NATIONAL OPEN UNIVERSITY OF NIGERIA

SCHOOL OF SCIENCE AND TECHNOLOGY

COURSE CODE: NSS213

COURSE TITLE: HUMAN PHYSIOLOGY FOR NURSES I

COURSE GUIDE

NSS213
HUMAN PHYSIOLOGY FOR NURSES I

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Published by
National Open University of Nigeria

First Printed 2009

Reprinted 2013

ISBN: 978-058-690-3

Printed by:

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INTRODUCTION

Physiology is the scientific discipline that deals with the process or functions of living things. It also examines how the parts of the body work and the ways in which they cooperate to maintain life and health of the individual.

One outstanding quality of physiology is that it integrates the individual functions of all the body's different cells and organs into a functional whole, the human or animal body. Indeed, life in the human being relies upon this total function, not on functions of the single parts in isolation from the others.

NSS213: Human Physiology is a two credit course for students in the BNSc. programme. The course is made up of 2 modules with 10 study units. It will introduce the learner to Physiology. At the end of the course, the learner is expected to demonstrate clear understanding of physiology and its application to nursing and holistic patients' care.

This course guide provides you with what to expect in the course, how to work through the course material as a distance learner saddled with the responsibility of studying on your own, and your overall responsibilities and expectations. Tutorial sessions are also linked up with the course to provide the needed support you require.

WHAT YOU WILL LEARN IN THIS COURSE

The overall aim of this course NSS213: Human Physiology is to reveal to you the dynamic nature of the human body. It will also help you to appreciate the functions of the cellular or molecular level in the overall performance of the individual cells and the chemical reactions that go with it.

As you learnt earlier, physiology is the study of the function of anatomical structures. Human physiology is the study of the functions of the human body. These functions are complex and much more difficult to examine than most anatomical structures. As a result, there are even more specialties in physiology than in anatomy, which include:

i. Cell physiology: This is the cornerstone of human physiology; it is the study of the functions of cells. It deals with events at the chemical and molecular levels.

ii. Special physiology: This is the study of the physiology of special organs. For example, renal physiology is the study of kidney function.

iii. Systemic physiology: Includes all aspects of the function of specific organ systems; cardiovascular physiology, respiratory physiology and reproductive physiology are examples of systemic physiology.

iv. Patho-physiology is the study of the effects of diseases on organ or system functions (pathos is the Greek word for "disease"). Modern medicine depends on an understanding of both normal physiology and patho-physiology.

COURSE AIMS

This course aims at providing the learners with in depth understanding of physiology so as to understand and predict the body's response to stimuli and also understand how the body maintains conditions within a narrow range of values in the presence of a continually changing environment.

COURSE OBJECTIVES

To achieve the aims set out above, the course sets the overall objective. In addition, each unit has specific objectives stated at the beginning of a unit. Learners are advised to read them carefully before going through the unit. You will have to refer to them during the course of your study to monitor your progress. You are encouraged to always refer to the unit objectives after completing a unit. This is the way you can be certain that you have done what was required of you in the unit**.**

The wider objectives of the course are to:

- Equip the students with the knowledge of the human body and how the body responds to stimuli
- Equip the students with the understanding of how various organs in the body function to maintain life.
- Provide the students with the basis of understanding disease conditions
- Help the students to know when there is deviation in the body function (homeostasis)

WORKING THROUGH THIS COURSE

To complete this course, you are required to study through the units, the recommended textbooks and other relevant materials. Each unit contains some self assessment exercises and tutor marked assignments that, you will be required to submit. This will be followed by an end of term examination.

COURSE MATERIALS

The following are the components of this course:

1. The course guide
2. Study Units
3. Textbooks
4. Assignment file
5. Presentation schedule

STUDY UNITS

This course is made up of three modules of seven units. These are:

Module 1 Endocrine Physiology

Unit 1 Introduction to Metabolism and Mechanism of Hormone Action
Unit 2 Pancreas and other Endocrine glands

Module 2 Physiology of Genito-Urinary System

Unit 1 Physiology of the Kidneys and Micturition
Unit 2 Renal Control of Fluid and Acid Base Balance

Module 3 Reproductive Physiology

Unit 1 Sexual Reproduction and Endocrine Regulation of Reproduction
Unit 2 Male and Female Reproductive Physiology
Unit 3 Fertilization, Pregnancy and Parturition

TEXTBOOKS AND REFERENCES

Carola, R.; Harley J.P. and Noback, C.R. (1990). *Human Anatomy and Physiology*. New York: McGraw-Hill.

Fox, S.I. (1996). *Human Physiology* Boston: Wm. C. Brown Publishers.

Guyton, A.C.; Hall J.E. (2000). *Textbook of Medical Physiology*. Philadelphia: Saunders Co.

Sherwood, Lauralee (1993). *Human Physiology from Cells to Systems*, Minneapolis: West Publishing Co.

Thibodeau, G.A. and Kevin, T.P. (2000). *Anatomy and Physiology*. St. Louis Mosby.

ASSIGNMENT FILE

The assignment file will contain the Tutor-Marked Assignment (TMA) which will constitute part of the Continuous Assessment (CA) of the course. There are 15 assignments in this course with each unit having an activity/exercise for you to do to facilitate your learning as an individual.

PRESENTATION SCHEDULE

This presentation schedule in this course provides with important dates for completion of each tutor marked assignment. Please try to meet the deadlines.

ASSESSMENT

There are two aspects to the assessment of the course. These are the Tutor-Marked Assignments and written examination. In tackling the assignments, you are expected to apply information, knowledge and strategies gathered during the course. The assignments must be turned in to your tutor for formal assessment in accordance with the stated presentation schedules. The works you submit to your tutor for assessment will count for 30% of your total course work.

At the end of the course you will need to sit for a final written examination of three hour's duration. This examination will also count for 70% of your total course mark.

TUTOR-MARKED ASSIGNMENT

There are 4 Tutor-Marked Assignments to be answered in this course, and you are advised in your own interest to submit the assignments at the stipulated time in your study centre. You will be able to complete the assignments from the information and materials contained in your reading and study units. There are other self-assessment activities contained in the instructional material to facilitate your studies. Try to attempt them all. Feel free to consult any of the references to provide you with broader view and a deeper understanding of the course. Extensions will only be granted for submission after deadline on exceptional cases.

FINAL EXAMINATION AND GRADING

The final examination of NSS213 will be of 3 hours duration and have a value of 60% of the total course grade. The examination will consist of questions which have bearings with the attempted self-assessment

exercises and Tutor-Marked Assignments that you have previously encountered. Furthermore, all areas of the course will be evaluated. Make sure you give enough time to revise the entire course.

COURSE OVERVIEW

This table indicates the units, the number of weeks required to complete the assignments.

Unit	Title of Work	Week Activity	Assessment
	Course Guide	1	
	Module 1 Endocrine Physiology		
1	Introduction to Metabolism and Mecharin of Hormone Action	2	
2	Pancreas and other Endocrine glands	3	
	Module 2 The Physiology of Genito-Urinary System		
1	Renal Control of Fluid and Acid Base Balance	5 & 6	
2	Sexual Reproduction and Endocrine Regulation of Reproduction	7	
	Module 3 Reproductive Physiology		
1	Physiology of the Kidneys and Micturition	8 & 9	
2	Male and Female Reproductive Physiology	10 & 11	
3	Fertilization, Pregnancy and Parturition	12 & 13	

HOW TO GET THE MOST OUT OF THE COURSE

In distance learning, the study units replace the university lecture. This is one of the greatest advantages of distance learning. You can read and work through specially designed study materials at your own pace, at time and place that suit you best. Think of it as reading the lecture notes instead of listening to a lecturer. In the same way that a lecturer might set you some reading task, the study units tell you when to read your other material. Just as a lecturer might give you an in-class exercise, your study units provide exercise for you to do at appropriate points.

The Following are Practical Strategies for Working through the Course:

- Read the course guide thoroughly.
- Organize a study schedule.

- Stick to your own created study schedule.
- Read the introduction and objectives very well.
- Assemble your study materials.
- Work through the units.
- Keep in mind that you will learn a lot by doing all your assignments carefully.
- Review the stated objectives.
- Don't proceed to the next unit until you are sure you have understood the previous unit.
- Review the course and prepare yourself for the final examination.

FACILITATORS/TUTORS AND TUTORIALS

There are 12 hours of effective tutorial provided in support of this course. Details will be communicated to you together with the name and phone number of your tutor(s) through the study centre.
Your tutor(s) will mark and comment on your assignments, keep a close watch on your progress and any difficulties you might encounter and also provide assistance to you during the course. Ensure that you submit your assignments on schedule. You will get a feedback from your tutor(s) as soon as possible to the assignments.
Do not hesitate to contact your tutor(s) or study centre on phone or email in case of any of the following circumstances:

- You do not understand any part of the study units or the assigned reading.
- You have difficulty with the self test or exercises.
- You have questions or problems with an assignment, tutor's comments or grading of an assignment.

You are encouraged to attend the tutorials to allow for face to face contact with your tutor(s) and ask questions which you needed answers immediately. It is also an opportunity to discuss any grey area with your tutor(s). You can equally prepare questions to the tutorial classes for meaningful interactions. You are sure to gain a lot from actively participating in the discussion.

Best of Luck.

MAIN COURSE

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MODULE 1 ENDOCRINE PHYSIOLOGY

Unit 1 Introduction to Metabolism and Mecharin of Hormone Action
Unit 2 Pancreas and Other Endocrine Glands

UNIT 1 INTRODUCTION TO METABOLISM AND MECHANISM OF HORMONE ACTION

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  - 3.1.1 Metabolic Rate
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1.0 INTRODUCTION

Homeostasis depends on the precise regulation of the organs and systems of the body. The nervous and endocrine systems are the two major systems responsible for - regulating and coordinating the activity of nearly all other body structures. The endocrine system exercises control over body structures and functions by sending chemical signals through the circulatory system to target cells/organs where they regulate metabolic processes. Metabolism literally means "change" and refers to all the chemical and energy transformations that occur in the body.

This unit will set the stage for endocrine function by providing a brief summary of energy production and utilization, and the metabolism of food substances as well as introduce how hormone action takes place.

2.0 OBJECTIVES

At the end of this unit you should be able to:

- explain basic terms in energy metabolism
- describe the various processes in carbohydrate metabolism
- explain metabolism of proteins and lipids
- classify hormones according to their chemical nature and explain the basic mechanisms in their actions.

3.0 MAIN CONTENT

3.1 Energy Metabolism

Every animal organism can oxidize carbohydrate, proteins and fats in order to release energy needed for its life processes, in addition to carbon dioxide (CO_2) and water (H_2O). This oxidation is not a one step process in the human body. It is rather a complex, slow and stepwise process of breakdown of these substances, with energy being liberated in small usable amounts. This process of breakdown is called catabolism. The body's energy output can be used up in the body (life processes) while extra energy can be stored in the body in the form of special energy rich in phosphates, proteins, fats and complex carbohydrates synthesized from simple molecules. This process of energy syntheses that takes up rather than liberates energy is called anabolism.

3.1.1 Metabolic Rate

Metabolic rate refers to the amount of energy liberated per unit time. It is measured by either the amount of heat generated by the body or the amount of oxygen consumed by the body per minute. The rate is usually influenced by a number of factors. For example it is increased by increased physical activity and by eating. The unit of measurement of energy commonly used in physiology is the Kilocalorie (Kcal). This is equivalent to 1000 calories. The metabolic rate determined at rest for an awake relaxed person in a room with comfortable temperature, 12 to 14 hours after the last meal is called the Basal Metabolic Rate (BMR). The BMR is determined by a person's age, sex and overall body surface area. BMR is higher in children and declines with age. Females have a slightly lower BMR in all ages than males. BMR is increased in pregnancy because of increased oxygen consumption. Anxiety and tension elevate BMR by causing increased epinephrine secretion and increased tension in

the body, while apathetic depressed individuals may have lower BMR. Hormones that have stimulatory effects on the body like the catecholamine and thyroxin can also raise the BMR.

3.1.2 Energy Balance

The first law of thermodynamics states that energy is neither created nor destroyed when it is converted from one form to another. This is applicable to every living organism. An energy balance therefore exists between caloric intake and energy output. If the caloric intake from food eaten is less than the energy output there is negative balance, this leads to breakdown of endogenous energy stores, for example glycogen, proteins and fats are catabolized and the individual loses weight. If the caloric intake exceeds energy loss (to heat and activity), the energy balance is positive - extra energy is stored in form of glycogen and fats and the individual gains weight.

The BMR of an average sized man is about 2000Kcal/day. To balance basal output so that the energy consuming tasks essential for life (survival) can be performed, the average adult must take in about 2000Kcal/day.

3.1.3 Cellular Respiration/Metabolism of Nutrients

The details of the metabolism of the end products of digestion are the concern of biochemistry. However, an outline of carbohydrate, protein and fat metabolism is essential to an understanding of the action of thyroid, pancreatic and adrenal hormones. These end products of digestion - glucose, fructose and galactose, amino acids, fatty acids are short chain products of, carbohydrate and fats. They are called intermediates. They can either be completely broken down to hydrogen atoms and carbon dioxide, with hydrogen atoms oxidized to form water, or they can be synthesized into larger molecules of carbohydrates, proteins and fats.

