production are controlled, identifying the principal stimulus in each case.
* List the principal causes of hypocalcaemia.
* List the principal causes of hypercalcaemia.
* Distinguish between primary, secondary and tertiary hyperparathyroidism.

**Recommended reading**

Laycock J F and Meeran (K) –*Integrated Endocrinology*, 1st Edition, Wiley-Blackwell (2012)

Marshall W J: *Clinical chemistry,* 7th edition (2012)

Holt & Hanley: *Essential Endocrinology and Diabetes*, Wiley-Blackwell, 6th edition (2012)

Tomlinson S, Heagerty A M, Weetman A P: *Mechanisms of disease - an Intro. to Clin Sci,* Edited. 2nd edition (2008) – basic science and clinical content

**CONTACT DETAILS**

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Administrative support: Ms Jo Williams (FEO)

Phone: 0207 594 9803

Email: [jo.williams@imperial.ac.uk](mailto:jo.williams@imperial.ac.uk)

**Lecture 1 Introduction (a)**

Professor John Laycock

j.laycock@imperial.ac.uk

***A BRIEF HISTORY OF ENDOCRINOLOGY***

***SELECTED MARKERS INCLUDE:***

* WILLIAM HARVEY (1628) Blood is pumped around the body; discovery of circulation
* CLAUDE BERNARD (1849) Proposed concept of internal secretion
* BERTHOLD (1849) Observed loss of male characteristics in castrated cocks
* THOMAS ADDISON (1856) Documented clinical adrenal insufficiency
* BROWN-SEQUARD (1889) Self-injection of testicular extract
* BAYLIS and STARLING (1905) Coined word hormone
* BANTING and BEST (1922) Extracted insulin from pancreas
* GEOFFREY HARRIS (1955) Established link between endocrine system (pituitary) and brain (hypothalamus)
* ROGER EKINS (1960) Development of radioimmunoassays
* SALVADOR MONCADA (1987) Identified nitric oxide as a local hormone

***SOME DEFINITIONS***

* ENDOCRINE GLAND A group of cells which secrete directly into the bloodstream
* ENDOCRINOLOGY Study of and their secretions
* HORMONE The molecule secreted by an endocrine gland into - i.e. not simply a metabolite or energy substrate
* ENDOCRINE relates to hormone’s action on target cells source
* PARACRINE relates to hormone’s action on e.g. within immediate area around source
* AUTOCRINE relates to hormone having an effect on
* [CRYPTOCRINE a term devised to indicate that a hormone can have an effect within its own cell of production   
  (i.e. hidden)]

***ENDOCRINE v. NERVOUS SYSTEMS***

**ENDOCRINE SYSTEM NERVOUS SYSTEM**

* release of chemical (hormone) into • release of chemical (neuro-transmitter)
* effect can be on many target cells • effect will be restricted to those target
* spread throughout the body cells actually
* effect will take place over a (relatively) • effect will be generated within

long time-span ranging from

**“CLASSIC” ENDOCRINE GLANDS**

**MORE RECENTLY IDENTIFIED ENDOCRINE GLANDS**

**Lecture 1 Introduction (b)**

Dr. Chris John

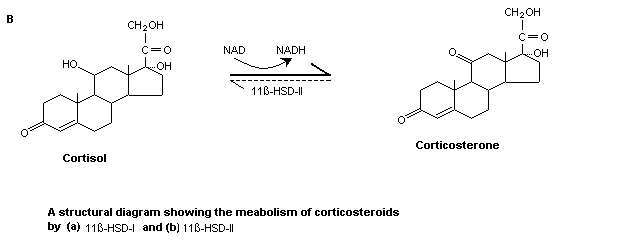
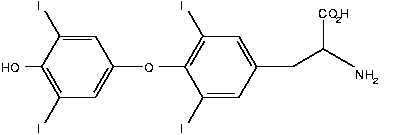
c.john@imperial.ac.uk

Learning objectives

* Define the terms hormone, endocrine gland, neurotransmitter and neurosecretion.
* Identify the features which distinguish endocrine from paracrine and autocrine systems.
* State that most hormones can be classified either as protein (and polypeptide) or steroid hormones, but that a few do not fall easily into either of these two groups and therefore form a third group.
* Describe the principal stages of protein/polypeptide hormone synthesis, how they are stored and the mechanism of their secretion into the circulation.
* Describe the different types of membrane receptor and the intracellular mechanisms of action induced by hormones.
* Explain how steroid hormones are synthesised and released into the circulation.
* Describe the receptors and mechanisms of action of steroid hormones.
* Define the terms negative and positive feedback and explain how any individual hormone system is controlled.

**Hormone Classification:**

1. Protein/polypeptide hormones
2. Steroid hormone
3. Miscellaneous



**ACTH**

39 amino acid polypeptide

Thyroxine

(Tyramine

derivative)

**TSH**

2 proteins: α is 96 amino acids; β is 112

Cortisol

(Cholesterol

derivative)

**Session 1: Introduction to the endocrine system (Dr. Chris John)**

anterior pituitary gland

adrenal gland

thyroid gland

Protein/polypeptide hormone

Stimulus

Nucleus

RER

Golgi

Vesicle

1.

2.

3.

Steroid hormone

Stimulus

1.

2.

3.

Cholesterol

Specific enzymes

1.

1.

2.

2.

Specific hormone

3.

3.

**Hormone Synthesis, Storage and Release:**

Endocrine Cell

**Lecture 2: The Hypothalamo-adenohypophysial axis**

**Hormone Transport:**

Plasma protein binding:

1.

2.

Hormone + Plasma Protein ⇔ Protein Bound Hormone

**Hormone Mechanism of Action:**

Protein/polypeptide hormone

Nucleus

Steroid hormone

1.

2.

3.

**α β γ**

e.g. ↑ Ca2+

1.

2.

3.

Protein synthesis

Target Cell

**Hormone Feedback:**

**Hypothalamus**

**Anterior Pituitary**

TRH

TSH

T3 + T4

Indirect -ve

Direct -ve

Auto -ve

Professor John Laycock

j.laycock@imperial.ac.uk

**Learning objectives**

* Draw a labelled diagram showing how hypothalamic hormones reach their target cells in the adenohypophysis (anterior pituitary) using the terms hypothalamic nuclei, neurosecretions and hypothalamo-hypophysial portal system.
* Identify the six chief adenohypophysial hormones and relate them to the hypothalamic hormones which control them, indicating whether the latter hormones stimulate or inhibit their production.
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* Draw a labelled diagram illustrating how prolactin release is controlled, using the term neuroendocrine reflex arc.
* Explain why hyperprolactinaemia is associated with a contraceptive effect on the reproductive system

HYPOTHALAMIC NUCLEI

NEURONES TO MEDIAN EMINENCE

NEUROSECRETIONS

(RELEASING/INHIBITING HORMONES

ADENOHYPOPHYSIS

ADENOHYPOPHYSIAL HORMONES



**ADENOHYPOPHYSIAL CELLS**

* SOMATOTROPHES produce SOMATOTROPHIN
* LACTOTROPHES produce PROLACTIN
* THYROTROPHES produce THYROTROPHIN
* GONADOTROPHES produce the GONADOTROPHINS
* CORTICOTROPHES produce CORTICOTROPHIN
* OTHER CELLS of undefined function

NOTE: adenohypophysial cells can also produce (and release) other molecules that may have paracrine and/or autocrine effects locally, or more distant endocrine effects

**ADENOHYPOPHYSIAL HORMONES**

* Are all protein/polypeptide hormones
* Are generally synthesized initially as precursor molecules called PROHORMONES
* Enzymatic cleavage of the prohormone can yield the bioactive hormone molecule
* The adenohypophysial hormones are stored within secretory granules and are released by exocytosis

**ADENOHYPOPHYSIAL HORMONES**

***PROTEINS:***

* *SOMATOTROPHIN (GROWTH HORMONE, GH) 191 aa*
* *PROLACTIN (PRL) 199 aa*

***GLYCOPROTEINS: consisting of  and  sub-units (92 aa  sub-unit common to all)***

* *THYROTROPHIN (Thyroid Stimulating Hormone, TSH) -sub-unit 110 aa*
* *GONADOTROPHINS both have 115 aa -sub-unit*

*- LUTEINIZING HORMONE (LH)*

*- FOLLICLE STIMULATING HORMONE* (FSH)

***POLYPEPTIDE:***

* *CORTICOTROPHIN (ADRENOCORTICOTROPHIC HORMONE, ACTH) 39 aa*

**HYPOTHALAMO-ADENOHYPOPHYSIAL AXIS**

*HYPOTHALAMIC HORMONES ADENOHYPOPHYSIAL HORMONES*

* ***somatotrophin releasing hormone***

***(SRH or GHRH))***

* somatostatin (SS)
* ***dopamine (DA)***
* thyrotrophin releasing hormone (TRH)
* gonadotrophin releasing hormone (GnRH)
* gonadotrophin inhibiting hormone (GnIH)
* corticotrophin releasing hormone (CRH)
* vasopressin (VP)

**ADENOHYPOPHYSIAL HORMONES AND THEIR MAIN TARGET CELLS**

* SOMATOTROPHIN
* PROLACTIN
* THYROTROPHIN
* GONADOTROPHINS
* (LH and FSH)
* CORTICOTROPHIN

ADENOHYPOPHYSIS

SOMATOTROPHIN

LIVER

SOMATOMEDINS

(IGF I and IGF II)

**SOMATOTROPHIN via SOMATOMEDINS**

(direct effect) (indirect effect)

`METABOLIC ACTIONS INCLUDE

* Stimulation of transport into cells

(e.g. muscle)

* Stimulation of synthesis
* Increased growth
* Stimulation of metabolism leading to increased fatty acid production
* Decreased utilization (due to increased insulin resistance) resulting in increased blood glucose concentration

Stress

Sleep (stages III and IV)

\_

exercise

+

oestrogens

\_

SS

Fasting

(hypoglycaemia)

GHRH

\_

amino acids

+

SOMATOTROPHIN

All the above STIMULATE

somatotrophin production

Negative

feedback loops

SOMATOMEDINS

(mainly IGF I)

**PROLACTIN’S EFFECTS**

HYPOTHALAMUS

sexual behaviour?

PITUITARY

(LHrelease)**Tutorial 1 Adenohypophysial disorders**

**BREAST**

**LACTOGENESIS**

**(normally post-partum women)**

Renal Na+/water

reabsorption

Effects on

IMMUNE SYSTEM

(e.g. stimulates T cells)

LH receptors

(testes, ovaries)

Steroidogenesis?

**PROLACTIN**

#### Case History

A 10-year-old boy was seen by his GP because the parents were concerned about his lack of growth which they had become increasingly aware of because his younger brother (aged 6.5 years) was already taller by 2 cm. His height and body weight were recorded as 120 cm and 25 kg respectively, giving a BMI of 17.4 kg/m2. The boy’s proportions were perfectly normal, and apart from the short stature no other abnormalities were seen on examination From the family history there was clearly no evidence of malnutrition or emotional deprivation, and the mid-parental height gave an expected height of 175 cm. The boy’s recorded height 2 years previously (according to the practice records) was 116 cm.