The energy liberated by catabolism of these substances is not used directly by cells but is used for formation (synthesis) of ATP from ADP and an inorganic phosphate group. When the energy is needed again, ATP is often converted back. ADP + Pi $\rightarrow$ ATP + Pi and the energy can be used to achieve chemical reactions, active transport and the synthesis of many chemical compounds.

3.2 Metabolism of Carbohydrates

Glucose is the most important common monosaccharide as far as cellular metabolism is concerned. Other monosaccharide includes fructose and galactose - all hexoses or 6-carbon chain products. Glucose is transported in the circulation to all tissues where it is used to produce energy. Excess

glucose in the blood is used to form glycogen, or partially broken down and its components used to form fat which is a long term energy store.

In cellular respiration energy is released by the step wise breakdown of glucose and other molecules, and some of this energy is used to produce ATP. The complete combustion of glucose in the presence of oxygen yields 38 ATP per glucose. However in the absence of oxygen some breakdown of glucose can take place by the pathway that leads to the production of lactic acid. This process produces a net gain of 2 ATP per glucose.

3.2.1 Glycolysis

This is a series of chemical reactions that occurs in the cytoplasm of most cells and results in the breakdown of glucose (6-carbon atoms) to two pyruvic acid molecules (each having three carbon atoms). Two ATP molecules are required to start this process and four ATP molecules are produced during the process, for a net gain of two ATP molecules. In the first step of glycolysis, the glucose molecule is modified by the addition of two phosphate groups from two ATP molecules pyruvate. The modified glucose molecule is then cleaved into two three carbon molecules each with a phosphate group. Each three carbon molecule is then oxidized and the released hydrogen and electrons can be used to produce NADH.

If the cell has adequate amount of oxygen, the pyruvic acid and NADH produced in glycolysis are used in aerobic respiration to produce additional energy (ATP). In the absence of oxygen, ATP can only be produced by anaerobic respiration.

3.2.2 Anaerobic Respiration

In order for glycolysis to continue, there must be adequate amounts of NAD available to accept hydrogen atoms. Therefore the NADH that is produced in glycolysis must become oxidized by donating its electrons to another molecule which in the long run passes its electron to oxygen in aerobic respiration so that NAD is continuously reformed.

When oxygen is not available in sufficient amounts the NADH ($+H^+$) produced in glycolysis is oxidized in the cytoplasm by donating its electrons to pyruvic acid. This results in the reformation of NAD and the addition of two hydrogen atoms to pyruvic acid (which is thus reduced), to produce lactic acid. The pathway by which glucose is converted to lactic acid is called anaerobic respiration and in man is referred to as the lactic acid pathway. Two ATP molecules are also produced by this pathway and this ATP becomes a source of energy during activities such as intense exercise when insufficient oxygen is delivered to tissues.

A cell can survive without oxygen as long as it can produce sufficient energy for its needs through this pathway and as long as lactic acid concentrations do not become excessive. Such tissues are better adapted to anaerobic conditions than others. Skeletal muscles survive longer than cardiac muscle, which in turn survives longer than the brain under anaerobic conditions. Anaerobic respiration can be seen as a sort of emergency procedure to produce ATP until the emergency (oxygen lack) has passed.

It can occur for only a limited period of time - longest for skeletal muscles and shortest for the brain. Anaerobic respiration is a common daily activity in skeletal muscles and does not harm the tissue. Lactic acid production by muscles is however associated with pain and muscle fatigue. Anaerobic respiration occurring in the heart is potentially dangerous.

3.2.3 Aerobic Respiration

Aerobic respiration of glucose also begins with glycolysis. Glycolysis produces two molecules of pyruvic acid, 2 molecules of ATP and two molecules of NADH $+H^+$ per glucose molecule. In aerobic respiration however the electrons in NADH are not donated to pyruvic acid and lactic acid is not formed. Rather the pyruvic acid leaves the cytoplasm and enters the mitochondria where carbon-dioxide is immediately removed from each pyruvic acid to leave a two carbon organic acid called acetic acid and acetic acid is combined with a co-enzyme (from pantothenic acid - a B. Vitamin) called coenzyme A producing acetylcoenzyme A (acetyl-CoA). 2 molecules of acetyl-C_oA and 2 molecules of CO_2 are therefore produced by the two molecules of pyruvic acid derived from each molecule of glucose. Carbon dioxide is carried in the blood to the lungs for elimination. The acetyl-CoA serves as substrates for enzymatic activity in the aerobic pathway.

3.3 The Krebs Cycle

This cycle is named after the principal person that discovered it. It is also known as the citric acid cycle. As soon as acetyl-CoA is formed, then the acetic acid component (2 carbon compound) can combine with oxaloacetic acid (4 carbon compounds) to make a molecule of citric acid (6 carbon compounds). Co-enzyme A acts only as a transporter of acetic acid. The formation of citric acid begins the citric acid cycle or tricarboxylic acid (TCA) cycle.

A series of 7 subsequent reactions take place which results in splitting of Co_2 molecules, regenerating oxaloacetic acid which can continue with another acetyl CoA to form another citric acid and reinitiate the cycle.

Four pairs of hydrogen atoms are also produced by the reduction of 3 NAD and one FAD molecules. Some ATP is also produced NADH and $FADH_2$ are eventually used in the electron transport chain to produce additional ATP. The electron transport chain is a series of electron transport molecules attached to the inner mitochondrial membrane. This electron-transport chain of molecules consists of a flavo protein (derived from the vitamin riboflavin), coenzyme Q (from Vitamin E) and some iron containing pigments called cytochromes. Electrons are transferred from NADH and $FADH_2$ to the electron - transport carriers in a definite sequence and direction.

In aerobic respiration NADH and $FADH_2$ become oxidized by transferring their pair of electrons to the electron transport system.

The oxidized forms of NAD and FAD are regenerated and can continue to "shuttle" electrons from the Kreb's cycle to the electron-transport chain. The electron transport chain thus acts as an oxidizing agent for NADH and $FADH_2$. By a series of oxidation and reduction each element in the chain functions as an oxidizing and a reducing agent until the last stage where the last) donates its electrons to oxygen in the final oxidation - reduction reaction. This whole process is an exergonic process and the energy derived is used to phosphorylate ADP to ATP. This manner of ATP product is called oxidative phosphorylation. In this last step of the electron transport chain, two hydrogen ions and two electrons combine with oxygen to form water. Without the oxygen to accept the hydrogen ions, the citric acid cycle and the electron-transport chain cannot function. It is the presence of oxygen to act as an oxidizing agent at this end point that makes this process of respiration aerobic.

For each glucose molecule, aerobic respiration theoretically produces a net gain of about 38 ATP molecules. Six carbon dioxide and six water molecules are also produced.

3.4 Metabolism of Other Nutrients

Amino acids derived from protein digestions when absorbed into the body are quickly taken up by cells especially in the liver. They are primarily used to synthesize needed proteins and only secondarily as a source of energy. When amino acids have to be used as a source of energy, the amine group ($-NH_2$) is removed producing ammonia and a ketoacid, energy is also released and NADH is formed which can enter the electron-transport chain to produce ATP. Ammonia, being toxic to the body is converted by the liver to urea which is carried by blood to the kidneys from where they are eliminated. The ketoacid can enter the citric acid cycle or be converted into pyruvic acid, acetyl-CoA or glucose.

Fatty Acids

Fat is the main energy storage molecules of the body. Between meals fat is broken down in adipose tissue, some of the fatty acids produced are released into the blood. Other tissues especially skeletal muscle and the liver use the fatty acids as a source of energy.

The metabolism of fatty acids occurs by a series of reactions wherein two carbon atoms are removed from the end of a fatty acid chain to form acetyl-CoA.

The metabolism of fatty acids occurs in the mitochondria, and oxygen is required. As the process continues, 2 carbon fragments are serially split off (at a time) until the entire fatty acid chain is converted into acetyl-CoA. Acetyl CoA can enter the citric acid cycle and be used to generate ATP. In the liver, two acetyl-CoA can also combine to form ketone bodies.

Ketone bodies carried by blood to other tissues like skeletal muscles can be converted back to acetyl-CoA which enters the citric acid cycle to produce ATP. The energy yield of this process is large. For example catabolism of 1 molecule of a 6 - carbon fatty acid through the citric acid cycle to Co_2 and H_2O generates 44 molecules of ATP compared with 38 molecules generated by catabolism of 1 molecule of 6 - carbon carbohydrate (glucose). Also lactic acid which is produced during anaerobic respiration (by exercising skeletal muscles) is delivered by blood to the liver where it is converted (oxidized) back to pyruvic acid. In the process NAD is reduced to NADH.

Pyruvic acid can be converted back to glucose or it can enter the mitochondria and join the citric acid cycle. The conversion of non carbohydrate molecules (amino acids, fatty acids, lactic acid), through pyruvic acid into glucose is a very important process called gluconeogenesis. It is very important in exercise and starvation.

3.5 Mechanism of Hormone Action

Hormones are regulatory molecules secreted into the blood by endocrine glands. The blood carries the hormones to target organs which react specifically to specific hormones. Many endocrine glands are discrete organs whose primary functions are the production and secretion of hormones. These are the organs classified in the endocrine system. However, there may be many other organs in the body performing other major functions but which may also be secreting hormones, such organs include the heart, livers, hypothalamus and kidneys.

3.5.1 Prohormones and Prehormones

Hormone molecules that affect the metabolism of target cells are often derived from less active precursor molecules. For example the precursor for polypeptide hormones may be longer chained prohormones cut and spliced together to make the hormone. Insulin, for example, is produced from proinsulin within the beta cells of the islets of Langerhans in the pancreas. The term prehormone is sometimes used to indicate larger precursor molecule from which the prohormone is derived. In the case of insulin we can have pre-proinsulin.

In some cases prehormone may be used to describe the hormones secreted by the endocrine glands but which are inactive in the target organs. In order to become active, the target cells have to first modify the chemical structure of the secreted hormones before they can affect the target cells. For example Thyroxin (T_4) must be changed to T_3 in the target cells before they can affect the metabolism of the target cells. Similarly testosterone (from the testes) and vitamin D_3 (from the skin) are converted into more active molecules within their target cells, before they can exert their effect.

3.5.2 Hormones Classification and Mechanism of Action

All hormones can be grouped into three general chemical categories:

1. Catecholamine (epinephrine and nor epinephrine).
2. Polypeptides and glycoprotein - these include shorter chain polypeptides such as antidiuretic hormone and insulin and large glycoprotein such as thyroid stimulating hormones.
3. Steroids such as cortisol and testosterone. Steroid hormones are lipids derived from cholesterol and thus are not water soluble.

Thyroid hormones are derivatives of the amino acid tyrosine. They contain iodine. They are not steroids but they like steroids in that are relatively small.

Steroids and thyroid hormones are active when taken orally (as a pill). Other types of hormones cannot be taken orally because they would be digested into inactive fragments before being absorbed e.g. polypephades. Each hormone exerts its own characteristic effects on target organs through the actions it has on the cells of these organs. However hormones that are in the same chemical category have similar mechanisms of action. The similarities are in the location of cellular receptor proteins and the events that occur in the target cells after the hormone has combined with its receptor protein.

Hormones are delivered to every cell of the body by the blood, but only the target cells are able to respond to these hormones. In order for a target

cell to respond to any given hormone, it must have specific receptor proteins for that hormone. The interaction of receptor protein and hormone is highly specific.

As mentioned earlier, the chemical nature of a hormone determines the location of its receptor proteins in its target cells. Based on the location of receptor proteins, hormones can be grouped into three categories:

1. Receptor proteins within the nucleus of target cells e.g. thyroid hormones and some steroid hormones
2. Receptor proteins within the cytoplasm of target cells e.g. steroid hormones.
3. Receptor proteins on the outside surface of the target cell membrane e.g. catecholamine and polypeptide hormones.

3.5.3 Steroid and Thyroid Hormones

These hormones are not water soluble in the plasma therefore they cannot travel dissolved in the plasma but are transported to their target cells attached to plasma carries proteins. They dissociate themselves from the carrier protein in the blood, (when they get to the target cells) and easily pass through the lipid part of the old membrane. Once inside the target cells, they can bind to their receptor proteins either in the cytoplasm or in the nucleus before exerting their effects.

Catecholamine hormones and polypeptide hormones cannot pass through the lipid barrier of the target cell membrane. Therefore they have to bind to their receptor proteins on the outer surface of the target cell membrane. Since they exert their effects within the target cells, their actions are mediated by other molecules within the target cells. Since the hormones themselves can be regarded as messengers from the endocrine glands, the intracellular mediators of the hormones actions can be called second messengers.

The beta adrenergic effects of epinephrine and nor epinephrine are mediated by cyclic adenonosine monophosphate (cAMP), while the alpha adrenergic effects are mediated by calcium ions ca^{2+}

3.5.3 Hormone Interactions

A number of different hormones may be acting on a given target tissue at a time. These hormones may antagonize each other or work together to produce effects that are additive or complementing. The response of a target tissue to a particular hormone is thus affected not only by the concentration of those hormones on that tissue. Such terms as synergistic, permissive and antagonistic effects can therefore be used to describe hormone interactions.