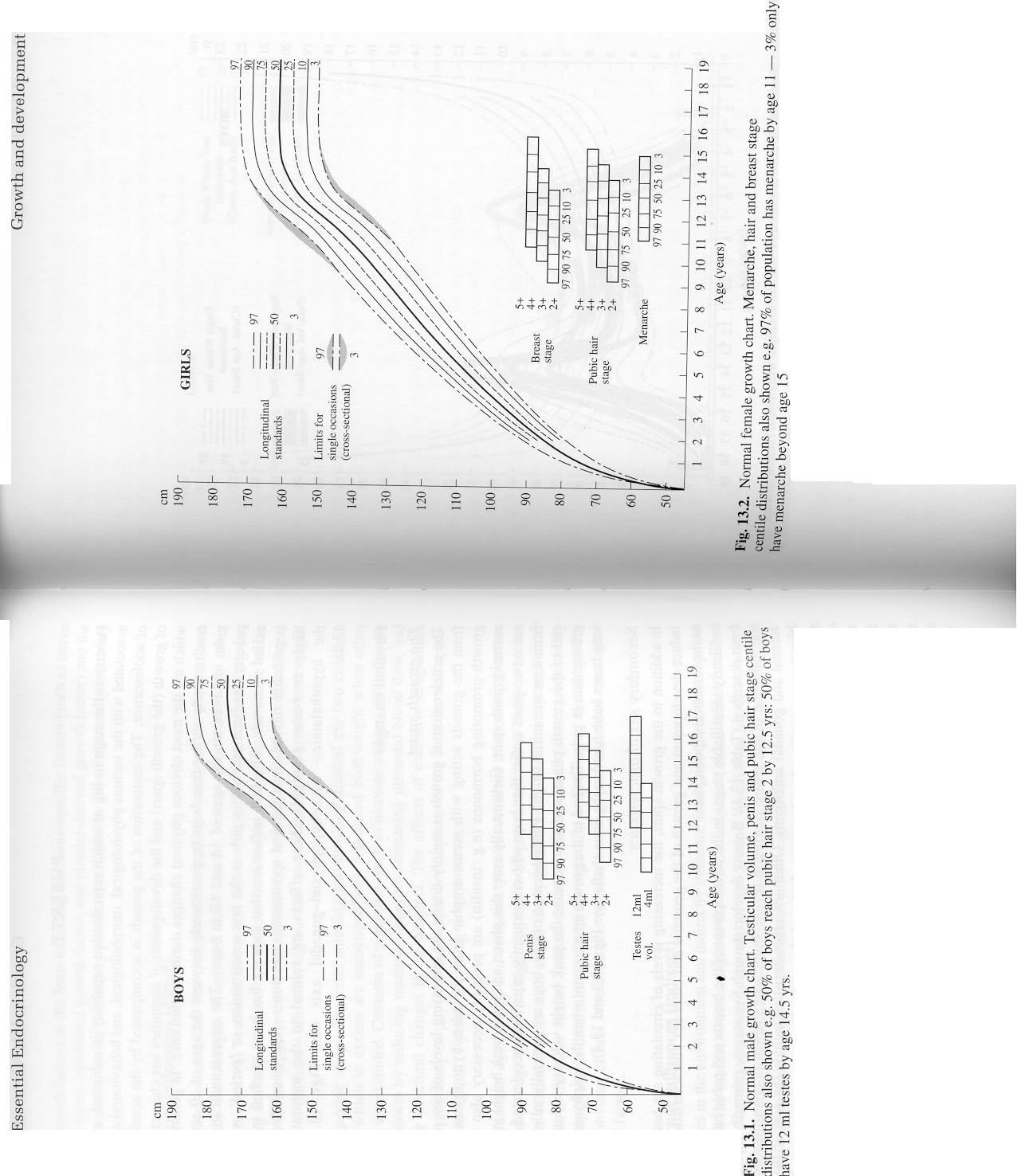
Standard growth curves are shown on the next page

***Questions:***

*1. Examine standard growth charts for boys and girls and interpret the various lines shown.*

*2. What are the various causes of short stature?*

*3. How would you design a GH stimulation test?*



**Session 1 Adenohypophysial hormones**

### 1. The following statements are correct True False

### Neurosecretion is limited to the release of neurotransmitter by a

### neurone to affect an adjacent neurone.

### Endocrine glands contain secretory granules.

### Steroid hormones are synthesised as larger precursors.

### Each hormone can only have one specific receptor.

### Protein/peptide hormones are released by exocytosis

### 2. The following statements are correct True False

### Intracellular protein kinases mediate the actions of many steroid

### hormones

### Many membrane receptors are associated with G proteins

1. Cytoplasmic calcium ions act as a second messenger system.

### Cyclic-AMP is a second messenger.

### Steroids are synthesised from cholesterol.

### 3. The following statements are correct True False

### Steroid hormones are stored in secretory granules.

### All known steroid receptors are located in the cell membrane.

### Circulating hormone levels are normally controlled by positive feedback

### Changes in blood glucose concentration and insulin release are related

### to each other by negative feedback.

1. The pituitary gland (hypophysis) consists of four lobes.

### 4. The following statements are correct True False

1. The adenohypophysis (anterior pituitary) is embryologically derived

from a dorsal growth of the buccal cavity.

1. The adenohypophysis is the source of six main steroid hormones
2. The hypothalamus exerts nervous control over anterior pituitary gland

secretory activity.

1. The principal hypothalamic influence over somatotrophin (growth

hormone) release is inhibitory.

1. All anterior pituitary hormones are polypeptides.

### 5. The following statements are correct True False

### a) Thyrotrophin releasing hormone (TRH) stimulates the thyroid gland.

1. Luteinizing hormone stimulates androgen production in the testes.
2. The adrenocortical hormone cortisol exerts a direct negative feedback

influence on corticotrophin (ACTH) production in the adenohypophysis.

1. Vasopressin stimulates the release of corticotrophin (ACTH) from the

anterior pituitary.

1. Somatostatin is synthesized in specific adenohypophysial cells.

### 6. The following statements are correct True False

1. Acromegaly is a condition in the adult associated with a lack of

circulating somatotrophin (growth hormone).

1. Prolactin release from the adenohypophysis is stimulated by

hypothalamic dopamine.

1. Prolactin stimulates post-partum lactogenesis.
2. Gonadotrophin releasing hormone stimulates the release of oestrogen from the adenohypophysis
3. Corticotrophin (ACTH) stimulates iodothyronine synthesis in the thyroid.

**Lecture 3: The Hypothalamo-neurohypophysial axis**

Professor John Laycock

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**Learning objectives**

* Draw a simple labelled diagram identifying the principal features of the neurohypophysial system.
* Name the two neurohypophysial hormones and indicate how their chemical structures differ.
* Describe the principal steps involved in the synthesis, storage and release of the neurohypophysial hormones.
* Name the receptors for vasopressin and the major intracellular pathway activated through each receptor.
* Name target cells for each of the vasopressin receptors.
* List the principal physiological actions of the neurohypophysial hormones.
* Relate the actions of the hormones to their receptor types.
* Draw a labelled diagram illustrating the principal physiological action of vasopressin on renal water reabsorption.
* Describe the control systems involved in the production of the neurohypophysial hormones
* Draw a simple diagram illustrating the neuroendocrine reflex arc for oxytocin.



**ACTIONS OF VASOPRESSIN**

* Its principal physiological action is in the renal

where it stimulates

resulting in its effect

**OTHER ACTIONS OF VASOPRESSIN**



**VASOPRESSIN RECEPTORS**

|  |  |  |
| --- | --- | --- |
|  | **V1 RECEPTORS** | **V2 RECEPTORS** |
| ● | linked via G proteins to phospholipase C which acts on membrane phospholipids | linked via G proteins to adenylyl cyclase which acts on ATP to form cyclic AMP |
| ● | to produce IP3 (and diacyl glycerol) which increase cytoplasmic [Ca2+] and other intracellular mediators | which activates protein kinase A which in turn activates other intracellular mediators |
| ● | which produce cellular response | which produce cellular response |

**VASOPRESSIN RECEPTORS**

|  |  |  |
| --- | --- | --- |
|  | **V1 RECEPTORS** | **V2 RECEPTORS** |
| *V1a*  ● | arterial smooth muscle (vasoconstriction) | collecting duct cells  (water reabsorption) |
| ● | Hepatocytes (glycogenolysis) | presently unknown sites (Factor VIII and von Willbrandt factor) |
| ● | CNS neurones (behavioural and other effects) |  |
| *V1b*  ● | adenohypophysial corticotrophs (corticotrophin production) |  |

COLLECTING DUCT CELL

TUBULE

LUMEN

PLASMA

OSMOTIC GRADIENT

ACROSS CELL

V2

VP

AC

ATP

cAMP

Activated

PKA

Other

intracellular

mediators

H2O

H2O

AQP2

Synthesis

of AQP2

Migration of aggraphores

H2O

AQP 3

AQP4

**CONTROL OF VASOPRESSIN**

Influences from higher centres, e.g. stress

+

Stimulus:

Decreased

Arterial blood pressure

baroreceptors

osmoreceptors

+

+

reduced

inhibition

Stimulus:

Increased

plasma

osmolality

**VASOPRESSIN**

nephron

Response:

decreased

plasma osmolality

Increased water reabsorption

**ACTIONS OF OXYTOCIN**

OXYTOCIN

**NEUROENDOCRINE REFLEX ARC**

HYPOTHALAMUS

NEURHYPOPHYSIS

OXYTOCIN

**Tutorial 2: Neurohypophysial disorders**

A 27-year old woman attended her GP's surgery complaining of a continuous unquenchable thirst. She felt a constant need to drink water and consumed around 20 large glasses every day. She also kept water beside her bed since she was woken every night by her thirst. She also needed to urinate very frequently. On referral to an endocrine clinic it was found that her fasting serum glucose level was normal and no glucose was detected in her urine. She was then given a water deprivation test in which she was not allowed to drink but was asked to provide urine samples every hour. After the 11.00 am sample had been taken she was given a dose of a modified form of vasopressin (DDAVP) as a nasal spray. The osmolality of her urine samples were measured (a high osmolality representing a concentrated urine).

### typical normal person’s response

### Time Urine osmolality (mOsm/kg H2O) Urine vol (mls) Uosm UV

### 9.00 h 130 175 620 95

### 10.00h 158 180 850 70

### 11.00 h 204 140 1090 50

### 11.01 h DDAVP Administered

### 12.00 h 886 70 1180 40

### *Questions:*

### *1. What would you expect to happen to the osmolality of urine during a water deprivation test?*

### *2. Why did the osmolality of her urine rise after the administration of DDAVP?*

### *3. What could be the underlying cause of her condition?*

### *4. What further measurements could be made?*

**Session 2 Neurohypophysial hormones**

1. The following statements are correct True False
   1. Vasopressin is a neurohypophysial (posterior pituitary) hormone.
   2. Vasopressin is synthesised in the posterior pituitary.
   3. Vasopressin is a neurosecretory molecule.
   4. Vasopressin is a releasing hormone for corticotrophin.
   5. One physiological effect of vasopressin is to vasoconstrict arteriolar

smooth muscle.

1. The following statements are correct True False
   1. Vasopressin stimulates water reabsorption in the renal proximal

tubules.

* 1. The renal action of vasopressin on water reabsorption is mediated by

the intracellular messenger cAMP.