Synergistic effects refer to when two or more hormones work together to produce a particular result. The effects may be additive or complementary. The action of epinephrine and norepinephrine on the heart is a good example of additive effect. Each of the hormones separately produces an increase in heart rate, acting together in the same concentrations; they stimulate an even greater increase in cardiac rate. A complementary synergistic action is demonstrated by FSH and testosterone. Each hormone stimulates a different stage of spermatogenesis during puberty so that both hormones are needed at that period to complete sperm development.

A hormone is said to have a permissive effect on the action of a second hormone, when it enhances the responsiveness of a target organ to the second hormone. For example glucocorticoids exert permissive effects on the actions of catecholamine without which the catecholamine will not be as effective as they are normally. Also oestrogen has a permissive effect on the action of progesterone on the uterus. Some of the effects will be discussed later.

Antagonistic effects refer to the action of one hormone out rightly inhibiting the effects of another. For example the high concentration of oestrogen in the blood during pregnancy inhibits the secretion and action of prolactin. Therefore, lactation is inhibited. Also the action of two hormones - insulin and glucagons from the islets of Langerhans are antagonistic.

4.0 CONCLUSION

The endocrine system is one of two major systems that regulate balance within the organs and systems of the body. Endocrine regulation and integration are brought about by hormones which are chemical messengers produced by ductless glands, and transported in the circulation to target cells where they regulate the metabolic processes. Metabolism refers to all the chemical and energy transformations that occur in the body.

5.0 SUMMARY

In this unit we have learnt about some introductory concepts that will help us understand hormone action better. These concepts concern metabolism and energy balance. The reason is that the major activity of hormones is to regulate metabolic activities in their target cells and metabolism has to do with energy transformations within the cell. The release of energy which is essential for the life processes in human is not a one step process; rather it is a complex step by step process of breakdown of substances with energy being released in small amounts at a time. Metabolic rate refers to the amount of energy liberated per unit time. It is measured in kilocalories (the large calorie) and is affected by such factors as the amount of physical activity and nutrient intake (eating). Since energy is

neither created nor destroyed but can only be changed from one form to another, an energy balance exists in living organisms between caloric intake and energy output (expenditure). A negative energy balance brought about by a caloric intake lower than energy output leads to breakdown of endogenous energy stores leading to weight loss. A positive energy balance leads to extra energy stores and weight gain. Energy released by the catabolism of nutrients is used to form ATP which is used to drive chemical reactions in the body. Glycolysis is a metabolic pathway for the breakdown of glucose where 6 carbon sugars (hexoses) are broken down to 2 pyruvic acid molecules (3 carbon molecules) with a net gain of 2 ATP molecules. Carbohydrate metabolism continues from there in an anaerobic or aerobic tissue respiration depending on whether oxygen supply is sufficient or not. In conditions of anaerobic respiration pyruvic acid is converted to lactic acid especially in skeletal muscles. Under aerobic conditions pyruvates enter the mitochondria where through a series of steps, 38 molecules of ATP, carbon-dioxide and water are produced from the complete breakdown of a molecule of glucose in the Kreb's or citric acid cycle. Proteins, necessary lipids and lactic acid can also be converted to glycognic forms by a process of gluconeogenesis, in order for them to enter the various pathways for the metabolism of carbohydrates. Hormones which are chemical messengers from ductless glands are classified according to their chemical structure. Those with similar chemical structures have similar mechanisms of action. The specification of each hormone depends on the site of the receptor molecule in the target organ. Hormonal interaction can occur in the target organs producing synergistic, additive or antagonistic effects.

6.0 TUTOR-MARKED ASSIGNMENT

Compare the fate of pyruvic acid in aerobic respiration with its fate in anaerobic respiration.

7.0 REFERENCES/FURTHER READING

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UNIT 2 THE PANCREAS AND OTHER ENDOCRINE GLANDS

1.0 Introduction
2.0 Objectives
3.0 Main Content
3.1 Description of the Pancreatic Islet Cells
3.1.1 Functions of the Pancreatic Hormones
3.1.2 Glucagon
3.1.3 Insulin
3.1.4 Insulin Deficiency and Insulin Excess
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3.3 Other Endocrine Glands in the Body
3.3.1 The gonads and placenta
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1.0 INTRODUCTION

The endocrine part of the pancreas which is the pancreatic islets (the Islets of Langerhans) secretes two major hormones - insulin and glucagon. Insulin promotes the lowering of blood glucose and the storage of energy in the form of glycogen and fats Glucagon has antagonistic effects that act to raise blood glucose concentrations.

There are also a few other organs in the body that secrete hormones which help to regulate activities like digestion, metabolism, growth, immune function and reproduction.

2.0 OBJECTIVES

At the end of this unit you should be able to:

- describe the location, structure and functions of the pancreatic islet cells
- list the hormones of the Islets of Langerhans and explain their functions

- discuss insulin deficiency and insulin excess and their consequences
- describe the regulation of pancreatic hormones
- describe the rest of the endocrine organs in the body and explain the functions of their hormones
- describe autocrine and paracrine regulation in the body.

3.0 MAIN CONTENT

3.1 The Pancreatic Islet Cells

The pancreas is both an endocrine and exocrine gland. The endocrine portion of the gland consists of clusters of cells called the pancreatic islets or islets of Langerhans, which are dispersed among the exocrine portions of the gland.

The Islet cells are ovoid in shape and are scattered as collections of cells throughout the pancreas but they are more plentiful in the tail than in the body and head of the pancreas. The islet cells make up only about 1 - 2% of the weight of the pancreas and they are about 1 - 2 million in number.

The cells of the islets can be divided into types based on their staining properties and structure. There are at least four distinct cells types secreting four different peptides with hormonal activity - the A (alpha), B (beta), D and F cells. The A or alpha cells secrete glucagon, the B or beta cells secrete insulin cells secrete insulin, the D cells secrete somatostatin and the F cells secrete the pancreatic polypeptide. The beta cells are the most common accounting for 60 - 75% of the cells in the islets and are located at the centre. The alpha cells make up about 20% of the cells of the islets and they surround the beta cells followed by the less common D and F cells.

3.1.1 Functions of the Pancreatic Hormones

At the microscopic level, the most conspicuous cells in the islets are the alpha and beta cells which secrete the major hormones of the islets of Langerhans - glucagon and insulin. The function of these two hormones is to keep the blood glucose levels within a normal range since this is vital for the nervous system.

3.1.2 Glucagon

Glucagon is glycogenolytic, gluconeogenic, lypolytic and ketogenic. These terms refer to the fact that it acts on various metabolic pathways to cause increase in blood glucose level.

The Apha cells secrete glucagon in response to a fall in blood glucose concentrations. Glucagon acts primarily on the liver stimulating it to hydrolyze glycogen to glucose (glycogenolysis). When the glycogen store in the liver is converted to glucose, and the glucose is released in the blood, blood glucose level rises.

Glucagon also stimulates lipolysis, that is, causes the breakdown of stored fat with consequent release of free fatty acids into the blood. This effect helps to provide energy for the body during fasting when the body's energy reserves must be utilized.

3.1.3 Insulin

Insulin is a polypeptide containing 2 chains of amino acids joined together by a disulphide bond. The Beta cells secrete insulin in response to a rise in blood glucose concentrations. Insulin basically promotes entry of glucose into tissues, and the conversion of this glucose into storage molecules of glycogen and fat.

Insulin is the major hormone that promotes anabolism in the body. When absorption of products of digestion is taking place, there is a rise in plasma levels of circulating energy substrates like glucose and amino acids, insulin promotes the cellular uptake of plasma glucose and its incorporation into energy reserve molecules of glycogen in the liver and muscles and of triglycerides in adipose tissue cells.

Insulin also promotes the cellular uptake of amino acids and their incorporation into proteins. The stores of large energy reserve molecules are thus increased while the plasma levels of glucose and amino acids are decreased.

The major target tissues for insulin are the liver, adipose tissue, muscles and the area of the hypothalamus that controls the appetite centre. Insulin increases the rate of glucose and amino acid uptake in these tissues.

3.1.4 Insulin Deficiency and Insulin Excess

Inadequate secretion of insulin or defects in the action of insulin (that is absolute or relative deficiency), produce a metabolic disturbance called diabetes mellitus. Diabetes mellitus can result from any of the following: too little secretion of insulin from the pancreas, insufficient numbers of insulin receptors on target cells, or defective receptors that do not respond normally to insulin.

In people who have diabetes mellitus, tissues cannot take up glucose effectively, causing blood glucose levels to become very high, a condition

called hyperglycemia. Because glucose cannot enter even the satiety centre of the brain, the satiety centre responds as if there were little blood glucose resulting in exaggerated appetite which worsens the problem. The excess glucose in the blood is excreted in urine, causing the urine volume to become much greater than normal. Excessive urine production makes the person to have a tendency to become dehydrated and thirsty. In addition fats and amino acids are broken down to provide an energy source for metabolism and this results in the wasting away of body tissues and acidosis as well as a general lack of energy.

There are two forms of diabetes mellitus. One is the insulin-dependent diabetes mellitus (IDDM). This is also called Type I diabetes. Here the beta cells are progressively destroyed and secrete little or no insulin. It accounts for only about 10% of known cases of diabetes. It occurs in people under the age of 20, therefore it is also referred to as juvenile diabetes. The second form is the non-insulin-dependent diabetes mellitus (NIDDM), also called Type II diabetes. This is present in about 90% of cases of diabetes. The non-insulin-dependent diabetes mellitus is usually diagnosed in people over 40 years of age.

An excessive secretion of insulin results in hypoglycaemia. This occurs usually when a diabetic is injected with too much insulin or when he has not eaten after an insulin injection. All known consequences of insulin excess are manifestations directly or in directly, of the effects of hypoglycaemia on the nervous system especially on glucose, the almost only source of energy used in the brain. Some of the symptoms include disorientation, convulsions, loss of consciousness and even death.

3.1.5 Other Pancreatic Hormones

The third hormone secreted by the islets of Langerhans of the pancreas is called somatostatin which is a polypeptide like the first two, and is secreted by the delta (D) cells.

The physiological role of islet secreted somatosatin is not clearly known. However some authorities claim that it may have a role to play in the regulation of islet secretions.

The fourth possible hormone of the islets of Langerhans of the pancreas is called pancreatic polypeptide and its physiologic function is unsettled.

3.2 Regulation of Pancreatic Hormones

Insulin and Glucagon secretion is largely regulated by the plasma concentration of glucose and to lesser degree amino acids. The plasma concentration of glucose and amino acids rises during the absorption of a

meal and falls during fasting (post-absorptive state), therefore the secretion of insulin and glucagon also fluctuates between the absorptive and post-absorptive state. These changes in insulin and glucagon secretion in turn cause changes in plasma glucose and amino acid concentrations and thus help maintain homeostasis via negative feedback.

During the absorption of a carbohydrate meal, the plasma glucose concentration rises. This rise stimulates the beta cells to secrete insulin while it inhibits the secretion of glucagon from the alpha cells. Insulin stimulates the cellular uptake of plasma glucose. The rise in insulin secretion therefore lowers the plasma glucose concentration.

Glucagon, however, has an antagonistic effect of raising blood glucose levels by stimulating glycogenolysis in the liver. The inhibition of glucagon secretion complements (supports) the effect of increased insulin during the absorption of a carbohydrate meal. A rise in insulin and a fall in glucagon secretion thus help to lower the high plasma glucose concentration that occurs during periods of absorption.

During fasting (post absorptive periods) glucose concentrations will usually be low. At this time, therefore, insulin secretion decreases and glucagon secretion increases. The result of these two events is that the cellular uptake of blood glucose into organs like muscles, liver and adipose tissue is prevented, while release of glucose from the liver (glycogenolysis) by the action of glucagon is promoted. A negative feedback loop is therefore completed helping to stop the fall in blood glucose levels that occur during fasting.

3.3 Other Endocrine Glands

There are other organs that secrete hormones which help to regulate digestion, metabolism, growth, immune function and reproduction, apart from the major ones already described. These include the gonads, the thymus glands, pineal body and so forth.

3.3.1 The Gonads and Placenta

The gonads (testes of the male and ovaries of the female) secrete sex hormones in addition to producing sperm cells and egg cells. The male sex hormones are called androgens while the female sex hormones are oestrogens and progestrogens. The principal androgen is testosterone and the main oestrogen is oestradiol while the principal progestogen is progesterone.

The testes is made up of the seminiferous tubules and the interstitial tissue between the folds of seminiferous tubules. The interstitial tissues contain

Leydig cells which secrete testosterone. Testosterone is responsible for the growth and development of the male reproductive structures (penis and scrotum) and male sex accessory organs (prostate, seminal vesicles, epididymis and vas deferens), muscle enlargement, growth of body hair, voice changes and increased male sexual drive (the secondary sexual characteristics).

The two classes of hormones in the female together contribute to the development and function of female reproductive structures and other female sexual characteristics - like enlargement of the breasts and distribution of body fat which influences the shape of the hip, breasts and legs. There is a cyclical release of oestrogen and progesterone from the ovaries and these controls the female menstrual cycle.

In the first half of the menstrual cycle, oestrogen is secreted by small structures in the ovaries called the ovarian follicles. These follicles contain the egg cell (ovum) and granulosa cells which secrete oestrogen. By about the mid cycle, one of these follicles grows large and mature and extrudes its ovum from the ovary in a process called ovulation. The empty follicle under the influence of luteinizing hormones (LH) from the anterior pituitary becomes a new endocrine structure called a corpus luteum. This corpus luteum secretes progesterone as well as oestradiol.

The placenta - the organ responsible for nutrient and waste exchange between the foetus and mother is also another endocrine gland in that it secretes large amounts of oestrogens and progesterone during pregnancy. It also secretes a number of polypeptide and protein hormones similar to some anterior pituitary hormones. These include the human chorionic ganadotropin (hCG) which is similar to LH, and somatomammotropin which functions like both growth hormone and prolactin.

The regulation of the hormones of the gonads is done by LH and FSH from the anterior pituitary gland.

3.3.2 The Thymus Gland

The thymus gland is a two-lobed organ positioned in front of the aorta behind the manubrium of the sternum in the upper part of the thoracic cavity. The size of the thymus varies from person to person, but it is relatively large in newborns and children and sharply regresses in size after puberty.

The thymus gland serves as the site for production of T-cells (thymus-dependent cells) which are lymphocytes involved in cell-mediated immunity. The thymus also secretes some hormones principally thyrosin which also help to stimulate and develop T cells.

3.3.3 The Pineal Body (Pineal Gland)

This is a small cone shaped gland located in the roof of the third ventricle behind the thalamus in the brain, where it is encapsulated in the meningeal covering of the brain. In a child it weighs about 0.20 and is 5mm to 8mm long and 9mm wide. It begins to regress from about age 7. Its secretion is highest in children between 1 - 5 years and decreases thereafter reaching lowest levels by the end of puberty.

The principal hormone of the pineal body is called melatonin. Melatonin is thought to inhibit the pituitary gonad axis in some species; hence a decrease in melatonin secretion is responsible for maturation of the gonads in their reproductive seasons.

In humans, it is thought to decrease the secretions of LH and FSH by decreasing the release of hypothalamic - releasing hormones. Melatonin therefore acts to inhibit the function of the reproductive system. There are suggestions that withdrawal of malatonin may play an important role in the onset of puberty in humans. Excessive secretion is associated with a delay in the onset of puberty.

3.3.4 Gastrointestinal Tract

Cells in the Lining of the stomach and small intestine secrete hormones that act on the gastrointestinal tract itself, the pancreas, gall bladder and liver. These hormones working together with the autonomic nervous system coordinate the activities of different regions of the digestive system and the secretions of pancreatic juice and bile, as well as the rate at which food passes from the stomach into the small intestine.

3.4 Autocrine and Paracrine Regulation

There are many regulatory molecules produced throughout the body which act within the organs where they are produced. These molecules may regulate different cells within one tissue, or may be produced within one tissue and regulate a different tissue within same organ.

These regulatory molecules differ from other regulatory molecules like hormones in that they are produced in many different organs and are active within the same organs where they are produced. These types of molecules are called autocrine regulators if they act within the same tissue where they were produced. Those ones which are produced within one tissue and regulate a different tissue of the same organ are called paracrine regulators. Since the same molecules can function as an autocrine or paracrine regulator in different situations, the term autocrine will be used in a generic sense to refer to both types of local regulation.

3.4.1 Examples of Autocrine Regulation

Autocrine regulators which act in the immune system are called cytokines, and those that promote growth and cell division in any organ are called growth factors. Cytokines are generally produced by T cells in the immune system. They are proteins or peptides secreted by one cell as a regulator of neighboring cells. Those cytokines produced by lymphocytes are called lymphocytes. However these cytokines are referred to as interleukins based on the specific molecular nature, since each cytokine has many different actions. Hence the name interleukin followed by a number is used to designate a cytokine once its particular amino-acid sequence is known. For example interleukin - 2 is secreted by helper T-lymphocytes and is required for the activation of killer T lymphocytes among other actions.

Cytokines produced by macrophages (found in connective tissues) stimulate proliferation of specific cells involved in the immune system. Neutrotrophins like nerve growth factor guide regenerating peripheral neurons that have been injured. Nitric oxide is another paracrine regulator produced by the endothelium of blood vessels and diffuses to the smooth muscle layer of the blood vessels where it promotes smooth muscle relaxation leading to dilation of blood vessels.

The endothelial layer of blood vessels also produces other paracrine regulators including endothelins (endothelin - I in humans) which directly promotes vasoconstriction and bradykinin, which promotes vasodilatation. These regulatory molecules are therefore very important in the control of blood flow and blood pressure.

3.4.2 Prostaglandins

A prostaglandin is a 20-carbon chain fatty acid derived from the precursor molecule arachidonic acid released from the phospholipids in the cell membrane under hormonal action. Prostaglandins constitute the most diverse group of autocrine regulators.

Prostaglandins are produced in almost every organ and they perform a wide variety of regulatory functions, some of which may even have opposing effects in different organs. For example, prostaglandins of the E series (PGE) cause smooth muscles of the bladder; bronchioles, intestine and uterus to relax, but they cause vascular smooth muscles to contract.

Functions of Prostaglandins

In the immune system, they promote aspects of the inflammatory process including the development of pain and fever. They are released by

damaged tissue and cause blood vessel dilatation, localized swelling and pain.

In the reproductive system, prostaglandins play a role in ovulation and Corpus luteum function in the ovaries and in contraction of the uterus. Excessive prostaglandin production may be involved in premature labour, dysmenorrheal and other gynecological disorders.

In the urinary system they are produced in the renal medulla and cause vasodilatation resulting in increased renal blood flow and increased excretion of water and electrolytes in urine. In the digestive system, the stomach and intestines produce prostaglandins that inhibit gastric secretion and influence intestinal motility and fluid absorption. Prostaglandins produced by platelets seem to be necessary for blood clotting to occur normally.

Prostaglandin Synthesis Inhibitors

These are a group of substances that interfere with the pathway for the synthesis of prostaglandin from arachidonic acid. They specifically inhibit the enzyme needed for the synthesis. Such drugs include aspirin (the most common), indomethacin, and ibuprofen. They reduce pain and inflammation, help prevent painful cramping of the uterus, relieve headache and so forth. They also produce unwanted side effects like gastric bleeding and prolonged clotting time.

4.0 CONCLUSION

The pancreas secretes two hormones insulin and glucagon. These two hormones have antagonistic effects in their regulation of blood glucose levels and other aspects of glucose metabolism. Insulin acts to lower blood glucose level while glucagons act to raise the level of blood glucose. There are many other hormonal substances produced by organs like the thymus, and pineal glands that perform very important roles in the body. Many other organs like the intestines, kidneys and placenta also produce hormones for specific activities.

Autocrine regulators are hormonal substances which are produced by some cells of certain tissues but they exert their effects either within the same cells or in other cells of the same tissues. There are many of them secreted in almost all the organs of the body where they also function without having to travel far in the circulatory system.

5.0 SUMMARY

In this unit we learnt about the endocrine part of the pancreas called the islets of Langerhans which principally secrete two hormones, insulin and glucagon both of which function to regulate blood glucose levels, but their actions are opposing to each other. The pineal body situated behind the thalamus in the brain secretes melatonin which principally acts to inhibit the function of the reproductive system in humans. The thymus gland acts as the site for the production of T-cells which are responsible for cell-mediated immunity in the body. The gonads in the male secret androgens, the principal hormone of which is testosterone. Testosterone acts for the growth and development of the male reproductive structures and the accessory sex organs. In the female the gonads produce oestrogens and progestogens. These two function together for the development of female reproductive structures and other female sexual characteristics. Cytokines are hormonal regulators in tissues and organs in the body. They do not travel far in the circulation instead they act in neighboring organs or tissues or within the same organs or tissues. Prostaglandins are very common autocrine regulators produced by most organs of the body. They perform many functions ranging from the immune system to the gastrointestinal, the blood vessels and the reproductive system.

6.0 TUTOR-MARKED ASSIGNMENT

Explain the actions of insulin and glucagon.

7.0 REFERENCES/FURTHER READING

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MODULE 2 PHYSIOLOGY OF GENITO-URINARY SYSTEM

Unit 1 Physiology of the Kidneys and Micturition
Unit 2 Renal Control of Fluid and Acid Base Balance

UNIT 1 PHYSIOLOGY OF THE KIDNEYS AND MICTURITION

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1.0 INTRODUCTION

The urinary system is made up of two kidneys, two ureters, a urinary bladder and one urethra that open to the outside. The major function of the kidney is to form urine from plasma filtrate. By this urine formation, the kidneys regulate the extracellular fluid environment of the body. Urine formed in the kidneys enters the renal pelvis and is conducted out of the body via the ureters to the urinary bladder from where after temporary storage it is expelled to the outside by the process of micturition. Urine contains excess water and ions.

2.0 OBJECTIVES

At the end of this unit you should be able to:

- briefly describe the gross anatomy of the urinary system
- explain the functional anatomy of the kidney
- describe the formation of urine in terms of the three basic renal processes of glomerular filtration, tubular reabsorption and secretion
- describe the process of micturition.

3.0 MAIN CONTENT

3.1 Anatomy of the Urinary System

The kidneys are bean shaped organs each about the size of a tightly clenched fist, weighing about 160grams and measuring about 12cm long and 6cm wide. Two kidneys lie on either side of the vertebral column below the diaphragm and behind the peritoneal cavity of the abdomen. On the medial side of the kidney is the ilium where the renal artery and nerves enter and where the renal vein and ureter leave the kidney.

A longitudinal section of the kidney shows that the kidney is divided into two distinct parts - the **cortex** and the **medulla**. The cortex is the outer portion which extends from the renal capsule inside and is reddish brown in colour while the medulla is the deeper portion that is lighter in colour and appears stripped in appearance. The medulla contains eight to fifteen conical structures called **pyramids,** the bases of which are located at the boundary between the cortex and the medulla. The tip of each pyramid tip project towards the centre of the kidney into a small depression called **minorcalyx**. Several minor calyces from different pyramids unite to form a major calyx which in turn joins others form a larger funnel-shaped structure called the **renal pelvis.** The renal pelvis narrows to form a small tube, the ureter which exits the kidney and connects to the urinary bladder.

The **Ureters** are small tubes that carry urine from the renal pelvis to the posterior inferior portion of the urinary bladder. The **urinary bladder** is a hollow muscular sac that lies in the pelvic cavity just behind the symphysis pubis. It is a storage sac for urine and the size and shape depend on the amount of urine present in it. It can change from triangular to ovoid as it bulges into the abdominal cavity and can hold from a few drops to a maximum of about one litre of urine.

The ureters and urinary bladder are lined on the inside by transitional epithelium that can stretch, changing its shape from columnar to flat as the volume of urine increases.

The walls of the ureter and urinary bladder are composed of layers of smooth muscle. It is the regular contraction of these smooth muscles that produce the force which causes urine to flow from the kidneys, through the ureters to the bladder, and from the bladder through the urethra to the outside.

The **urethra** is a tubular organ that drains the urinary bladder inferiorly and anteriorly. The female urethra measures 4cm long and opens on to the vulva, while the male urethra measures about 20cm long and opens at the tip of the penis. The openings of the urethra are controlled by two muscular sphincters - the internal urethral sphincter and the external urethral sphincter. The internal sphincter is made up of smooth muscles of the bladder and is under involuntary control. The external sphincter is composed of skeletal muscles and is under voluntary control.

3.2 Functional Anatomy of the Kidney

The kidney tissue is made up of over a million nephrons. The **nephron** is the functional unit of the kidney responsible for the formation of urine. Each nephron is made up of tubules and associated blood vessels. The tubules consist of an expanded portion called the renal corpuscle (**Bowman's capsule and Glomerulus**), a promximal convoluted tubule, a loop of Henle and distal convoluted tubule which empties into a collecting duct.

The **glomerular (Bowman's) capsule** surround the glomerulus and both of them make up the renal corpuscle and they are found in the cortex as well as both convoluted tubules. The Loop of Henle and collecting tubule enters the medulla.

Arterial blood supply normally enters the kidney through the renal artery. This artery divides and further divides into arcuate and interlobar arteries till they subdivide into numerous afferent arterioles in the renal cortex. The afferent arterioles carry blood into capillary network called glomeruli (singular-glomerulus). These glomeruli produce a blood filtrate (glomerular filtrate) that enters the urinary tubules. The remaining blood in the glomerulus leaves the glomerulus through the efferent arteriole which breaks up again into tiny capillaries that surround the tubules.

The Bowman's capsule contains two layers of epithelial cells around the glomerular capillaries. The space between these two layers continues with the lumen of the proximal convoluted tubules and receives the glomerular filtrate. The wall of the proximal convoluted tubules have a single layer of cuboidal cells through which, salt, water and other needed molecules can diffuse back into the peritubular capillaries during the process of reabsorption. Fluid from the proximal convoluted tubules passes to the

Loop of Henle. The fluid goes down into the medulla through the descending limb of the loop and back into the cortex through the ascending Loop. Here the tubule coils again and becomes **the distal convoluted tubule**. This is the last portion of the nephron that terminates as it joins a collecting tubule (duct). The collecting tubule extends from the cortex into the medulla and empties its contents into a calyx.

The descending limb of the Loop of Henle has very thin walls made up of simple squamous epithelium. The remaining parts and the collecting duct are made up of simple cuboidal epithelium.