* 1. Vasopressin-stimulated water reabsorption involves the insertion of

aquaporin molecules into the basal (serosal) membranes of its target

renal cells.

* 1. Vasopressin V1 receptors are linked to the adenyl cyclase-cyclic AMP

system.

* 1. Stimulation of baroreceptors results in increased vasopressin release

into the circulation.

1. The following statements are correct True False
   1. Oxytocin is a nonapeptide
   2. Oxytocin is synthesised in the hypothalamus
   3. Oxytocin stimulates uterine myometrial contractions at labour.
   4. The efferent limb of the milk ejection reflex involves the release of

oxytocin

* 1. Oxytocin stimulates milk production during lactation

**Lecture 4: Insulin secretion and intermediary metabolism**

Dr Stephen Robinson

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**Learning objectives**

* Explain why the blood glucose concentration is closely regulated and list the hormones that control it.
* Draw a labelled diagram illustrating the relationship between the different types of cell in the islets of Langerhans. Describe the endocrine pancreas.
* Give an overview of the principal metabolic pathways for carbohydrates, proteins and fats, and the hormones that regulate these pathways.
* Describe the structure of a typical islet of Langerhans, identifying the different cellular components and their principal endocrine secretions.
* Describe the main features of insulin synthesis, storage and secretion.
* List and describe the principal actions of insulin
* Discuss the insulin receptor and its function.
* Draw a labeled diagram illustrating the factors which regulate the release of insulin.
* Describe the synthesis, storage and secretion of glucagon.
* List and describe the principal actions of glucagon.
* Draw a labeled diagram illustrating the factors which regulate the release of glucagon.
* Describe in your own words what the diagnosis of diabetes means to patients (video)
* Describe the beta-cell sensing mechanism of glucose
* Describe the endocrine regulation of intermediary metabolism



# Video comments 1

## T1DM is defined as elevated glucose where insulin is required to prevent ketoacidosis

## T2DM is more common and is a considerable health burden.

## It is defined in terms of glucose but is also related to hypertension and dyslipidaemia

## We treat to help symptoms, complications (morbidity) and mortality

# Video comments 2

## Diet is important

## Insulin can be given and we attempt to do this physiologically

## Capillary glucose monitoring (the lack of a physiological feedback loop)

## Hypoglycaemia occurs when there is imbalance between diet exercise and insulin

# WHAT’S SO SPECIAL ABOUT GLUCOSE?

## Glucose is a very important energy substrate, particularly for the CNS which relies on

## it almost entirely under normal conditions.

## If the blood glucose concentration falls much below normal levels of 4-5 mM

## (*hypoglycaemia*), then brain function is increasingly impaired.

## Below a blood glucose concentration of 2mM unconsciousness, coma and ultimately

## death can result

# THE PANCREAS

## Importance of pancreas in pathogenesis of diabetes established

**PANCREATIC ISLETS OF LANGERHANS**

Most of pancreas (98%) is associated with exocrine secretions via duct to small intestine

Small clumps of cells within pancreatic tissue (remaining 2%) are called **islets of Langerhans**





**ISLETS OF LANGERHANS**

**α-cells → GLUCAGON**

**β-cells → INSULIN**

**δ-cells → SOMATOSTATIN**













# Conclusions

## Diabetes is a common chronic condition

## Failure of feedback control of insulin has physiological and emotional effects

## Insulin stimulation pathways discussed

Insulin processing and secretion discussed

**Lecture 5: Diabetes mellitus (introduction)**

Dr. Stephen Robinson

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## Learning objectives:

## List and describe the effects of insulin across intermediary metabolism

## Describe and explain the metabolic changes in the fed and fasted state

* List the principal signs and symptoms of diabetes mellitus, and relate them to the underlying pathophysiology.
* Distinguish between Diabetes Mellitus types 1 and 2.
* Explain the aetiology of type 1 diabetes mellitus.
* Define insulin resistance and explain how it is related to diabetes, dyslipidaemia, hypertension and ischaemic heart disease.
* Describe the consequences of insulin resistance on glucose, lipid and protein metabolism

## Explain how reduced insulin action is related to T2DM

* Describe the physiology and risks of obesity.
* Describe the pathophysiology of type 2 diabetes

## Explain the metabolic changes associated with insulin induced hypoglycaemia

Insulin actions

GLUCOSE GROWTH

- ↓ HGO VASCULAR EFFECTS

- ↑ muscle uptake OVARIAN FUNCTION

PROTEIN CLOTTING

- ↓ proteolysis -PAI-1

LIPID ENERGY EXPENDITURE

- ↓ lipolysis - relation to leptin

- ↓ ketogenesis



# Glucose and Glycogen

## Glucose present in blood all time, not only after meals

## Glycogen in liver is stored glucose



Fuel stores in normal weight man

|  |  |  |  |
| --- | --- | --- | --- |
| STORE | Weight (Kg) | Energy (KJ/g) | Time |
| CHO (liver + muscle | 0.5 | 16 | 16 hours |
| Protein | 8-9 | 17 | 15 days |
| Fat | 9-10 | 37 | 30-40 days |



# The brain needs energy

## Can use

## Glucose

## Ketone bodies

## Cannot use

## Fatty acids







# Fasted state

Low insulin to glucagon ratio ↑ proteolysis

[glucose] 3.0 – 5.5mmol/l ↑ Lipolysis

↑ [NEFA] ↑ HGO from glycogen and gluconeogenesis

↓ [amino acid] when prolonged Muscle to use lipid

Brain to use glucose, later ketones

↑ Ketogenesis when prolonged

Liver

Pancreas Muscle

Adipocytes

# Fed state

Stored insulin Stop HGO,

released then 2nd phase ↑ Glycogen

High [insulin] to ↓ gluconeogenesis

[glucagon] ratio ↑ protein synthesis

↓ proteolysis

↑ Lipogenesis

Liver

Pancreas Muscle

Adipocytes

# Presentation of T1DM

## Absolute insulin deficiency

## Proteolysis with weight loss

## Hyperglycaemia

## Glycosuria with osmotic symptoms

## Ketonuria

Liver

Pancreas Muscle

Adipocytes

**Insulin induced hypoglycaemia**

↑ insulin Glucose enters muscle

↑ Glucagon ↑ HGO later with

↑ Catecholamines glycogenolysis and

↑ Cortisol gluconeogenesis

↑ Growth hormone Lipolysis increased

Liver

Pancreas Muscle

Adipocytes

**Insulin resistance**

Glucose metabolism Enough insulin to

↑ circulating NEFA suppress

Total (LDL) Chol (N or ↑) - Ketogenesis

Triglyceride (↑ or ↑↑) - proteolysis

HDL Chol (↓ or ↓↓)

Non metabolic pathways

stimulated

Metabolic actions

INSULIN

Mitogenic or growth pathway



# Presentation of T2DM

## Insulin resistance

## 60-80% obese

## Dyslipidaemia

## Later insulin deficiency

## Hyperglycaemia

## Less osmotic symptoms

## With complications

# Healthy eating or diet?

## Total calories control

## Reduce calories as fat

## Reduce calories as refined carbohydrate

## Increase calories as complex carbohydrate

## Increase soluble fibre

## Decrease sodium

# Summary

## Insulin effects across intermediary metabolism

## Insulin deficiency effect and T1DM

## Insulin induced hypoglycaemia

## Reduced insulin action and T2DM

**Tutorial 3: Diabetes Mellitus**

# Case 1

A 23-year old journalist presents with a 3-month history of weight loss. She drinks up to 3.5 litres (water, tea, lemonade) a day and passes similar volumes of urine, and wakes up at night three times to pass urine. There are no abnormal physical signs. Her urine has ++++ of glucose and ketones. Capillary glucose was 23 mmol/l.

Questions:

1. What is the diagnosis?

2. Why does she have glucose in her urine and why is she passing so much urine?

3. Why is her plasma glucose high and what would her plasma insulin concentration be if we measured it (but no need clinically)?

Case 2

# A 58 year old bus driver presents with angina pectoris due to coronary artery disease. He is overweight (Body Mass Index, BMI = 32 kg/m2). During investigation he is found to have a fasting plasma glucose of 12 mmol/l (normal FPG < 6.0 mmol/l). He is started on a diet for his diabetes

Questions:

1. What is the diagnosis and what (if we bother to measure it) is his plasma insulin concentration likely to be?
2. What are the important features of his diet? How does energy restriction help?
3. Other advice to reduce chance of morbidity?

**Session 3 The pancreatic hormones and diabetes mellitus**

1. The following statements are correct True False

a) Insulin acts to increase hepatic glucose output

b) Increased plasma amino acid concentrations stimulate insulin secretion

c) Increased plasma non-esterified fatty acid concentrations stimulate

insulin secretion

d) Two moles of C peptide are produced for each mole of insulin as

pro-insulin is processed

e) Insulin resistance is readily treated with insulin

2. The following statements are correct True False

a) Most insulin resistance is associated with abnormalities in the insulin

receptor

b) Alpha cells of the islets produce insulin

c) Insulin resistance is associated with decreased very low density

lipoprotein – triglyceride concentration

d) Delta cells in the islets produce secretin

e) Insulin stimulates the active uptake of glucose uptake into muscle

3. The following statements are correct True False

a) Glucagon acts on the liver to increase glycogen breakdown

1. A high waist to hip ratio is associated with insulin resistance
2. Leptin is produced by the brain
3. Obese people eat and expend more energy than lean people
4. Type 2 diabetes is more common than type I diabetes

4. The following statements are correct True False

a) Insulin resistance and reduced insulin secretion characterise Type 2

diabetes

b) Hyperglycaemia causes glycosuria and therefore polyuria

c) glycosuria is diagnostic of diabetes mellitus

d) Glucagon increases hepatic glucose output

e) Somatostatin inhibits insulin release

**Lecture 6: The thyroid and iodothyronines**

Professor John Laycock  
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**Learning objectives**

* Describe the anatomy of the thyroid and the structure of the follicles.
* List the main hormones produced by the follicular and parafollicular cells of the thyroid.
* Describe by means of a labelled diagram the principal features of iodothyronine synthesis, storage and release.
* Describe the physiological actions of the iodothyronines.
* Explain the mechanism(s) of action of the iodothyronines.
* Describe the control mechanisms of iodothyronine production with particular reference to the hypothalamo-pituitary-thyroidal axis.
* Describe the principal clinical effects of excess circulating iodothyronines, and name the condition described.
* Describe the principal clinical effects associated with a deficiency in circulating iodothyronines, and name the condition described.
* Understand the principles of treatment issues in the individual patient.





**IODOTHYRONINES (T3 and T4)**

1. Transported in blood ***mostly*** bound to plasma proteins

a) (>75% T3 and T4)

b) albumin (<5% T3 and T4)

c) prealbumin (15-20% T4, very small amounts of T3)

1. Only 0.05% T4 and 0.5% T3 unbound (***bioactive components***)

**IODOTHYRONINES**

1. LATENT PERIODS: T3 T4
2. BIOLOGICAL HALF-LIVES: T3 T4

**DEIODINATION OF THYROXINE**

1. is the main product of the thyroid gland
2. it is largely deioninated to the ***more bioactive*** molecule in target tissues tissues
3. can also be deiodinated in a different position to produce the ***biologically inactive*** molecule known as ( )

**MAIN ACTIONS OF THE IODOTHYRONINES**

1. INCREASE

(in most peripheral tissues, resulting in calorigenesis)

1. INCREASE PROTEIN, CARBOHYDRATE AND FAT METABOLISM

therefore important for and ; (both anabolic and catabolic metabolism influenced, the overall effect depending on the general thyroid status)

1. POTENTIATE SOME OF THE ACTIONS OF THE (e.g. tachycardia, glycogenolysis, lipolysis)
2. INTERACT WITH OTHER ENDOCRINE SYSTEMS (eg. Oestrogens)
3. HAVE EFFECTS ON

* INCREASE VITAMIN A (and retinal) SYNTHESIS



**Lecture 7: General Thyroid disorders**



Professor Karim Meeran

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Anatomy of the thyroid gland. The thyroid gland is a shield shaped gland in the neck.