DIAGRAM OF A NEPHRON

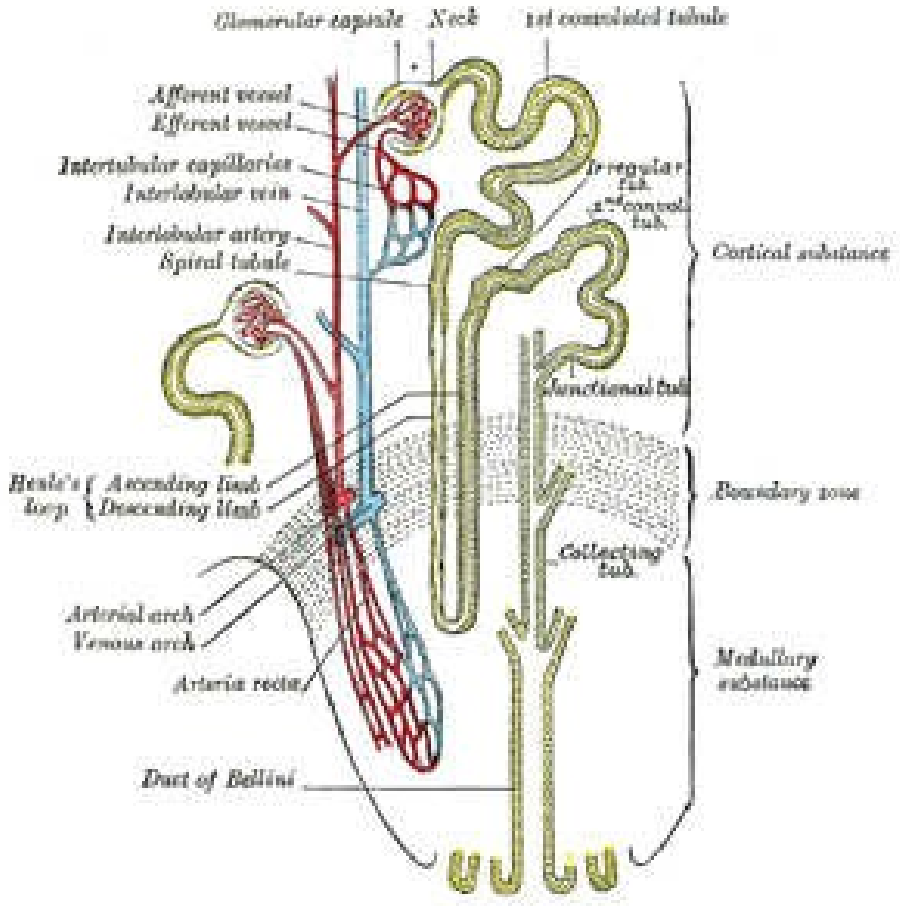

Fig. 1: The Nephron of the Human Kidney

http://en.wikipedia.org/wik

3.3 Formation of Urine

The formation of urine involves three processes which are filtration, reabsorption and secretion.

3.3.1 Filtration

Is involved with the passage of plasma through the filtration membrane of the renal corpuscle. An average of 21% of the blood pumped by the heart each minute flows through the kidneys. A significant percentage of this volume averaging about 180 litres of fluid, pass through the filtration membrane into the Bowman's capsule as filtrate daily. However only about 1% of the filtrate eventually becomes urine.

The filtration membrane is made up of the wall of the glomerular capillaries in close contact with the inner visceral layer of the Bowman's capsule. Filtration through this membrane is facilitated by the presence of large pores (called fenestrate) which allows some substances but not others to pass from the blood into the Bowman's capsule. The glomerular capillaries are therefore very permeable to water and dissolved solute but blood cells and proteins are too large to pass through. The inner layer of the Bowman's capsule also possesses special products which have a lot of foot like processes called pedicels which wrap themselves around the glomercular capillaries. The narrow slits (openings) between adjacent pedicels also provide passageways through which filtered molecules pass to enter the lumen of the glomerular (Bowman's) capsule. Although some plasma proteins such as albumin may be small enough to pass through the fenestrate and slits, their negative charges prevent (repel) them from passing through the negatively charged filtration membrane. Thus only a small amount of plasma proteins is present in the filtrate.

The filtrate in the Bowman's capsule is formed under pressure - the filtration pressure. This filtration pressure is the net pressure resulting from the hydrostatic pressure of the blood (Glomerular capillary blood pressure) forcing the filtrate into the glomerular capsule and the opposing forces that promote return of filtered water. These opposing forces result from the hydrostatic pressure of the fluid in the glomerular capsule and the osmotic pressure of plasma which promotes osmotic returns of filtered water because the protein concentration of the filtrate is lower than that of plasma. The result is a net filtration pressure of about 10mm Hg. When the net filtration pressure increases, the volume of filtrate and ultimately of urine increases, and vice versa.

The filtration pressure is therefore influenced by factors such as blood pressure in the glomerular capillary, the blood protein concentration and the concentration of solutes that enter the Bowman's capsule. Conditions

in which filtration pressure decreases include periods of excitement, rigorous physical activity, or emergency conditions such as a sudden decrease in blood pressure during cardiovascular shock.

The fluid that enters the glomerular capsule is called ultrafiltrate. The volume of filtrate produced per minute by both kidneys is called the Glomerular Filtration Rate (GFR).

3.3.1.1 Regulation of Glomerular Filtration

Since the net filtration pressure responsible for inducing glomerular filtration is due to an unbalance of opposing physical forces between the glomerular capillary plasma and Bowman's capsule fluid, alteration in any of these physical forces can affect glomerular filtration.

Under normal conditions however, the opposing forces which are the hydrostatic pressure of fluid in the Bowman's capsule and the osmotic pressure of plasma colloids, do not vary substantially and therefore do not need regulation. They can only change pathologically and inadvertently affect Glomerular Filtration Rate (GFR). For example, an uncontrollable reduction in plasma protein as occurs in severe burns can lead to increased glomerular filtration rate because of increased net filtration pressure and vice versa. Also obstruction in the urinary tract can lead to damming up of fluid behind the obstruction and this can lead to uncontrollable increase in the Bowman's capsule hydrostatic pressure. This will in turn decrease filtration rate due to lowered net filtration pressure.

Unlike the situations described above, under normal circumstances (all other factors remaining constant) it is the glomerular capillary blood pressure which can be controlled or regulated to adjust the GFR to suit the body's needs. Under normal circumstances the glomerular capillary blood pressure depends on the rate of blood flow in the glomerular which in turn depends on the magnitude of the mean systemic arterial blood pressure and the resistance offered by the afferent arterioles.

There are two mechanisms for the regulation of GFR and both of them are directed at adjusting the glomerular blood flow by regulating the caliber and therefore the resistance of the afferent arteriole. The two mechanisms are autoregulation and sympathetic control.

1. Autoregulation of GFR

The main force that drives blood into the glomerulus is the arterial blood pressure. Therefore the glomerular capillary blood pressure and accordingly the GFR will both increase with increase in arterial blood pressure and a fall in arterial blood pressure will lead to a decrease in

GFR. By autoregulation the kidneys themselves can maintain a constant blood flow, within limits, in the glomerular capillaries thereby preventing spontaneous changes in GFR. This is an intrinsic regulatory mechanism initiated by the kidneys to ensure a constant glomerular capillary blood flow and a stable GFR despite changes in the arterial blood pressure. This is achieved by changing the caliber of the afferent arterioles and thereby adjusting resistance to flow through these vessels. For example, when there is rise in arterial blood pressure which can push up the GFR, this can be prevented by constriction of the afferent arteriole which decreases the flow of blood into the glomerulus. This adjustment now lowers the glomerular blood pressure and GFR is maintained at normal. On the other hand when GFR falls as a result of lowered arterial blood pressure, vasodilation of the afferent arteriole occurs so that more blood is permitted to flow through, thereby raising the glomerular blood pressure which then maintains the GFR at normal levels.

Autoregulation is important because unintentional shifts in GFR could lead to dangerous imbalances of fluid, electrolytes and wastes. When mean arterial blood pressure falls outside the autoregulatory range of (280mmHg < 180mmHg), the mechanism will not be able to compensate for it, therefore the second control mechanism is called intrinsic sympathetic control.

2. Extrinsic Sympathetic Control of GFR

This mechanism is external to the kidneys and can actually override autoregulatory responses even if the mean arterial pressure is still within the range of autoregulation. This extrinsic control is mediated by the sympathetic nervous system. When there is decreased blood volume, for example, following hemorrhage or burns, the resultant fall in arterial blood pressure, is detected by the baro-receptors in the aortic and carotid sinus. These initiate neural reflex responses to normalize the blood pressure. The cardiovascular centre in the brain stem works by increasing sympathetic activity to the heart and blood vessels to increase cardiac output and peripheral resistance. This raises the blood pressure inspite of the low plasma volume, which must be restored to normal in the long run. One of the ways to compensate for the decreased plasma volume will be a reduction in urine output because of the need to conserve more fluid for the body. This reduction is brought about by a reduction in GFR, which occurs as a result of the baro-receptor reflex response to a fall in blood pressure. The afferent arterioles like other arterioles in the body constrict by sympathetic stimulation to help increase total peripheral resistance. This vasoconstriction in the afferent arteriole causes less blood to flow into the glomerulus, with a resultant fall in glomerular capillary blood pressure, a fall in GFR and a reduction in urine volume. Some water and salts that would have been lost are now saved for the body as part of the long term

plan to restore plasma volume to normal. Conversely when blood pressure is raised (may be because of an increased plasma volume following intake of excessive fluid) the opposite responses occur.

3.3.2 Reabsorption in the Tubules

The glomerular ultrafiltrate usually contains all plasma constituents which were non-discriminately filtered through the glomerular capillaries except plasma proteins. In addition, the waste products and excess materials that needs to be eliminated from the body. The filtered fluid also contains nutrients, electrolytes and other substances that the body cannot afford to lose in the urine. It is therefore, important that the essential materials that are filtered be returned to the blood by a process of tubular reabsorption. Thus, of about 180 litres of glomerular ultrafiltrate produced per day, the kidneys normally excrete only 1 to 2 litres of urine per day. Approximately 99% of the filtrate must thus be returned to the vascular system to maintain blood volume and pressure. In the same way only a small percentage, if any, of filtered plasma constituents that are useful to the body are present in the urine, most having been reabsorbed and returned to the blood. Only excess amounts of essential materials like electrolytes may be excreted in urine. In contrast a large percentage of filtered waste products are present in urine. They are not reabsorbed to any extent since they may even be potentially harmful if allowed to accumulate. Tubular reabsorption is thus a highly selective process. In most cases, the quantity of each material reabsorbed is the amount required to maintain the proper compositions and volume of that material in the blood.

To make reabsorption possible, the tubules generally have a high reabsorptive capacity for substances needed by the body and a poor or no reabsorptive capacity for substances of no value. For essential plasma constituents regulated by the kidneys, the absorptive capacity may vary depending on the body's needs. That is if there is a lack of the material in the body, more of it will be reabsorbed and vice versa.

The wall of the tubules is made up of a layer of epithelial cells throughout their length and lies close to the surrounding peritubular capillaries. Adjacent epithelial cells of the tubule do not come in contact with each other except at the apical side - closest to the lumen of the tubule where they are joined by tight junctions.

Interstitial fluid lies in the gaps between adjacent cells and between the tubes and capillaries. The tight junctions largely prevent substances except water from moving between the cells.

Each cell has four exposed surfaces - the apical side facing the lumen, the opposite side facing the capillary and the lateral sides facing the narrow spaces between adjacent epithelial cells.

Therefore substances to be reabsorbed must pass from the tubular fluid across the apical membrane and cytoplasm of the tubular epithelial cells, and the basolateral membrane of the tubular cells, into the interstitial fluid and through the interstitial fluid to penetrate the wall of the capillary before joining the blood plasma. These sequences of steps are called transepithelial transport and are of two types: passive reabsorption and active reabsorption. Passive absorption involves the movement of substances down electrochemical and osmotic gradients with no energy expenditure while active reabsorption is against electrochemical gradient and therefore requires energy. The reabsorption of sodium is crucial to the entire reabsorption process and is therefore highlighted.

3.3.2.1 Active Reabsorption of Sodium

The tubular filtrate is ISO osmotic with the plasma, therefore substances cannot move across into the capillaries by osmosis. It is only by active transport that the concentration of the filtrate can be altered and this is achieved by the active transport of Na^+ from the tubular fluid (filtrate) to the capillary blood.

Na^+ transports are so important that up to 80% of the total energy requirement of the kidneys is used for it. Unlike other solutes, Na^+ is reabsorbed throughout the tubule to different extents, about 65% from the proximal tubule 20% from the Loop of Henle and 15% from the distal tubule.

In the proximal tubule sodium reabsorption plays a key role in the reabsorption of Cl^-, water, glucose, amino acids and urea. Though the concentration of Na^+ in the ultra filtrate and in the plasma is the same, the epithelial cells of the proximal tubule have a much lower concentration of Na^+. This is partially as a result of the low permeability of the cell membrane to Na^+ and partially due to the active transport of Na^+ out of the cell by the Na^+ K^+ pump that exists in all cells. In the peritubular epithelial cells the Na^+/K^+ pumps are located at the basolateral sides of the peritubular epithelial cells.

This pump activity keeps the inside of the epithelial cells low in Na^+ while it builds up the Na^+ concentration in the interstitial fluid in the lateral spaces surrounding the cells.