Draw it below (copy the diagram):

What is the origin of the thyroid?

Where is the foramen caecum?

What is the adult thyroid weight?

How many lobes are there? Which is the largest?

What glands are found embedded within the thyroid?

What important nerve runs very close to the thyroid gland and what does it supply?

List the three problems that can occur with development of the thyroid.

What term is used to describe an individual who has irreversible brain damage caused by lack of thyroxine in foetal and neonatal life?

The thyroid follicular cell: the site of thyroxine synthesis. See John Laycock’s handout.

The thyroid gland is responsible for the synthesis, storage and secretion of thyroid hormones.

Thyroid hormones regulate growth, development and metabolic rate.

Thyroid disease affects approximately 5% of the population. Is it more common in males or females?

Primary Hypothyroidism (Myxoedema).

This is caused by primary thyroid failure.

What are the two causes of hypothyroidism?

What biochemical findings occur in an individual with primary hypothyroidism?

Thyroxine level:

TSH level:

List the features of primary hypothyroidism.

Why is treatment of hypothyroidism essential?

What is the treatment of hypothyroidism?

Thyrotoxicosis or hyperthyroidism.

What biochemical findings occur in an individual with hyperthyroidism?

Thyroxine level:

TSH level:

List the features of an overactive thyroid gland.

Watch the video of patients with hyperthyroidism and list the features below:

Graves disease causing hyperthyroidism.

**Tutorial 4: Thyroid disorders**

**Case 1.**

A 25-year old lady who had recently undergone a divorce presented to her GP. She was upset about this and wanted something to calm her down and help her to sleep. She had been very irritable for the last 18 months. On direct questioning she admitted to a history of palpitations, weight loss and sweating over the past year. Two aunts had previously undergone neck operations and she had noticed a swelling in her own neck over the past year.

On examination she had a fine tremor and looked thin. Her pulse was 112 beats per minute and her blood pressure 106/70mm Hg. She had a swelling in her neck which moved with swallowing. It was soft, extended symmetrically either side of the midline and was not tender to the touch. Her GP sent off a blood sample to the hospital to obtain measures of thyroid activity.

**Case 2.**

A 32-year old woman presented to her GP with progressive tiredness over the last 2 years since the birth of her daughter. She wanted a vitamin preparation to give her more energy. She had been let go from her job as a cashier in her local supermarket 6 months earlier because her throughput of customers had slowed down so much. On direct questioning, she admitted to being constipated, intolerant of the cold and one stone heavier than before the birth of her child. Her periods were now much heavier and lasted longer than ever. There was no illness other than ischaemic heart disease in her family.

On examination she was pale, had an increased Body Mass Index (BMI) and appeared disinterested in her GP’s questions. Her pulse was 54 beats per minute, and her blood pressure 110/75 mm Hg. She had slow relaxing reflexes but there were no other abnormal findings on examination. Her GP sent off a blood sample to the hospital to obtain measures of thyroid activity.

***Please address the following points or questions:***

1. Which of the patients above has a) an overactive and b) an underactive thyroid. Indicate the likely results of thyroid function testing in each case.

2. Outline the key clinical features that suggest the diagnosis of underactive and overactive thyroid disease in each case.

3. What anatomical structures are likely to be affected by an enlarged thyroid gland?

**Session 4 The iodothyronines and thyroid disorders**

1. The following statements are correct True False

1. The thyroid gland develops from the front of the tongue
2. The thyroid gland is situated in the neck
3. The normal adult thyroid weighs about 400 g.
4. Thyroid surgery occasionally results in change to a patient’s voice

because of damage to the adjacent parathyroid glands.

1. The thyroid gland contains five lobes.

2. The following statements are correct True False a) a) Thyroxine is synthesised from the amino acid tyrosine.

b) Thyroxine is a chlorinated molecule.

c) Thyroid follicles are made up of a centre of extracellular fluid

surrounded by follicular cells.

d) Thyroglobulin binds to about 25% of the bound thyroid hormones in

the circulation.

e) Thyronine binding protein (thyronine binding globulin) binds to about

75% of the thyroid hormones in the circulation.

3. The following statements are correct True False a) a) Less than 1% of thyroxine in the circulation is free (unbound) in the

circulation

b) T3 has a longer half life than T4

c) TSH stimulates inorganic iodide uptake by the thyroid gland.

d) TSH stimulates synthesis of thyroxine

e)TSH stimulates release of stored thyroxine

4. The following statements are correct True False a) a) The immune system can cause hypothyroidism.

b) The immune system can cause hyperthyroidism.

c) Patients with severe hypothyroidism usually have a high plasma TSH

level

d) Hyperthyroidism is associated with weight gain.

e) Hyperthyroidism is associated with an increased appetite.

**Lecture 8: The Adrenals and their hormones**

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**Learning objectives**

Describe the anatomy of the adrenal gland, identifying the medulla and the cortical zones.

List the main hormonal products from the adrenal medulla and the adrenal cortex.

Draw simple pathways identifying the main intermediates in the synthesis of the adrenal steroids.

State that the adrenal steroids exert their main effects via intracellular receptors and genomic mechanisms.

Identify the main mineralocorticoid in humans and describe its principal actions.

Describe the control mechanisms for meneralocorticoid hormones.

Identify the main glucocorticoid in humans and describe its principal actions.

State that cortisol plays an important role in the endocrine response to stress.

Describe the principal features of the hypothalamo-pituitary-adrenal axis.

State that adrenal androgen production in women can be clinically important in conditions of overproduction.

Describe the effects of excess and deficiency of cortisol.

* Understand the principles of treatment issues in the individual patient.

Recognise the necessity for adrenal steroids for survival.



**ADRENAL HORMONES**

**ADRENAL MEDULLA ADRENAL CORTEX**

*CATECHOLAMINES* *CORTICOSTEROIDS*

(80%) MINERALOCORTICOID**S**

(epinephrin)

(20%) GLUCOCORTICOIDS

(norepinephrin)

(DOPAMINE) (SEX STEROIDS)

*(mainly* ***ANDROGENS)***

****

****

**CORTICOSTEROID TRANSPORT IN THE BLOOD**

1. **CORTISOL**

% bound to corticosteroid binding globulin (CBG, also known as )

15% bound to albumin

10% free (unbound) bioactive

1. **ALDOSTERONE**

~60% bound to CBG

~40% free (unbound) bioactive

**ALDOSTERONE**

1. stimulates **reabsorption** in distal convoluted tubule and cortical collecting duct
2. stimulates **K+ and H+** , also in distal convoluted tubule and cortical collecting duct







***CORTISOL:***

***CIRCADIAN RHYTHM***

ACTH

CORTISOL

0800

2000

h

**EFFECTS OF LARGE AMOUNTS OF CORTISOL**

1. ACTION
2. ACTION
3. ACTION

All associated with decreased production of molecules such as prostaglandins, leukotrienes, histamine, etc. as well as on the movement and function of leukocytes and the production of interleukins

**Lecture 9: Adrenal Disorders**

Professor Karim Meeran

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**Adrenal failure** (cortisol deficiency)=Addison’s disease

**Adrenal overactivity** (cortisol excess) = Cushing’s syndrome

**Anatomy of the adrenals:**

Left adrenal vein drains into the left renal vein whereas the right adrenal vein drains directly into the Inferior Vena Cava.

Both adrenals have many arteries but only one central vein.

The spleen is next to the left adrenal, so it can be easily damaged during the operation to remove the left adrenal.

Therefore one must immunise a patient with HIB and pneumovax before elective left adrenalectomy.

The adrenal gland synthesises cortisol, aldosterone and sex steroids from cholesterol.

Hormones can be peptides (eg: prolactin, growth hormone and ACTH) or steroids (eg: testosterone, oestrogen, cortisol) or amines (eg: adrenaline).

Various enzymes (eg: 17-hydroxylase) convert cholesterol into active steroids.

**Draw the simplified pathway of steroid synthesis below:**

Cholesterol

Progesterone

11 deoxycorticosterone

corticosterone

Aldosterone

Pro-opio-melanocortin (POMC) is a precursor to ACTH and Melanin-Stimulating Hormone (MSH). What happens to MSH levels when ACTH levels are high?

# Addison’s disease

Primary adrenal failure

Commonest cause in world = adrenal tuberculosis

Commonest cause in UK: autoimmune destruction of adrenals.

**Urgent treatment of Addisonian Crisis:**

Addisonian crisis arises from fall in blood pressure to very low levels as a result of cortisol and aldosterone deficiency. Untreated, collapse and death will occur.

**1.**

**2.**

**3.**

**Adrenal Overactivity:**

**Biological actions of excess cortisol:**

Watch the video and then list the features of Cushing’s syndrome.

What causes Cushing’s syndrome?

List four possible causes of Cushing’s syndrome.

**1.**

**2.**

**3.**

**4.**

**List 6 signs that you might find in a patient with Cushing’s syndrome.**

**1.**

**2.**

**3.**

**4.**

**5.**

**6.**

What is the difference between Cushing’s syndrome and Cushing’s disease.

What do you think would happen to a patient who developed a tumour of the adrenal cortex that was secreting aldosterone?

**Tutorial 5: Adrenal disorders**

**Case history 1.**

A 30 year old man suffers from Adrenal failure. What symptoms will he complain of? Briefly explain why he has such a good tan, despite not going on a sunny holiday.

**Case history 2.**

A 55-year old female complains that she has been increasing in weight over the past five years. She also has a five-year history of high blood pressure.

1. What are the most likely hormonal causes of this high blood pressure?

A year ago, she fell over and fractured her hip. A bone density scan revealed that she had osteoporosis.

2. What are the causes of osteoporosis?

Three months ago, she developed polyuria and polydipsia. She saw her general practitioner who noted that she had glycosuria on dipstick testing.

*3. What important tests should be performed?*

Over the last few weeks, she has had progressive weakness, affecting her thighs, with difficulty climbing stairs.

4. What is this condition called? How would you examine the patient for this?

On direct questioning she notes that the shape of her face has changed and that she has gained a lot of weight ‘around her tummy’. She also mentions that she bruises easily, and that a wound on her shin that she had six months ago has not healed.

5. What clinical signs would you expect to find on examination?

6. On the basis of your overall interpretation, what is the likely diagnosis?

7. Why is it important to make sure you take a thorough medication history in this patient?

**Session 5 Adrenals**

1. The following statements are correct True False

a) The adrenal cortex is the site of synthesis of catecholamines

b) The left adrenal vein drains directly into the inferior vena cava

c) The left adrenal gland is very close to the kidney

d) All corticosteroids are synthesized from the initial precursor cholesterol

e) Aldosterone is synthesised in the zona glomerulosa cells

2. The following statements are correct True False

1. Aldosterone secretion is principally controlled by the pituitary gland.
2. Aldosterone is a mineralocorticoid.
3. Aldosterone stimulates renal sodium excretion
4. Renin directly stimulates aldosterone production in the adrenals
5. Angiotensin I is a potent vasoconstrictor molecule

3. The following statements are correct True False

1. Increased renal sympathetic stimulation results in renin release
2. Cortisol is the principal glucocorticoid in humans
3. Corticotrophin (ACTH) stimulates the adrenal production of cortisol
4. Cortisol is an important stimulator of the normal inflammatory response
5. Cortisol release is stimulated by stress

4. The following statements are correct True False

1. Cortisol stimulates protein catabolism
2. Addison’s disease can be associated with hyperpigmentation
3. Addison’s disease can be caused by tuberculosis
4. Hypoglycaemic episodes are common in patients with Cushing’s

syndrome

1. Cushing’s syndrome can be caused by the excessive use of

anti-inflammatory glucocorticoids

**5.** The following statements are correct True False

a) progesterone is an aldosterone precursor

b) oestrogens are precursors for androgens

c) aldosterone stimulates distal tubular water reabsorption

d) cortisol stimulates insulin release

e) LH stimulates adrenocortical androgen synthesis

**Lectures 10 and 11 The Gonads (1 and 2)**

**Learning objectives**

1. Describe the stages of gametogenesis and the process of steroidogenesis in male and female gonads.
2. Label diagrams illustrating the principal structures of the testes and ovaries.
3. Draw simple flow charts illustrating the synthesis of progesterone, 17b-oestradiol and testosterone.
4. Describe the principal ovarian and endometrial changes that occur during the menstrual cycle.

### Relate the synthesis of the major gonadal steroids in males and females to the relevant hormones of the hypothalamo-adenohypophysial axis.

1. Describe how the cyclic production of ovarian steroids is linked to the endometrial, cervical and other changes of the menstrual cycle.
2. Describe the actions of the gonadal steroids in males and females.
3. Identify the principal features of the control systems operating on the production of the gonadal steroids, with particular reference to negative and positive feedback loops, in males and females.
4. Define the terms primary and secondary amenorrhoea.
5. List the principal causes of infertility with particular references to endocrine causes.
6. Name the two major functions of the testes and, with the use of a simple diagram, describe how they are regulated by the hypothalamo-pituitary axis.
7. With the use of simple diagrams that distinguish between the follicular (early, mid, late) and luteal phases of the menstrual cycle, summarise the endocrine regulation of ovarian function.

**Lecture 10: The Gonads (1)**

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***THE GONADS***

***IN MALES: IN FEMALES:***

DEVELOP AS THE TESTES DEVELOP AS THE OVARIES

***FUNCTIONS OF THE GONADS:***

1. PRODUCTION OF *IN MALES*

FOR (production of mature spermatozoa)

REPRODUCTION

*IN FEMALES:*

( )(production of ripe ova)

2. PRODUCTION OF *IN MALES:* ( )

*IN FEMALES:* ( )

(androgens)

***SPERMATOGENESIS***

GERM CELL 44+XY (diploid)

SPERMATOGONIA 44+XY (diploid)

(mitotic division)

PRIMARY SPERMATOCYTES 44+XY (diploid)

(first meiotic division)

SECONDARY SPERMATOCYTES 22X or 22Y (haploid)

(second meiotic division)

SPERMATIDS 22X or 22Y (haploid)

SPERMATOZOA 22X or 22Y (haploid)

***PRODUCTION OF GAMETES***

1. MALES:
2. Gametogenesis begins at puberty.
3. Some primary spermatocytes continually return to quiescent stage; consequently, pool of spermatogonia available for subsequent spermatogenic cycles is maintained.
4. throughout life males retain spermatogenic capability, producing 300-600 sperm/gm testis/*second*

***OOGENESIS***

GERM CELL 44XX (diploid)

OOGONIA 44XX (diploid)

(mitotic division)

PRIMARY OOCYTES 44XX (diploid)

(first meiotic division)

SECONDARY OOCYTES (+ first polar body) 22X (and 22X) (haploid)

(second meiotic division)

OVUM (+ second polar body) 22X (and 22X) (haploid)

**reproductive system**

either sex : gonads

internal duct system

external genitalia













folicular

luteal

phase





**Session 6 Lecture 11: The Gonads II**

Professor John Laycock

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1. **ANDROGENS**

**TESTOSTERONE**

*Reduction Aromatization  
(5**-reductase) (Aromatase)*

more potent androgen Oestrogen

**DIHYDROTESTOSTERONE (DHT) e.g. 17-OESTRADIOL**

Prostate Adrenals

Testes (seminiferous tubules) Testes (Sertoli cells)

Seminal vesicles Liver

Skin Skin

Brain Brain

Adenohypophysis

**Testosterone and DHT**

Bind to

(in blood) (in seminiferous fluid)

**Sex Hormone Binding Globulin (SHBG) Androgen Binding Globulin (ABG)**

#### SHBG 60%

and

Albumin 38%

FREE 2% *bioactive component*

**-ve -ve**

Hypothalamic **GnRH**

**LH** pituitary **FSH**

Leydig cells Sertoli cells

#### Testosterone Inhibin

**and DHT**

### PRINCIPAL ACTIONS OF ANDROGENS

1. **FETUS**

* Development of male internal and external genitalia
* General growth (acting with other hormones)
* Behavioural effects

1. **ADULT**

* Spermatogenesis
* Growth and development of: male genitalia

Secondary (accessory) sex glands

Secondary sex characteristics

* Protein anabolism
* Pubertal growth spurt (with GH)
* Feedback regulation

### OESTROGENS

Definition: any substance (naturel or synthetic) which induces mitosis in the endometrium

Examples: 17-oestradiol (main one during menstrual cycle; most potent)

Oestrone

Oestriol (main estrogen of pregnancy)

#### PRINCIPAL ACTIONS OF OESTROGENS

* Final maturation of follicle during menstrual cycle
* Induces LH surge resulting in ovulation
* Stimulates proliferation (mitosis) of the endometrium
* Effects on vagina, cervix
* Stimulates growth of ductile system of breast
* Decreases sebacious gland secretion
* Increases renal salt (and water) reabsorption
* Increases plasma protein synthesis (hepatic effect)
* Metabolic actions (e.g. on lipids)
* Stimulates osteoblasts
* Influences release of other hormones (e.g. prolactin, thyrotrophin)
* Feedback regulation
* Behavioural influences

***Important to note protective effects on cardiovascular system and against osteoporosis.***

1. **PROGESTOGENS**

Definition: any substance (natural or synthetic) which induces secretory changes in the endometrium.

Examples: progesterone

17-hydroxyprogesterone

### PRINCIPAL ACTIONS OF PROGESTERONE

* Stimulates secretory activity in endometrium and cervix
* Stimulates growth of alveolar system of breast
* Decreases renal NaCl reabsorption (competitive inhibition of aldosterone)
* Increases basal body temperature

**MECHANISM OF ACTION**

Steroid hormones have important *genomic* effects, and non-genomic effects may also be possible.

hormone

receptor

ACTIONS

h-r complex

New protein

mRNA

**5. Amenorrhoea and infertility**

Definition of amenorrhoea: absence of menstrual cycles; ***primary*** if they have never happened and ***secondary*** if they did happen but have stopped (can be physiological). Oligomenorrhoea means infrequent cycles. Causes: various, but can be due to absence of LH surge (e.g. due to insufficient oestrogenic effect at end of follicular phase), etc.

Infertility means unable to get pregnant (or, for men, to impregnate); various causes, e.g. physical problems, psychological, endocrine. Here, focus on possible endocrine problems (i.e. see above, and infertility in males). Prolactin can be an endocrine cause of infertility.

**Hypothalamo-pituitary-gonadal feedback loops**

Summary: Endocrine control of testicular function

1. **Androgen production**

* stimulated by GnRH/LH system (feedforward)
* reduced by testosterone
  + direct negative feedback to reduce LH release from anterior pituitary gland
  + indirect negative feedback to slow hypothalamic GnRH pulse generator.

**2. Spermatogenesis**

* stimulated by GnRH/FSH sytem
* also requires GnRH/LH/tesosterone system for complete spermatogenesis
* limited by inhibin negative feedback (direct and indirect)

**Endocrine control of ovarian function**

* 1. During the follicular phase of the cycle, rising estradiol levels are dependent on the co-ordinated action of LH and FSH in the thecal and granulosa cells respectively, and involves a local positive feedback loop to enhance estradiol production.
  2. Emergence of the Graafian follicle involves a selective negative feedback loop by estradiol and inhibin on the GnRH-FSH system such that all follicles which are still FSH-dependent regress (atresia).
  3. Ovulation is triggered by a positive feedback loop exerted by estradiol to:
     + increase the frequency and pulsatility of GnRH release and
     + enhance the selectivity of the anterior pituitary gonadotrophs to GnRH.
  4. In the non-pregnant state, during the luteal phase the high levels of progesterone, along with estradiol and inhibin, exert a powerful negative feedback on LH and FSH release; luteolysis and menstruation ensue.

**2 EARLY**

**-**

**MID FOLLICULAR PHASE**

**Local positive feedback loop in developing**

**follicles enhances**

**estradiol**

**production**

***THECAL CELL***

***GRANULOSA CELL***

**FSH**

**LH**

**androgen synthesis**

**LH**

**receptor**

**+**

**FSH**

**receptor**

***THECAL CELL***

***GRANULOSA CELL***

**FSH**

**LH**

**androgen synthesis**

**LH**

**receptor**

**+**

**FSH**

**receptor**

**HYPOTHALAMO**

**-**

**PITUITARY**

**-**

**TESTICULAR AXIS**

**Leydig**

**cell**

**Sertoli**

**cell**

**TESTIS**

**HYPOTHALAMUS**

**pulse generator**

**GnRH**

**ANTERIOR**

**PITUITARY**

**GLAND**

**LH FSH**

***oestradiol***

**OVARY**

**HYPOTHALAMUS**

**pulse generator**

**GnRH**

**ANTERIOR**

**PITUITARY**

**GLAND**

**LH FSH**

**developing follicles**

**HYPOTHALAMO**

**-**

**PITUITARY**

**-**

**OVARIAN AXIS**

**1. EARLY FOLLICULAR PHASE**

**-**

**GnRH**

**/LH/FSH**

**feedforward**

**(stimulates) and**

**estradiol**

**negative**

**feedback**

***inhibin***

**LH FSH**

**GLAND**

**PITUITARY**

**ANTERIOR**

**GnRH**

**pulse generator**

**HYPOTHALAMUS**

**OVARY**

***oestradiol***

***ve***

***-***

***indirect***

***ve***

***-***

***direct***

**follicle**

**Graafian**

**3. MID FOLLICULAR PHASE:**

**4. LATE FOLLICULAR PHASE**

***oestradiol***

***(progesterone)***

**OVARY**

**HYPOTHALAMUS**

**pulse generator**

**GnRH**

**ANTERIOR**

**PITUITARY**

**GLAND**

**LH FSH**

***LH surge***

**ovum**

***ovulation***

**5. LUTEAL PHASE:**

***progesterone,***

***oestradiol***

***inhibin***

**OVARY**

**HYPOTHALAMUS**

**pulse generator**

**GnRH**

**ANTERIOR**

**PITUITARY**

**GLAND**

**LH**

**FSH**

**Corpus**

**luteum**

#### Tutorial 6: The Gonads

Case History:

A 44-year old mother of two children presents to her GP complaining of headaches, tiredness, oligomenorrhoea and the occasional expression of milk from her breasts (galactorrhoea). Her doctor estimates her visual fields and concludes that there is some loss in peripheral vision. He takes a blood sample for laboratory analysis, the results of which are given below.