A concentration gradient is therefore created between the tubular ultrafiltrate and the inside of the tubular epithelial cells across the apical membrane, and this favors the diffusion of Na^+ from the tubular ultrafiltrate into the epithelial cells of the tubule. As Na^+ enters the cell, they are actively pumped out again through the basolateral membrane into the interstitial fluid by the Na^+/K^+ pump.

The buildup of Na^+ in the interstitial fluid creates a potential difference across the basolateral membrane of the tubule hence an electrical gradient is created. This favors the passive movement of negatively charged Cl^- towards the region of high Na^+ concentration in the tissue fluid. Chloride ions therefore follow sodium ions out of the filtrate to the interstitial fluid. The resultant accumulation of NaCl especially in the lateral spaces between the epithelial cells increases the osmotic pressure of the tissue fluid and an osmotic gradient is created between the tubular fluid and the interstinal fluid surrounding the proximal tubule. Since the cells of the tubules are permeable to water, water moves by osmosis from the tubular filtrate into the epithelial cells then across the basolateral membranes into the interstitial fluid.

The salt and water reabsorbed from the filtrate then move passively into the surrounding capillaries and this way are returned into the general circulation.

Following proximal tube reabsorption of water and salt, the volume of the ultrafiltrate is reduced to about a third of original volumes through the remaining fluid which is still ISO osmotic with the blood.

In the Loop of Henle, an additional constant amount of salt and water is reabsorbed into the blood. This reabsorption like in the proximal tubule is constant regardless of a person's state of hydration or total Na^+ load. Up to 8% or more of the total glomerular ultra filtrate is reabsorbed constantly in the beginning parts of the nephron (proximal tubule and Loop of Henle) and this is done by the expenditure of much energy. The remaining 15% or less enters the distal convoluted tubule and collecting ducts. However this is still much, amounting to about 27 liters of fluid per day and this amount must be reabsorbed to varying degrees but this time according to the body's need. This later reabsorption in the distal tubule and the collecting duct is controlled by the action of hormones. The most important hormonal regulation of Na^+ is the rennin-angiotensin aldosterone system.

3.3.2.2 Reabsorption of Glucose and Amino Acids

Nutritionally important substances like glucose and amino acids that are filtered are also reabsorbed completely back into the blood in the proximal tubule. This is accomplished by a co-transport mechanism dependent on active transport of Na^+ a secondary active transport process. The energy for the secondary active transport mechanism for the reabsorption of glucose and amino acids is at the expense of energy already used in the reabsorption of Na^+. Therefore glucose and amino acids get a free ride of the energy used. The absorption of glucose and amino-acids requires the presence of Na^+ without which the co transport carrier is inoperable.

In the case of glucose, the quantity that is filtered in the filtrate is the same concentration that we have in the plasma and that is 100mg/100ml of plasma. Therefore at normal GFR of 125 ml/min, 125mg of glucose pass into the Bowman's capsule per minute. The amount of glucose in the filtrate at any given time is dependent on the plasma glucose concentration, given a constant GFR. However the maximum amount of glucose that can be carried per minute by the glucose carrier mechanism for active reabsorption is 375mg/min.

Normally, the 125mg of glucose filtered per minute can be conveniently reabsorbed by the glucose carrier mechanism therefore no glucose appears in urine. When more glucose is filtered per minute than can be reabsorbed (more than 375mg) the maximum amount is reabsorbed and the rest (excess) remains in the filtrate to be excreted. Therefore the plasma glucose concentration must be greater than 300mg/100ml (more than 3 times the normal value) before glucose can spill into the urine.

The plasma concentration at which the maximum amount of any substance can be transported before it starts appearing in the urine is known as the renal threshold. In normal situations therefore, when GFR is 125ml/min the renal threshold for glucose is 300mg/ml of plasma which gives the transport maximum of 375mg/min. From this point any further increase in the plasma glucose, leads to increase in the filtered load of glucose and this is accompanied by a directly proportional increase in the amount of glucose excreted in urine.

In diabetes mellitus there is deficiency of insulin which is a hormone that helps to facilitate the transport of glucose into many body cells. This deficiency results in poor entrance of glucose into the cells; therefore those that cannot enter remain in the plasma making plasma glucose levels high. As a result, people with diabetes have glucose excreted in their urine whenever the plasma level of glucose exceeds the renal threshold for glucose.

Regulation of blood glucose is not by the kidneys. The kidneys only maintain whatever plasma level set by other mechanisms through reabsorption. However when excessively high levels are present, they overwhelm the kidneys' reabsorptive capacity. This same general rule applies to other organic plasma constituents such as amino acids and water-soluble vitamins.

3.3.2.3 Reabsorption of Other Substances

A variety of other substances are transported by secondary active transport with the energy provided by the active transport of Na^+ out of the renal tubules. Examples include some amino acids, phosphates (PO_4) Cl^-, H^+,

lactates, citrates etc. The kidney directly contributes to the regulation of many electrolytes, such as calciumion, (Ca^{++}) and PO_4^- because the renal thresholds of these inorganic ions equal their normal plasma levels. Since the tubules can absorb up to the normal plasma levels worth of these substances, the excess ingested in our diets is quickly spilled into the urine and this brings plasma levels to normal. The more of these substances ingested beyond the body's needs, the more the excretion. In this way the kidneys maintain the desired plasma levels while eliminating the excess. Chlorideions (ct) which are negatively charged ions are passively reabsorbed down the electrical gradient following the active reabsorption of positively charged sodiumions Na^+

Water is passively reabsorbed by osmosis throughout the length of the kidney tubules following the reabsorption of solutes. 80% of the filtrated water is reabsorbed as an obligation by the proximal tubule and the Loop of Henle. The remaining 20% is absorbed variably in the distal tubule depending on the body's need of water (state of hydration), this occurs under hormonal control.

Water is reabsorbed down its osmotic gradient which is created by the transport of Na^+ and other solutes from the lumen of the tubules. The result is that the fluid in the lumen is now less concentrated while the one in the peritubular spaces (interstitial fluid) are more concentrated. Water moves out of the lumen into the peritubular spaces and this build up of interstitial fluid are also pulled into the peritubular capillaries by osmosis because of the concentration of plasma proteins in the peritubular capillaries following extensive filtration of water by the glomerulus.

Urea reabsorption is also affected by the active transport of Na^+. After water follows Na^+ out of the lumen of the tubules the higher concentration of urea in the tubules favors its passive reabsorption from the lumen of the tubules. Only 50% of the filtered urea is reabsorbed since the walls of the tubules are only partially permeable to urea. The remaining 50% is eventually eliminated. When there is impaired kidney function less than half of the filtered urea is eliminated and this leads to accumulation of more urea in the plasma. An elevated blood urea is one of the first chemical characteristics seen in the plasma of patients with severe renal impairment.

Unwanted waste products filtered into the kidney tubules are generally not reabsorbed besides urea. Such substances as creatinine and phenols even though they are concentrated in the tubular fluid following water reabsorption they are unable to permeate the tubular wall, therefore they remain in the tubules to be excreted.

3.3.3 Tubular Secretion

By tubular secretion selected substances have a second chance of entering the tubular lumen in order that they might be eliminated from the body through urine. In the process of secretion the steps of reabsorption are reversed. There is transepithelial transport. The most important substances secreted are hydrogen ions (H^+), potassium ions (K^+) and organic anions and cations. H^+ secretion is very important in the control of acid-base balance of the body. They are secreted by the proximal, distal and collecting tubules. The extent of secretion depends on the acidity of body fluids. When the body fluids are too acidic more H^+ are secreted. Secretion reduces when H^+ concentrations in body fluids are too low.

K^+ is selectively moved in opposite directions at different parts of the tubules. At the proximal tubule they are actively reabsorbed with Na^+ and in the distal tubules they are actively secreted. The filtered potassium is almost completely reabsorbed but about 10 to 15% of filtered potassium needs to be excreted in urine, therefore these have to be secreted back by the distal tubules, under controlled conditions.

When plasma K^+ levels are high potassium secretion is adjusted to ensure that enough is added to the filtrate for elimination to reduce plasma concentration of K^+ to normal. However, during K^+ depletion, secretion of K^+ in the distal tubule is reduced to a minimum in order to conserve much of the available ones for the body. The process of K^+ secretion is linked to the energy driven Na^+/K^+ pump in the distal and collecting tubules. As Na^+ is pumped out into the lateral space, K^+ is pumped into tubular cells. The high concentration of K^+ in the tubular cells favors the passive diffusion of K^+ into the tubular lumen through the numerous available potassium channels. As K^+ moves into the tubular lumen, its concentration in the interstitial fluid is kept low making it possible for passive diffusion of K^+ from the capillaries into the interstitial fluid for onward active transport into the peritubular cells.

The secretion of K^+ is affected by many factors, the most prominent one being the hormone aldosterone. This hormone can stimulate the secretion of K^+ into the filtrate in the distal portions of the kidney nephrones, as well as simultaneously enhance the absorption of Na^+. Another factor that affects K^+ secretion is the acid base balance of the body.

Other substances like organic cations and anions have secretory carriers in the nephron tubules that enable them to be secreted into the proximal tubules for excretion in urine. Some of the organic ions include some blood-borne chemical messengers like prostaglandins which having served their purpose need to be rapidly removed in order not to prolong their biological activity. Others are foreign organic chemicals, including food

additives, environment pollutants (e.g. pesticides), drugs and other non-nutritive organic substances that gained entry into the body. The liver first converts these substances into ionic forms to facilitate their secretion by the organic ionic system and thus accelerate their elimination. Drugs like penicillin are eliminated by this organic ion secretory system. This is why the dosage of such drugs has to be repeated regularly and frequently in order to maintain effective plasma levels of the drugs. All these substances are left behind to be excreted in urine.

3.4 Plasma Clearance and Urine Excretion

Plasma clearance refers to the volume of plasma cleared of a particular substance per minute. The blood that leaves the kidneys through the renal veins normally lacks those materials that were left to be excreted in urine i.e. the concentration of those substances in the renal vein leaving the kidney is lower than in the renal artery entering the kidney. By excreting those substances in urine, the kidneys clears the plasma that flow through them of these substances. Plasma clearance does not refer to the amount of that substance removed but to the volume of plasma from which that amount was removed. It is a more useful measure of the kidneys effectiveness in removing various substances from the internal fluid environment. It is calculated by the following formula:

$$\frac{\text{Clearance rate of a substance (ml/min)}}{\text{plasmac content of the substances (quantity/ml plasma)}} = \frac{\text{Urine concentration of substance quantity/ml urine}}{\text{plasmac content of the substances (quantity/ml plasma)}} X \text{Urine flow rate (ml/min)}$$

The clearance rate of that substance is therefore equal to the GFR since all the volume of filtrate filtered per minute will be cleared. An example is inulin, a harmless carbohydrate product of onions and garlic.

The plasma clearance rate for different substances varies depending on how the kidneys handle each substance.

For example: If a substance is filtered but not reabsorbed or secreted, the amount of that substance excreted in urine per minute will be equal to that filtered by the glomerulus. Also if a substance is filtered and reabsorbed but not secreted, its plasma clearance rate is always less than the GFR. This is because less than the filtered volume of plasma would have been cleared of the substance. For example the plasma clearance rate for glucose is normally zero. All the filtered glucose is reabsorbed to join the returning filtrate so none of the plasma is cleared of glucose. For urea that is partially reabsorbed, only part of the filtered plasma is cleared of urea, since about 50% of the filtered plasma (i.e. 62.5ml of plasma) is cleared of urea per minute.

Finally if a substance is filtered and secreted but not reabsorbed, its plasma clearance rate will be greater than the GFR. This is because, in addition to the part of the plasma containing the non-absorbed substance, which must be cleared, an additional volume of plasma from which the substance is secreted is also cleared. If for example 125ml of filtered plasma is cleared of non-absorbed H^+ and an additional quantity secreted is equivalent to the quantity present in 25ml of plasma, the clearance rate for H^+ then becomes 150ml/minute.

3.5 Micturition

The urine that has been formed by the kidneys is transmitted through the ureters to the urinary bladder. This movement of urine is facilitated by gravitational pull and peristaltic contractions of the smooth-muscles of the ureter. The ureters enter the bladder obliquely passing through the walls before opening into the cavity, and this prevents backflow of urine from the bladder to the kidneys. Urine can be temporarily stored in the bladder before it is conducted to the exterior through the urethra.

Micturition or urination is the process of bladder emptying. The process is governed by two mechanisms; the micturition reflex and voluntary control. Micturition is controlled by a reflex centre in the second, third and fourth sacral levels of the spinal cord. Filling of the urinary bladder activates afferent fibers of stretch receptors within the bladder wall which send impulses to the micturition centre in the spinal cord. There is resultant stimulation of the parasympathetic supply to the bladder. Parasympathetic stimulation causes the bladder (detrusor) muscles to contract while motor neuron to the external sphincter is inhibited. The internal urethral sphincter relaxes and is pulled open as the bladder wall contracts. The external sphincter relaxes since its motor neuron supply is inhibited. With both sphincters open, urine is voided by the force of bladder contraction. This reflex governs bladder emptying completely in infants.

With bladder filling also, the brain perceives a sense of urgency and produces a conscious urge to urinate. This urge appears before the external sphincter finally relaxes and thus the sphincter is also under voluntary control. When urination is consciously allowed, motor fibers supplying the external urethral sphincters are inhibited and the sphincters relax and open.