Oestradiol 160 pmol/l (low)

Progesterone <1.0 nmol/l (low)

LH 2.2 U/l (low)

FSH 1.5 U/l (low)

Prolactin 36,000 mU/l (very high)

A proper examination of the patient’s visual fields by perimetry confirmed a bitemporal hemianopia.

Questions:

1. What are the principal characteristic features of the initial history?
2. What are the important diagnostic features from the laboratory findings?
3. What is your diagnosis?
4. Explain why the ovarian steroid concentrations are low.
5. What is the relevance of the bitemporal hemianopia?

**Session 6 The Gonads**

SBA

1. The following statements are correct True False

1. The fetal gonads only develop into testes after the Y chromosome

(if present) is activated

1. Androgens are only produced by the testes
2. The gonadal hormones are derived from a prohormone
3. Testosterone is an early precursor of progesterone
4. The most active androgen in males is testosterone

2. The following statements are correct True False

1. Spermatozoa are derived from the testicular germ cells
2. The testicular Sertoli cells produce inhibin
3. In the male, most androgens are produced by the Leydig cells
4. Oestrogens are aromatized to androgens
5. The average menstrual cycle lasts about 28 days

3. The following statements are correct True False

1. The central (mid) event of the menstrual cycle is menstruation
2. During the menstrual cycle the principal oestrogen produced is

oestriol.

1. There is an increase in the blood progesterone concentration during

the early follicular phase.

1. Both progesterone and oestradiol are released during the luteal phase.
2. Ovulation is induced by a large increase in circulating progesterone

concentration

4. The following statements are correct True False

1. Just prior to ovulation the circulating concentration of FSH increases.
2. During the luteal phase the circulating LH concentration reaches its

peak.

1. Secondary amenorrhoea is present during pregnancy.
2. Chronic high circulating prolactin concentrations are associated with

a loss of libido.

1. The basal body temperature increases at ovulation

**Lecture 12: The parathyroids and calcium metabolism**

Professor John Laycock

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**Learning objectives**

* List the functions of calcium in the body.
* Identify the principal organs involved in calcium metabolism.
* Identify the bone cells and their functions.
* List the principal hormones which regulate blood calcium ion concentration, and their sites of synthesis.
* Briefly describe how parathormone, 1,25-dihydroxycholecaciferol (calcitriol) and calcitonin are synthesized.
* Describe the principal effects of parathormone, 1,25-dihydroxycholecaciferol and calcitonin on bone, the kidneys and the intestinal tract.
* Describe the mechanisms of action of parathormone, 1,25-dihydroxycholecaciferol and calcitonin.
* Explain how parathormone, 1,25-dihydroxycholecaciferol and calcitonin production are controlled, identifying the principal stimulus in each case.
* List the principal causes of hypocalcaemia.
* List the principal causes of hypercalcaemia.
* Distinguish between primary, secondary and tertiary hyperparathyroidism.

# ROLE OF CALCIUM IONS

1. *PRINCIPAL EXAMPLES*
2. **Maintenance of neuromuscular excitability**
3. release of neurotransmitters and hormones (excitation-secretion coupling)
4. intracellular messenger
5. involved in muscular contraction
6. blood clotting factor (factor IV)
7. intracellular co-enzyme activity

# CALCIUM

* Most calcium is present in the body as calcium salts
* It is mainly found in (99%, approx. 1kg) as complex hydrated calcium salt (hydroxyapatite crystals)
* In blood, some is present as ionized calcium (Ca2+), some bound to protein and the tiny bit left as soluble salts
* **Only the ( ) Ca2+ is bioactive**





**CALCIUM ION REGULATION**

[Ca2+] INCREASED BY: [Ca2+] DECREASED BY:

1,25 (OH)2 VITAMIN D3

(DIHYDROXY- CHOLECALCIFEROL)



***PARATHYROID HORMONE***

***(PTH) ACTIONS***

**PTH**

KIDNEYS

BONE

osteoclasts

stimulated

osteoblasts

inhibited

SMALL

INTESTINE

Increased Ca

2+

reabsorption

Stimulates

1



hydroxylase

activity

Increased

1,25 (OH)

2

D

3

synthesis

Increased Ca

2+

absorption

Increased

absorption

Increased

excretion

Increased bone

resorption

# 



***PTH REGULATION***

***PTH***

INCREASED PLASMA [Ca

2+

]

**DECREASED**

PLASMA [Ca

2+

]

+

\_

CATECHOLAMINES

(via



receptors)

+

*PARATHYROID*

*GLANDS*

*-*

*ve*

*feedback*

***DIHYDROXY-CHOLECALCIFEROL***

***SYNTHESIS***

CHOLECALCIFEROL

*VITAMIN D*

*3*

7-DEHYDROCHOLESTEROL

In skin

UV light

25 HYDROXY-CHOLECALCIFEROL

*25 (OH) D*

*3*

synthesized

in LIVER

and stored in this form

1,25 DI-HYDROXY-CHOLECALCIFEROL

*1,25 (OH)*

*2*

*D*

*3*

**synthesized**

**in KIDNEYS**

**main BIOACTIVE form**

***1,25 (OH)***

***2***

***D***

***3***

***: ACTIONS***

***1,25 (OH)***

***2***

***D***

***3***

BONE

increased

osteoblast

activity

KIDNEYS

Ca

2+

Increased Ca

2+

absorption

PO

4

3-

Increased PO

4

3-

absorption

small intestine

Ca

2+

Increased Ca

2+

and

reabsorption



**Some endocrine causes of hypocalcaemia**

* Hypoparathyroidism
* Pseudohypoparathyroidism
* Vitamin D deficiency

#### Causes of Hypoparathyroidism include

* consequence of thyroid surgery
* idiopathic
* hypomagnesaemia
* suppression by raised plasma calcium concentration
* Pseudohypoparathyroidism, also known as Allbright hereditary osteodystrophy, is due to a to PTH (multiple underlying causes). Features include particular physical appearance (short stature, round face, reduced IQ, subcutaneous calcification and a variety of bone abnormalities (e.g. shortening of metacarpals). Associated endocrine abnormalities occur e.g. hypothyroidism, hypogonadism. Believed to be due to defective Gs protein.

#### Key differential diagnosis features

**Plasma Ca Plasma PO4 PTH**

HYPOPARATHYROIDISM

PSEUDOHYPOPARATHYROIDISM

VITAMIN D DEFICIENCY

**Vitamin D Deficiency**

*Rickets* in

*Osteomalacia* in

Clinical feature is the decreased calcification of bone matrix resulting in and in children, and in adults.

#### Some endocrine causes of hypercalcaemia

*Primary hyperparathyroidism*

*Tertiary hyperparathyroidism*

*Vitamin D toxicosis*

Note: *Secondary hyperparathyroidism* is not associated with hypercalcaemia, but with low or normal plasma calcium levels.

#### Hyperparathyroidism

1. Adenoma **Primary hyperparathyroidism**

[Ca2+]

PTH

PARATHYROIDS

1. Low plasma [Ca2+] e.g. renal failure **Secondary hyperparathyroidism**

[Ca2+]

PTH

PARATHYROIDS

[Ca2+]

1. Initial Chronic low plasma [Ca2+] **Tertiary hyperparathyroidism**

Autonomous glands

[Ca2+]

PARATHYROIDS

PTH

[Ca2+]

**The parathyroids and calcium metabolism**

1. The following statements are correct True False

a) The main store of calcium is in the liver

b) Osteoclasts are bone-resorbing cells

c) There are usually two parathyroid glands in humans

d) Parathyroid hormone (PTH) stimulates the urinary reabsorption

of phosphate

e) PTH receptors are present on osteoclasts

2. The following statements are correct True False

1. Excess circulating PTH lowers the serum calcium concentration
2. PTH secretion is stimulated by an increase in circulating plasma

calcium ion concentration

1. 25-hydroxyvitamin D is produced in the kidneys
2. 1,25 dihyroxyvitamin D stimulates sodium absorption from the gut
3. Hypocalcaemia causes tetany

3. The following statements are correct True False

1. Hypoparathyroidism is associated with hypocalcaemia
2. In secondary hyperparathyroidism the serum calcium concentration

may be normal

1. Hypercalcaemia can be associated with kidney stones
2. Calcitonin is produced by the parathyroid glands
3. Calcitonin stimulates renal calcium excretion

**Glossary of endocrine terms**

Generally you would not be expected to know eponymous names but sometimes that is the most commonly used description.

**Addison’s disease:** Adrenocortical (adrenal steroid) deficiency.

**Adrenal gland:** Endocrine gland which lies on top of each kidney (also known as supra-renal gland). There is structural and functional separation: the inner *medulla* secretes catecholamines, while the outer *cortex* which secretes steroids has three zones, the outer glomerulosa which secretes mineralocorticoids (e.g. aldosterone) and the inner fascilculata and reticularis which secrete glucocorticoids (e.g. cortisol) and small amounts of androgens.

**Adrenaline:** Nowadays also called *epinephrine*, which acts mostly via β1 and β2 adrenergic receptors to produce its actions; these include chronotropic (increased heart rate), metabolic and bronchodilator effects.

**Adrenergic receptor:** Recognises (i.e. binds to) catecholamines, or certain adrenergic pharmacological agents. Various sub-types include the 1 and 2, and the 1, 2 and 3 receptors.

**Adrenocorticotrophic hormone:** ACTH, see corticotrophin.

**Aldosterone:** A mineralocorticoid (steroid) hormone produced by adrenal glands (cf.). An important stimulus is low renal blood flow, the effect of which is mediated through the renin-angiotensin system (cf.). It acts on renal distal convoluted tubules (and early cortical collecting ducts) to conserve sodium in exchange for potassium and/or hydrogen ions.

**Alpha glucosidase inhibitors:** Acarbose is used in diabetes to reduce rate of oligosaccharide absorption from the gut.

**Amenorrhoea:** Absence of menstrual cycles; primary if they never occurred, secondary if they did occur but have now ceased.

**Angiotensins I and II:** Angiotensin I is a decapeptide produced by the action of renin on angiotensinogen. Angiotensin converting enzyme (ACE) acts on Angiotensin I to produce the octapeptide Angiotensin II. The latter is a potent vasoconstrictor and stimulates aldosterone secretion from the adrenal glands.

**Angiotensin converting enzyme inhibitors (ACE-I):** these are a class of drugs used to prevent conversion ofangiotensin I to angiotensin II (cf.) and are, therefore, used to treat hypertension and cardiac failure.

**Atrial naturetic peptide (ANP):** A peptide produced by the cardiac atria (and other tissues, e.g. ventricles) which causes a natriuresis i.e. “it does exactly what it says on the tin”. It also has other effects, e.g. it is a vasodilator. A related peptide first found in the brain is called brain natriuretic peptide.

**Autocrine:**  Hormonal (e.g. regulatory) effect on the cell that produced that hormone itself.

**Axis:** A series of intercommunicating links by which one system (e.g. central nervous system) communicates with an endocrine gland. For example, the hypothalamus-pituitary-adrenal axis links the hypothalamus to the pituitary to the adrenal cortex by means of specific hormones. Usually the axis forms part of the feedback loop.

**Acromegaly:** Excessive growth of soft tissues (e.g. resulting in cardiomegaly, hepatomegaly, etc.) and cartilaginous extremities after end of puberty (when epiphyses are fused and long bones do not grow any more). Caused by too much growth hormone (cf. somatotrophin).

**Adeno:** Secretory gland, e.g. adenohypophysis (the “glandular” part of the hypophysis, or pituitary).

**Adenohypophysis:**  Also known as the anterior lobe of the pituitary gland, it is the glandular (i.e. made up of typical secretory cells) part of pituitary. The specific cells of the adenohypophysis are named after the principal hormones they produce (e.g. corticotrophs, thyrotrophes).

**Biguanide:** Metformin, the only biguanide, reduces hepatic gluconeogenesis and increases insulin sensitivity. Especially useful for overweight type 2 diabetics. It has been used to reduce insulin resistance in the absence of diabetes.

**Calcitonin:**  A hormone produced by the parafollicular (or C) cells of the thyroid, it increases renal calcium loss and reduces bone resorption. Minor player in human physiology. Marker for medullary thyroid carcinoma.

Cholesterol: the most abundant steroid in animals, it is a precursor for various hormones. Carried in several forms in blood, associated with lipoproteins for instance, the particles are classified on the basis of centrifugation properties. Low density lipoprotein cholesterol (LDL-C) is atherogenic whilst increased high density lipoprotein cholesterol (HDL-C) concentrations are associated with a lower prevalence of ischaemic heart disease (IHD).

**Corticotrophin**: this hormone, also known as adrenocorticotrophic hormone (ACTH) is released from the anterior pituitary, for instance in response to stress, via hypothalamic corticotrophin releasing hormone (CRH). Diurnal rhythm, stress and feedback control are all factors which influence ACTH release via CRH. Its main action is to stimulate glucocorticoid (and, to a much lesser extent, androgen) production in the inner zones of the adrenal cortex.

Corticotrophin releasing hormone (or factor): CRH (or CRF) is produced in hypothalamus in response to stress and other stimuli; its production is suppressed by endogenous steroids. It stimulates the corticotroph cells in anterior pituitary to produce ACTH.

**Cortisol:** The principal glucocorticoid (steroid) hormone produced by the two inner zones of the adrenal cortex in humans.This hormone has many actions but it is particularly important in the body’s response to stress. In the kidneys it is inactivated by a specific enzyme so that it cannot bind to the mineralocorticoid receptors present, to which cortisol also has a high affinity.

**Cushing’s Disease:** Excess of steroid hormones (mainly the glucocorticoid cortisol) from the adrenal cortex due to the excessive pituitary secretion of corticotrophin (cf.).

**Cushing’s Syndrome:** Excess of steroid hormones (mainly the glucocorticoid cortisol) from the adrenal cortex due to a variety of causes. May be due to glucocorticoid excess, either directly from an overactive adrenal (endogenous production from an adrenal adenoma), or indirectly from an exogenous source e.g. as a result of a steroid treatment, (i.e. doctor-induced). It can also be due to excessive corticotrophin (ACTH) stimulation of the adrenals, the source of the ACTH being either the pituitary gland (cf. Cushing’s disease) or an ectopic (cf.) source.

**Dawn phenomenon**: The increase in insulin requirements in the early morning probably mediated through the glucose-producing effect of growth hormone, in the absence of nocturnal hypoglycaemia (See Somogyi effect) or inadequate insulin.

**Diabetes insipidus (DI);** Fluid balance disorder associated with the excretion of large volumes of urine (*diabetes)* which istasteless (i.e. *insipidus*) because it is so dilute; caused by a vasopressin (ADH) deficiency or lack of effect. Central (or cranial) DI is due to lack or absence of circulating vasopressin, while nephrogenic DI is due to a renal collecting duct resistance to the action of the hormone.

**Diabetic ketoacidosis**: a term denoting the combination of hyperglycaemia, ketosis and acidosis which can lead to complications in type 1 diabetes.

**Diabetes mellitus (DM):** clinical condition associated with the excretion of large volumes of urine (*diabetes*) tasting of honey (*mellitus* is honey, in Latin). Increased plasma glucose levels (normal fasting plasma glucose <6mmol/l, impaired fasting glucose 6-7mmol/l and diabetes mellitus >7mmol/l); associated with macrovascular and microvascular complications. Type 1 DM is due to an insulin deficiency, the patient being ketosis prone; found especially, but not exclusively, in the young. Type 2 DM is due to an insulin resistance; it is more prevalent than type 1, and more common with age. Type 2 is not mild diabetes despite the fact the glucose levels are not necessarily very elevated.

**Dihydroxycholecalciferol:** A steroid hormone also known as 1,25-dihydroxy-vitamin D3, being a metabolite of vitamin D3 (cf.). It is produced from 25-hydroxy-vitamin D3 in the kidneys in response to parathormone (cf.) stimulation of the 1-hydroxylase enzyme. Its principal physiological effect is to increase intestinal absorption of calcium (and phosphate) into the blood.

**Dopamine:** A precursor of adrenaline and noradrenaline. Has DA1 and DA2 receptor effects. Dopamine inhibits prolactin secretion via the DA2 receptor on lactotrophs.

**Ectopic:** From (or in) an abnormal site (e.g. the ectopic production of the posterior pituitary hormone vasopressin from a carcinoma of the lung).

**Endogenous:** produced within the body.

**Eu-:** normal, as in euadrenal or euthyroid; i.e. normal amounts of circulating hormone and hormone effects are present.

**Exogenous:** from a source outside the body.

**Feedback:** Mechanism by which hormone, either directly or through its action alters (usually decreases, i.e. negative) further hormone secretion. Instances of positive feedback, when a hormone, under certain very specific conditions, actually stimulates further production of itself do exist (cf. oestrogen).

**Fibrate:** Class of drugs used in treatment of dyslipidaemia. Used especially if triglyceride high and HDL-C low, for example in diabetic dyslipidaemia.

**Follicle stimulating hormone:** FSH, glycoprotein hormone produced by anterior pituitary that stimulates testicular spermatogenesis or ovarian follicular maturation. Elevated levels suggest gonadal failure, for example after the menopause or after mumps-induced orchitis (testicular failure).

**Galactorrhoea:** production of milk from the breasts.

**Gigantism:** Excessive growth of long bones, before end of puberty, when epiphyses are not fused. Caused by too much growth hormone.

**Glucagon:** Polypeptide hormone produced by α-cells of islets of Langerhans (cf.) in response to hypoglycaemia. Acts on liver to stimulate glycogenolysis, and therefore increases hepatic glucose output.

**Glycoprotein hormone**: Combination of polypeptide/protein and carbohydrate side chains (e.g. LH, FSH).

**Gonad**: An organ that produces sex cells (haploid gametes, spermatozoa or ova), i.e. ovary or testis.

**Gonadotrophins:** Luteinizing hormone (LH) and follicle stimulating hormone (FSH) from the adenohypophysis.

**Graves’ disease**: Autoimmune condition associated with thyrotoxicosis (and later hypothyroidism) and various extra-thyroidal conditions which include thyroid-associated opthalmopathy (exopthalmos, external opthalmoplegia and chemosis; lid lag is a feature of thyrotoxicosis of any aetiology). Predominately antibody mediated auto-immunity although the antibodies are not generally useful in the diagnosis or in monitoring the condition.

**Growth hormone**: Also known as somatotrophin (cf.).

**Growth hormone releasing hormone:** GHRH produced by hypothalamus in response to stress/hypoglycaemia; it stimulates pituitary growth hormone secretion.

**Hashimoto’s disease**: Autoimmune condition associated with hypothyroidism. Predominately cell mediated immunity, although antibodies to the peroxidase enzyme (thyroid microsomal) are associated with the condition and may be used clinically for diagnosis.

**Honeymoon period**: Soon after insulin treatment is begun in type 1 diabetes mellitus many patients require less insulin than later, a phase sometimes termed the honeymoon period. It does not mean the diabetes has gone!

**Hormone**: A substance released into the blood stream which acts as transport system enabling it to reach target tissues sometimes at some distance away from the source.

**Hyperosmolar non-ketotic coma**: HONK-C is a coma associated with a hyperglycaemia with an inevitable high plasma osmolality but with minimal ketosis or acidosis. Typically in type 2 diabetics with some renal impairment.

**Hypothalamus:** Part of the brain lying below the thalamus and around the third ventricle. It has many varied functions, a particularly important one being the neural influence it has on the function of the pituitary gland which is attached to it by a stalk (cf. adenohypophysis, neurohypophysis).

**Hypopituitarism**: (cf. Simmond’s disease). It is a deficiency of one or several pituitary hormones. Pan-hypopituitarism is a term used to denote deficiency of all pituitary hormones.

**Hypophysis**: Also known as pituitary gland.

**Iatrogenic**: means doctor-induced, e.g. following a treatment.

**Impaired glucose tolerance:** Increased glucose levels (fasting plasma glucose 6-7mmol/l) associated with the macrovascular, but not microvascular, complications of diabetes mellitus. It is an insulin resistant state, and is associated with a diabetic dyslipidaemia and hypertension.

**Inhibin:** Imaginatively named glycoprotein hormone released by Sertoli cells of testis and granulosa cells of ovary to inhibit FSH (cf.) secretion by pituitary.

**Insulin-like growth factors:** Two IGFs (1 and 2) also known as somatomedins. IGF-1 is produced in liver under control of growth hormone. It has many of the actions ascribed to growth hormone on linear growth before epiphyses have fused, on intermediary metabolism, and on psychological function.

**Insulin resistance:** A state whereby a cell, organ, system or whole body requires increased insulin concentrations for a given effect, e.g. to maintain euglycemia.

**Intracrine:** Synthesised from precursor within effector cell. For example dihydrotestosterone (a potent androgen) is formed from testosterone (the precursor) within the (effector) cells of the prostate.

**Iodine: 131**-I has a half-life of 8 days, useful in treatment of thyrotoxicosis and ablating thyroid malignancy. Iodine is essential (in its intracellular reactive form) for the synthesis of the iodothyronines hormones of the thyroid gland.

**Iodothyronines**: Iodinated hormones produced by the follicular cells of the thyroid gland, thyroxine being the principal molecule.

**Islets of Langerhans**: Small groups of endocrine cells within the exocrine pancreas which secrete insulin (β-cells), glucagon (α-cells) and somatostatin (γ-cells).

**Lactic acidosis**: Very high lactate levels and acidosis often with mild hyperglycaemia in diabetes. A combination of increased production (in anaerobic tissues) and decreased utilisation (by the liver) are responsible.

**Luteinising hormone (LH):** Glycoprotein hormone released by anterior pituitary which ripens follicles and causes egg release (ovulation) following an LH surge. It helps convert ruptured follicle cell remnants into corpus luteum. In males, LH stimulates the testicular Leydig cells to synthesize the androgen testosterone.