The voluntary control of micturition learned during toilet training, in early childhood can override the micturition reflex so that bladder emptying can take place at the person’s convenience rather than at the point when bladder filling first activates stretch receptors. This ability is developed generally between the ages of 2 and 3.

Urination however cannot be delayed indefinitely as the bladder continues to fill and input from stretch receptors increases, a time comes when the reflex inhibitory supply to the external sphincter cannot be overridden again by voluntary input and so the sphincter relaxes and the bladder empties.

Urinary incontinence is the inability to prevent discharge of urine and it occurs as a result of disruption of the descending pathways that mediate voluntary control of the external sphincter and pelvic floor muscles. In this case bladder emptying becomes governed again by the uncontrollable spinal reflex for micturition as in infants.

4.0 CONCLUSION

The kidneys contribute to homeostasis more than any other single organ in the body. They do thus by eliminating all waste products of bodily metabolism and by regulation of electrolyte composition, volume and PH of the internal environment. They accomplish the regulatory functions by eliminating in urine substances unneeded by the body, or excess quantities of ingested salt and water; while conserving useful substances for the body. The kidneys are able to maintain the plasma constituents within the narrow range compatible with life despite wide variations in intake and losses through other avenues.

5.0 SUMMARY

In this unit we learnt that the urinary system is made up of two kidneys that form urine and other organs that help to conduct urine from the kidney till it gets to the urethra. By the formation of urine, the kidneys regulate the extracellular fluid environment of the body. The kidney is a bean-shaped organ lying posteriorly on either side of the vertebral column below the diaphragm. A longitudinal section of the kidney shows that it is made up of an outer cortex and an inner medulla. Minorcalyces drain the kidneys; they join up to form the major calyces which finally join together to form the renal pelvis. The pelvis narrows to form a small narrow tube called the ureters which exists in the kidney and connects to the urinary bladder. The bladder may store urine temporarily before conducting it to the exterior through the urethra. The functional unit of the kidney is the nephron which is made up of the glomerulus, the proximal convoluted tubule, Loop of Henle, distal convoluted tubules and collecting duct. Through these tortuous system tubules and associated capillaries, urine is formed from plasma and concentrated through the process of filtration, reabsorption and secretion. Plasma clearance refers to the volume of plasma cleared of a particular substance per minute. The kidneys clean the plasma that flows through them of those substances that are excreted in urine. The renal clearance rate becomes a useful measure of the kidney's

effectiveness in removing various substances from the internal environment. Micturition is the process of bladder emptying. It is governed by the micturition reflex which is under parasympathetic reflex centre in the second, third and fourth sacral levels of the spinal cord. The second control of micturition is by voluntary control of the brain.

6.0 TUTOR-MARKED ASSIGNMENT

Describe the Benin-Angiotensin - Aldosterone System of Control of Sodium and Potassium Levels in the blood.

7.0 REFERENCES/FURTHER READING

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UNIT 2 RENAL CONTROL OF FLUID AND ACID BASE BALANCE

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1.0 INTRODUCTION

Homeostasis depends on maintaining constituents present in the internal fluid environment. Regulation of fluid balance involves two separate components; control of the volume of extra cellular fluid (ECF) which includes the volume of circulating plasma; and control of the osmolarity (solute concentration) of the ECF. Volume of ECF is controlled by maintaining electrolyte balance while osmolarity is controlled by maintaining water balance. This balance is maintained by adjusting the output of salts and water in the urine as necessary. The kidneys help to regulate the concentration of electrolytes - Na^+, K^+, Cl^-HCO^3 and PO_4^- by matching their urinary excretion to amounts ingested. The control of Na^+ is important in the regulation of blood volume and pressure. The control of K^+ is required to maintain proper function of cardiac and skeletal muscles. The kidneys also contribute to the maintenance of acid-base balance by controlling the output of Hydrogen and bicarbonate ions.

2.0 OBJECTIVES

At the end of this unit you should be able to:

- review concepts related to fluid and acid base balance
- explain how fluid and electrolyte balance are maintained by the kidneys

- describe the role of Aldosterone in Na^+/K^+ balance
- explain the mechanism for the control of Aldosterone secretion
- describe renal control of acid-base balance
- discuss some clinical applications of renal function.

3.0 MAIN CONTENT

3.1 Review of Concept Basic to Fluid and Acid-Base Balance

The largest single constituent of the body is water. On the average, fluid which is mostly water, constitutes 60% of the total body weight. Life depends on maintaining the proper amount of body water, the correct proportion of water and electrolytes in the fluids and proper acid-base balance. Homeostasis is portrayed very vividly here and imbalances can have severe consequences.

Body water is distributed between two major fluid compartments: The fluid within the cells, intracellular fluid (ICF) and the fluid surrounding the cells, extra cellular fluid (ECF). The ICF compartment holds about two thirds of the total body fluid. The remaining third is found in the ECF compartment. The ECF compartment is further distributed into interstitial fluid (in between and immediately surrounding the cells), blood plasma and lymph and several other negligible transcellular compartments like fluids in the eyes, ears, cerebrospinal fluids etc. Plasma makes up one fifth of the ECF and is the liquid portion of the blood. The interstitial fluid represents the other four-fifths of the extra cellular fluid compartment. It is the fluid that lies in the spaces between the cells. Interstitial fluid constitutes the true internal environment since it bathes the tissue cells. The two most important extracellular fluids for the purpose of our discussion are the interstitial fluid and plasma.

Table XI.I: Summary of Body Fluid Compartments

Compartment	**Volume of fluid (In litres)**	**Percentage of body fluid (%)**	**Percentage of body weight (%)**
Total body fluid	42	100	60
intracellular fluid (ICF)	28	67	40
Extracellular fluid (ECF)	14	33	20
- Plasma	2.8	6.6	4
- Interstitial fluid	11.2	26.4	16
Lymph	Negligible	Negligible	Negligible
Transcellular fluid	Negligible	Negligible	Negligible

Several barriers exist to separate the various body-fluid compartments and these limit the movement of water and solutes between the various compartments. Plasma and interstitial fluid are separated by blood vessel wall but water and solutes in plasma, with the exception of plasma proteins, are freely exchanged that they are nearly identical in composition. This exchange is made possible by passive movement of constituents across the thin pore-lined capillary walls. Any change in one is quickly reflected in the other.

The composition of the ECF however differs considerably from that of ICF. The plasma membrane permits passage of some materials while excluding others. The major differences between the ECF and ICF are:

(1) ICF contains cellular proteins that are unable to pass through the cell membranes to leave the cell and,

(2) There is unequal distribution of $\underline{Na^+}$ and $\underline{K^+}$ and their attendant anions as a result of the membrane bound Na^+ K^+ ATPase pump present in all cells. The pump actively shuttles Na^+ out of cells and K^+ into cells; making Na^+ the principal cation of ECF and K^+ the principal cat ion of ICF. The unequal distribution of Na^+ and K^+ across the both sides of the cell membrane and the selective permeability of the cell membrane are responsible for the electrical properties of cells notable among which is the initiation and propagation of action potentials in excitable tissues.

Cell membranes are however freely permeable to water. The movement of water from one body fluid compartment to another is controlled by two forces: hydrostatic pressure is the force exerted by a fluid against the surface of the compartment for example the pressure of blood on the inside of the capillary walls or of interstitial fluid on the outside of the capillary walls. Osmotic pressure is the pressure of the solution that is related to the concentration of non-permeable solute.

The body maintains balance of any particular substance by maintaining a readily available pool in the ECF. This amount of substance in the pool may be increased by ingestion or metabolic production or decreased by excretion or metabolic consumption. Input must be equal to output for balance to be maintained. The ECF pool can also be altered by storing some substances within the cells for example calcium stored in bones and glycogen stored in the liver and muscles. The storage depot can therefore be depleted or expanded as the need arises in the ECF .i.e. depending on whether there is deficit of the substance or surplus. When total body input of a particular substance equals its total output, a stable balance exists. When the gains (input) exceed the losses (output) a positive balance exists i.e. an increase in the total amount of the substance in the body. However, when the losses for a substance exceed its gains, a negative balance is said to exist.

3.2 Maintenance of Fluid Balance

ECF serves as the intermediary between the cells and outside and exchange of substances between ICF and the external environment occurs through the ECF. Plasma volume and composition can be directly controlled in itself, however, the free exchange across capillary walls ensures that any change in plasma volume or composition is quickly reflected in the interstitial fluid. Any mechanism that regulates plasma in effect regulates the entire ECF. The ICF is influenced by changes in the ECF only to the extent that the cell membrane is permeable to the substances concerned.

Maintenance of fluid balance is concerned with two factors; regulation of ECF volume and ECF Osmolarity. These two are closely related and are concerned with salt and water load in the body. The maintenance of ECF volume helps to maintain the blood pressure. It is primarily concerned with the maintenance of salt balance. Maintenance of osmolarity is concerned with water balance.

3.2.1 Maintenance of Electrolyte Balance

The control of electrolyte balance is important in regulating ECF volume and this in turn affects the regulation of blood pressure. A reduction in ECF volume by decreasing the plasma volume causes a fall in blood pressure and an increase in ECF volume has an opposite effect. When any of these occurs the body can use some temporary measures like altering the cardiac output and total peripheral resistance or fluid shift from the interstitial compartment into the vessels to expand the blood volume. However the responsibility for long term regulation of blood pressure rests with the kidneys which control urinary output and the thirst mechanism which controls intake.

The kidneys help to regulate the concentration of plasma electrolytes sodium, potassium, chlorides, bicarbonates and phosphates by matching the urinary excretion with the amounts ingested.

3.2.2 Role of Aldosterone in Na^+/K^+ Balance

Approximately, 90% of the filtered Na^+ and K^+ are reabsorbed in the early part of the nephron, before the distal tubules. This reabsorption occurs constantly without hormonal regulation. The final concentration of Na^+ and K^+ in the urine is varied according to the needs of the body by processes that occur in the late distal tubule and the collecting duct. At this point renal reabsorption of Na^+ and secretion of K^+ is regulated by aldosterone which is the principal mineral: corticoid secreted by the adrenal cortex.

The extent of reabsorption of the remaining 10% of Na^+ is inversely proportional to the total Na^+ in the body. When body Na^+ is too much, little Na^+ is reabsorbed and more is excreted. In the event of Na^+ depletion in the body, most or all of this regulated Na^+ is reabsorbed with minimal loss in urine. This then conserves Na^+ for the body, which would have been lost in urine. This Na^+ reabsorption is made possible by aldosterone through the system of hormone action called *Renin angiotensin aldosterone system.*

Na^+ load in the body is reflected by ECF volume. Na^+ and its corresponding anion Cl^- account for 90% of the ECF's osmotic activity. Above normal levels of Na^+ increases ECF's osmotic activity with the extra solute (NaCl) holding more water. This extra water increases ECF volume. Conversely, a fall in the body's total Na^+ results in less being held and a reduction in blood volume. An increase or reduction in ECF is reflected in plasma volume (increase or decrease). The most important result of change in plasma volume is a corresponding change in blood pressure (either increase or decrease). With maximum aldolsterone secretion, all the Na^+ are filtered (accompanied by Cl^- of aldosterone) with urine excretion of salts being zero. In 80% of the filtered, 10% is absorbed and only a minimal 20% is excreted. The amount of aldosterone is responsible for regulating the conservation and excretion of Na^+ between these two extremes.

Also about 90% of the filtered K^+ is excreted in urine. However aldosterone when present causes the secretion of K^+ from the blood into the distal tubule and collecting duct to be eliminated in urine, aldosterone therefore causes secretion of K^+ from the peritubular blood in the distal tubule for elimination while causing reabsorption of Na^+ i.e. it promote Na^+ retention and K^+ loss by stimulating the reabsorption of Na^+ and secretion of K^+ across the wall of the distal tubules and cortical portion of the collecting duct. This also means that aldosterone contribute to an increased blood volume and pressure by Na^+ retention.

3.2.3 Control of Aldosterone Secretion

By negative feedback mechanism, aldolsterone secretion is increased when there is low Na^+ or a high K^+ concentration in the blood. A rise in blood K^+ levels directly stimulates the secretion of aldosterone from the adrenal cortex. Decrease in plasma Na^+ level also promotes aldosterone secretion indirectly. Granular cells of the afferent arterioles of the juxtaglomerular apparatus secret renin. (The juxtaglomerular apparatus is the place in each nephrone where the afferent arteriole comes into contact with the distal tubule. When there is fall in blood volume and pressure, the flow of blood on the granular cells as well as sympathetic nerve activity stimulate the secretion of renin. Renin catalyzes the conversion of

angiotensinogen (a protein in the blood) to angiotensin I. Angiotensin I is then converted to angiotensin II by angiotesin converting enzyme (ACE) in the lungs, angiotensin II stimulates the adrenal cortex to secrete aldosterone. An increased renin secretion, which occurs when a fall blood pressure and volume occurs, acts via the production of angiotensin II to stimulate aldosterone secretion. When aldosterone is secreted, less sodium is excreted in urine (more is reabsorbed) and retained in the blood leading to increase in blood pressure and volume.

Conversely, when the blood Na^+ level is raised, the cells of the distal tubule at the juxtaglomerular apparatus (called the macula densa) respond to the high level of Na^+ in the tubular filtrate. The cells of the macula densa inhibit the granular cells of the afferent arteriole from secreting renin. This in turn decreases aldosterone secretion and less Na^+ is reabsorbed while more is secreted in urine.