**Macrovascular complication:** Refers to atheromatous disease typically complicating diabetes mellitus and insulin resistant states. Ischaemic heart disease, cerebrovascular disease, renal artery stenosis and peripheral vascular disease are main features.

**Macroalbuminuria:** Albumin excretion in excess of 300mg/day is termed macroalbuminuria. It is usually detectable on dipstix testing.

**Menstrual cycle:** The cyclic (approximately monthly) ovarian, endometrial and other changes that take place throughout the reproductive life of a woman, the central event being the release of the egg (ovulation).

**Microalbuminuria:** Minute amounts of albumin are lost in a healthy individual’s urine daily. However, albumin excretion of 30-300mg/day, termed microalbuminuria, represents early nephropathy especially in Type 2 diabetes mellitus. Many patients with macrovascular disease, with or without diabetes, have some proteinuria therefore the prediction of nephropathy is less useful in T2DM. However, microalbuminuria is a marker for ischaemic heart disease in the general population.

**Microvascular:** Refers to the cause of retinopathy, nephropathy and neuropathy which are complications of long-term diabetes mellitus. However, the later, and to an extent the others, are metabolic as well as vascular disorders.

**Neurohypophysis** hypothalamus but secreted by the pituitary (cf. vasopressin, oxytocin). : Also known as the posterior lobe of the pituitary gland, it consists mainly of large (magnocellular) nerve axons originating from cell bodies in the hypothalamus grouped to form the supraoptic and paraventricular nuclei. The secretions from these axons are released from the nerve endings in the neurohypophysis directly into the bloodstream; these neurosecretions are therefore hormones which are synthesised in the

**Neuropathic:** As in neuropathic foot, where neuropathy has caused specific complications.

**Noradrenaline:** Also known as norepinephrine, it exerts mostly α-1 and β-1 adrenoreceptor effects (so that e.g. on cardiovascular system it is more a vasoconstrictor and pressor molecule, rather than having much effect on the cardiac output). Its usual source is as a neurotransmitter from sympathetic post-ganglionic nerve endings, but it is also released from the adrenal medulla as a hormone.

**Oestrogen:** A natural or synthetic steroid that has oestrogenic effects. Oestrogens, are synthesized from androgen precursors, mainly in the ovaries (cf. menstrual cycle), the placenta (during pregnancy) and the testes (in minute quantities). They stimulate bone growth and have several metabolic effects. The principal oestrogen during the menstrual cycle is 17-oestradiol.

**Oligomenorrhoea:** infrequent menstrual cycles.

**Optic chiasm;** The decussation of the most medial optic nerve fibres. When compressed by a pituitary tumourit causes bitemporal hemianopia.

**Ovulation:** the release of a ripe ovum usually in mid-menstrual cycle, induced by the LH surge.

**Oxytocin:** A polypeptide hormone synthesised in the hypothalamus and secreted from nerve endings in the neurohypophysis. Its main well-described physiological actions are associated with constriction, either of the smooth muscle cells (myoepithelial cells) lining the ducts in the mammary glands producing milk ejection during lactation, or of the smooth muscle lining the uterus (myometrial cells) causing contraction during parturition.

**Paget’s disease:** Osteitis deformans, a chronic disease of bone remodelling of unknown aetiology. There is thickening and softening in focal areas through the skeleton causing deformity of long bones.

**Paracrine:** Hormone action on adjacent cells to those cells producing it, within the same tissue, e.g. somatostatin produced by -cells in the islets of Langerhans (cf.) acts on the β- and -cells within the same islets.

**Parathormone (PTH):** Polypeptide hormone produced by the parathyroid glands in response to low plasma calcium concentration. It acts on bone to mobilise calcium and kidneys to reduce calcium loss and stimulate the production of dihydroxycholecalciferol (cf.).

**Polycystic Ovary Syndrome:** A condition in which there is an increased number of follicles and stroma within the ovary. It is often associated with hyperandrogenism, and oligomenorrhoea. When associated with the latter there is often insulin resistance also.

**Portal circulation:** Where the blood in one capillary bed enters veins from which it then flows into another capillary bed before entering the general venous circulation. Within the endocrine system thecirculation from hypothalamus to pituitary (called the hypothalamo-hypophysial portal system), is the chief example. It is vital for the delivery of hypothalamic releasing hormones to the anterior pituitary cells.

**Pressor:** Any agent which increases blood pressure.

**Primary:** Where hormonal deficiency or excess is due to an abnormality in the endocrine gland itself. For example, primary hyperparathyroidism is where an adenoma or hyperplasia of the parathyroid glands causes an increased parathormone concentration that is inappropriate to the ambient calcium concentration. Another example is primary hypothyroidism, which is due the thyroid itself not producing iodothyronine hormones.

**Progestogen: A** steroid hormone produced by the corpus luteum during the post-ovulatory menstrual cycle (i.e. its plasma concentration is increased during the luteal phase), and by the placenta during pregnancy. It is an early precursor for many other steroid hormones derived from cholesterol.

**Proinsulin:** Produced by β-cell, C-peptide (connecting peptide) is removed to leave intact insulin. C-peptide and intact insulin are therefore secreted in equimolar amounts. Some pro-insulin is secreted with intact insulin and this proportion of immature insulin is increased early in type 2 diabetes.

**Prolactin:** Protein hormone that stimulates milk secretion. Secreted by pituitary, only pituitary hormone only under negative control by hypothalamus, dopamine inhibits prolactin secretion.

**Receptor:** Whether cell surface, cytoplasmic or nuclear, receptors are molecules found in target cells which bind to specific hormones. This linkage allows the hormone-receptor complex to interact with intracellular systems which then mediate the hormonal effects in the target cells.

**Releasing Hormones:** These are almost invariably peptidergic molecules released from hypothalamic nerve endings into the hypothalamo-hypophysial portal circulation. They stimulate the release of specific adenohypophysial hormones. Certain hypothalamic hormones (e.g. somatostatin, dopamine) are inhibitory molecules with regard to their influence on adenohypophysial hormone release.

**Renin:** An enzyme that converts the circulating protein angiotensinogen to the polypeptide angiotensin I. It is released from the juxta-glomerular cells (apparatus) of the renal afferent arterioles in response to reduced renal blood flow or sympathetic stimulation. Angiotensin I is then converted to angiotensin II by converting enzyme. Through this renin-angiotensin system (RAS) blood pressure is increased (angiotensin II) and sodium conserved (aldosterone).

**Secondary:** Where hormonal deficiency or excess is consequent upon another cause. For example, hypocalcaemia can cause secondary hyperparathyroidism when the parathyroid hormone concentration elevation is appropriate to the ambient calcium concentration. Another example is the secondary hypothyroidism which is a consequence of pituitary thyrotrophin (TSH) defiency.

**Sertoli cell:** The seminiferous tubules are composed of Sertoli cells. They are stimulated by FSH (cf.) and play an important role in spermatogenesis, and they are a source of inhibin which has a negative feedback action on FSH production.

**Simmond’s disease:** Anterior pituitary hormone failure usually due to benign pituitary tumours.

**Somatostatin:** A polypeptidehormone synthesized in the gastrointestinal tract, the d-cells of the pancreatic islets of Langerhansm and the hypothalamus. It is alsofound in other parts of the brain where it functions as a neuropeptide. It is generally an inhibitory molecule; for instance it inhibits insulin and growth hormone secretions from the appropriate endocrine glands..

**Somatotrophin:** Also known as growth hormone, it has important actions other than on linear growth (e.g. metabolic). A protein hormone produced by anterior pituitary, its release is stimulated by GHRH and inhibited by somatostatin, both produced by hypothalamus. Has direct actions and also acts through the mediation of IGF-1 (cf.).

**Somogyi effect**: Nocturnal hypoglycaemia following the hyperglycaemia induced by counter-regulatory hormones (e.g. glucagon etc). The situation is complicated by the increasing insulin production which normally occurs in response to raised morning glucose levels, which in reality represented the after effects of hypoglycaemia. See also Dawn phenomenon.

**Statin:** One of a group of drugs that inhibit HMG co-A reductase and consequently reduces cholesterol, especially LDL-cholesterol. These drugs have been shown to reduce ischaemic heart disease in primary and secondary prevention.

**Sulphonylurea:** Hypoglycaemic agent used in treatment of type 2 diabetes mellitus. Acts on specific receptor to increase insulin secretion from β-cell in pancreatic islets of Langerhans (cf.), therefore requires some residual β-cell function.

**Synacthen:** Artificial ACTH (corticotrophin) used in the assessment of adrenocortical function.

**Technetium:** 99-Tc is a radioisotope (half-life 6 hours) useful for scanning several systems, including the thyroid; radioactive iodine has a long half-life and is less useful as an imaging tool.

**Tertiary:** The condition which arises when persistent (long-term) increased hormone production is maintained and becomes inappropriate after the initial defect (i.e excessive stimulation) is corrected. For example, when the hypocalcaemia causing secondary hyperparathyroidism if prolonged, as in renal failure; even when the stimulus for increased parathormone (PTH) production, i.e. the decreased circulating calcium level, has been corrected there may be continued excessive PTH production from the now-autonomous parathyroid glands (i.e. tertiary hyperparathyroidism).

**Thionamide:** Pharmacological agent (carbimazole and propylthiouracil) used in treatment of thyrotoxicosis.

**Thyrotrophin releasing hormone:** TRH. Peptide hormone produced by hypothalamus in response to low circulating iodothyronine (thyroid hormone) concentrations and some forms of stress.

**Thyrotrophin:** or thyroid stimulating hormone (TSH)**:** A glycoprotein hormone produced by anterior pituitary gland in response to elevated TRH (cf.) or low circulating iodothyronine (thyroid hormone) concentrations. Therefore elevated in primary hypothyroidism, and used as diagnostic test for primary hypothyroidism.

## Triglyceride: Fatty acids join glycerol to form tri-acylglycerol or triglyceride (“fat”). Elevated in poorly controlled diabetes, some dyslipidaemia and insulin resistant states. Tends to be elevated when HDL-C (cf.) is low, and is a risk factor for ischaemic heart disease (IHD).

**Trophic:** Hormone that “nourishes” i.e. encourages growth (e.g. thyroid-stimulating hormone stimulates growth of the thyroid, the gonadotrophins stimulate growth of the gonads).

**Tyrosine:** Is an amino acid precursor for certain hormones (e.g. catecholamines, iodothyronines).

**Vasopressin:** arginine vasopressin (AVP), also known as antidiuretic hormone. Polypeptide hormone synthesised in hypothalamus but released from nerve endings in the posterior pituitary gland (cf. neurohypophysis) in response to increased plasma osmolality and decreased blood volume. It is also released from other hypothalamic fibres which terminate in the median eminence. This hormonal component is released into the hypothalamo-hypophysial portal system, which transports it to the anterior pituitary where it acts as a corticotrophin releasing hormone.

**Vitamin D:** Fat-soluble vitamin, metabolic products of which increase calcium absorption from the intestine. Precursor 7-dehydrocholesterol is converted to cholecalciferol (vitamin D3) in presence of sunlight. Cholecalciferol is hydroxylated at the 25 position in the liver and then at the 1 position in the kidney to form dihydroxycholecalciferol (1,25(OH2)D3), the bioactive metabolite.

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