3.3 Renal Acid-Base Regulation

Acid-base balance refers to the precise regulation of free hydrogen ion (H^+) concentration in body fluids. The kidneys are the most potent acid-base regulatory mechanism. The kidneys control the pH of the body by adjusting three interrelated factors:

(1) H^+ excretion;
(2) (HCO_3^-) bicarbonate excretion and
(3) Ammonia (NH_3) excretion

Specifically the kidneys help regulate the body pH by excreting H^+ and reabsorbing bicarbonates (HCo_3^-).

H^+ enters into the tubular filtrate by filtration and later by secretion in the proximal and late distal tubule as well as the cortical collecting duct. Reabsorption of HCo_3^- is indirect since the apical membranes of the tubulular cells are impermeable to HCO_3^-. When necessary (i.e. when urine is acidic) HCO_3^- has to combine with H^+ to form carbonic acid. Carbonic acid is then converted to CO_2 and H_2O by the action of the enzyme carbonic anhydrase in the apical membranes. The CO_2 can now be absorbed into the tubulular cells. Inside the tubulular cells there is high concentration of Co_2 and this leads to the reversal of the reaction leading to formation of carbonic acid which in turn dissociates back to bicarbonate (HCO_3^-) and H^+. The HCO_3^- then diffuses from within the cell through the basolateral membrane to enter the blood. The H^+ that was produced can pass back into the filtrate if necessary. When there is acidosis in the body almost all the H^+ goes back into the filtrate where they are used to help reabsorb all the filtered bicarbonates.

In alkalosis however, the body needs to retain its H^+ so less H^+ is secreted in the filtrate. This makes less H^+ available to combine with HCO_3^-. Therefore, less bicarbonate is reabsorbed. The result is that more bicarbonate is excreted in urine to compensate for the alkalosis.

When blood pH is less than 7.35 (acidosis) urine pH almost always falls below 5.5 the nephrons by the mechanism already described may not be able to produce a urine pH much less than 4.5. In this case, further excretion of H^+ is provided for by phosphates and ammonia. Phosphates enter the filtrate by filtration and ammonia by deamination of amino acids in the tubulular cells.

3.4 Clinical Applications

Renal function is very important for maintaining homeostasis in the body therefore urine can be collected and used as a mirror of the plasma's chemical composition. Further, the kidney's ability to regulate blood volume is exploited clinically in the management of high blood pressure.

3.4.1 Renal Function Tests and Kidney Diseases

Kidney function can be assessed by the measurement of GFR and the measurement of total blood flow to the kidney. Plasma creatinine concentration can also be measured as an index of renal function. These tests help to diagnose diseases of the kidneys like glomerulo-nephritis and renal insufficiency.

Glomerulo nephritis, an autoimmune inflammation of the glomerulus is believed to involve a person's own antibodies raised against his glomeruli for some reasons. The result is always the destruction of a variable number of glomeruli with the result that the remaining glomeruli became more permeable to plasma proteins. Leakage of protein into the urine (proteinuria) leads to decreased plasma colloid osmotic pressure and can therefore lead to oedema.

When nephrons are destroyed as in chronic glomerulo-nephritis, pyelonephritis, loss of a kidney or when there is a reduced renal function caused by damage from diabetes mellitus, arteriosclerosis, or kidney stones, a condition of renal insufficiency may occur. The result is normally retention of salt and water and uraemia (high concentration of urea in plasma). Inability to excrete urea is accompanied by elevated plasma H^+ levels (acidosis) and elevated K^+ levels. These are considered more immediately dangerous than the high levels of urea. Urea and other wastes in the patient=s blood easily pass through the membrane pores while plasma proteins are left behind just as it occurs in glomerular filtration.

3.4.2 Use of Diuretics

Diuretics are drugs that increase the volume of urine passed. They are given to people who need to lower their blood volume because of hypertension, congestive cardiac failure or oedema. Commonly used diuretics act on renal nephrons in different ways. They are categorized as carbonic anhydrase inhibitors, loop diuretics, thiazides, or potassium sparing diuretics.

The Most powerful diuretics can inhibit salt and water reabsorption by up to 25%. The drugs act by inhibiting active transport of salt (Na^{++} and Cl^{-}) out of the ascending limb of the Loop of Henle. A common example is furosemide. Thiazide diuretics such as hydrochloric thiazide inhibit salt and water reabsorption by as much as 8% through inhibition of salt and water transport in the first segment of the distal tubule. Carbonic anhydrase inhibitors (e.g. acetazolamide) are much weaker diuretics and act by prevention of water reabsorption that occurs when bicarbonate is reabsorbed primarily in the proximal tubule.

The presence of extra solutes in the filtrate can cause less water to be reabsorbed leading to osmotic diuresis. This can occur in diabetes mellitus due to the presence of glucose in the filtrate and urine. This extra solute causes excretion of excessive amounts of water in urine (as less is reabsorbed) leading to dehydration. Mannitol is sometimes used for this purpose.

Diuretics as previously discussed result in excess secretion of K^{+} and resultant excessive loss in urine. Potassium sparing diuretics for example spironolactones are used to block aldosterone stimulation of Na^{+} reabsorption and K^{+} secretion.

4.0 CONCLUSION

The many dangers presented by renal insufficiency and the difficulties encountered in attempting to compensate for this condition are reminders of the importance of renal function in maintaining homeostasis in the body. The kidneys' ability to regulate blood volume and chemical composition according to the body's changing needs requires great complexity of function. It is the coordination of renal function with the function of the cardiovascular and respiratory systems that maintain this homeostasis.

5.0 SUMMARY

We have learnt from this unit that up to 60% of the total body weight is fluid, mostly water and that this water is distributed in several compartments of body fluids, (Principally ICF and ECF). Life depends on maintaining the correct proportion of water and electrolytes as well as acid base balance. The maintenance of fluid and electrolyte balance helps to maintain the volume and pressure of fluids in the body. The kidneys help to regulate both the volume and concentration of body fluids by matching urinary excretion with the amounts ingested and/or required in the body.

Aldosterone, a hormone secreted by the adrenal cortex promotes sodium retention and potassium loss by stimulating Na^+ reabsorption and K^+ secretion. This way it contributes to increasing blood volume and pressure. Regulation of aldosterone secretion therefore is directly by high K^+ in the blood and indirectly by Na^+ concentration through the renin-angiotensin-aldosterone system. By these mechanisms therefore blood volume and pressure are regulated. Acid-base regulation in the body is brought about by the kidneys through the excretion of H^+ and reabsorption of bicarbonates. Knowledge of renal functions and the mechanism of normal urine production can be utilized clinically to diagnose and manage people with kidney diseases.

6.0 TUTOR-MARKED ASSIGNMENT

Explain how the nephron handles K^+ and how the urinary excretion of K^+ is regulated by aldosterone.

7.0 REFERENCES/FURTHER READING

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MODULE 3 PHYSIOLOGY OF THE GENITO-URINARY SYSTEM

Unit1 Sexual Reproduction and Endocrine Regulation of Reproduction
Unit 2 Male and Female Reproductive Physiology
Unit 3 Fertilization, Pregnancy and Parturition

UNIT 1 SEXUAL REPRODUCTION AND ENDOCRINE REGULATION OF REPRODUCTION

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1.0 INTRODUCTION

The reproductive system is responsible for the survival of the species and has profound effect on a person's life. It is only through reproduction that the complex genetic blueprint of each specie survives beyond the lives of the individual members of the species. Reproduction provides the mechanism through which the incredible complexity of structure and function in living organisms could be transmitted from one generation to another.

In sexual reproduction genes from two individuals are combined in random and new ways with each new generation. This offers the advantage of introducing variability into population. It is some of these variability that make it possible for some members of a population to survive and adapt to changes in their environment over time. In sexual reproduction also germ cells (sperm and ova) are formed within the

gonads by a process of reduction division (meiosis). By this process the normal number of chromosomes in most cells (46) is divided into two so that each gamete receives 23 chromosomes. When a sperm cell and an ovum fuse together in the process of fertilization, the original number of chromosomes is restored in the fertilized cell (zygote). This zygote continues growing by mitotic cell division into an adult member of the next generation. At puberty mature sperm cell or ovum will be formed again within the gonads and the life cycle continues.

The functions of the testes and ovaries are regulated by gonadotropic hormones from the anterior pituitary gland. These hormones stimulate the gonads to secrete their own sex steroid hormones. The sex steroids in turn inhibit the gonadotropic hormones by a negative feedback mechanism. This unit will examine sex determination and regulation of reproduction.

2.0 OBJECTIVES

At the end of this unit you should be able to:

- explain the mechanism of sex determination and understand how testes and ovaries are formed
- explain the development of accessory sex organs and external genitalia
- explain some disorders of embryonic sexual development
- describe the interaction between the hypothalamus, pituitary gland and gonads
- describe the onset of puberty
- explain the role of the pineal gland in reproduction.

3.0 MAIN CONTENT

3.1 Sex Determination

Reproduction depends on the union of the male and female gametes or germ cells, each half a set of chromosomes to form a new individual with a full unique set of chromosomes. Following fertilization each zygote inherits twenty-three chromosomes from its father and twenty-three from its mother. This gives the offspring forty six chromosomes that are arranged in twenty three pairs. The pairs are matched i.e. each look like the other and contain similar genes (e.g. for height for eye colour etc). They are therefore said to be homologous pairs. There is however an important exception in the sex chromosomes whereas each cell that contains 46 chromosomes has two number 1 chromosome, and two number 2 chromosomes and so forth till pair number 22, the twenty-third pair called the sex chromosome does not have identical chromosomes. The

first 22 pairs are called autosomal chromosomes and the 23rd is the sex chromosome. In a female the sex chromosome consists of two X chromosomes while in a male there is an X chromosome and one Y chromosome. The X and Y chromosomes look different and contain different genes. This is the exceptional pair of homologous chromosomes.
Almost all cells in the body reproduce themselves by the process of mitosis. In this process chromosomes replicate themselves (make duplicate copies of themselves), then the identical chromosomes are separated so that a complete set of genetic information is distributed to the two new daughter cells. However in the specialized case of gametes the cells reproduce themselves by a process of reduction division called meiosis. Mitosis guarantees that new daughter cells receive exactly the same genetic information as the parent cell. If the parent cell has 23 pairs of chromosomes as in most body cells, each daughter cell will also have 23 pairs of chromosomes. Gametes cannot be formed by mitosis, because if a sperm cell presents 46 chromosomes and an ovum presents 46, the resultant 92 chromosomes will not be a normal human cell. In meiosis the problem is solved because the number of chromosomes in the gametes is halved. Each sperm therefore has 23 chromosomes and each ovum has 23 chromosomes, such that when the two unite, the resultant cell, the zygote has 46 chromosomes. In mitosis the nucleus divides only once but in meiosis twice. In mitosis the daughter cells having the same number of chromosomes (46) as the parent cell are said to have the diploid number (2n). All body cells except sex cells are diploid. In meiosis the daughter cells have only half the parental number, or the haploid number (1n). Gametes are haploid.

In the first meiotic division the replicated chromosomes do not just separate into two individuals as in mitosis. The doubled chromosomes sort themselves into homologous pairs, one chromosome from mother one from father and the pairs separate so that each of two daughter cells receives a half set of doubled chromosomes. In the second stage of meiotic division the doubled chromosomes within each of the two daughter cells separate and are distributed into two cells yielding four daughter cells, each containing half set of chromosomes, a single member of each pair. It should be noted that during this process, the maternally and paternally derived chromosome of each homologous pair are distributed to the daughter cells in random assortments containing one member of each chromosome pair without regard to its original derivation. This means that not all the mother-derived chromosomes go to one daughter cell and father derived chromosomes go to the other cell. Rather more than 8 million different mixtures of the twenty three paternal and maternal chromosomes are possible, making it possible for new combinations to always occur.

3.1.1 Formation of Testes and Ovaries

The gonads are similar in appearance in males and females for the first forty days of embryonic life following conception. During this time, cells that will form sperm (spermatogonia) and those that will form ova (oogonia) migrate from the yolk sac to the embryonic gonads. They still have the potential to become either male or female at this stage. A person's genetic sex depends on the combination of chromosomes at the time of conception. This determines the gonad sex i.e. whether it is an ovary or testes that will develop. From about the 7^{th} week of intrauterine life the embryonic gonad tissues of the genetic male begins to differentiate into testes under the influence of the sex determining region of the Y chromosome (XY). The XY gene, the single gene responsible for sex determination triggers a chain of reactions that lead to physical development of a male. It induces the development of the gonads into testes. It is the absence of the XY gene which leaves the gonads undifferentiated, that starts the development of the embryonic gonad into ovaries during the 9^{th} week.

Along the same line, the sex differentiation that leads to the development of anatomical sex through the development of external genitalia and reproductive tract depends on the genetically determined gonadal sex. Embryos of both sexes have the potential to develop either male or female reproductive tract or external gentalia. Differentiation along male type reproductive system is induced by masculinizing hormones i.e. androgens secreted by the developing testes. The most potent androgen is testosterone. The absence of this testicular hormone in female foetus results in the development of female type reproductive system.

The structures that will eventually produce sperm within the testes are called seminiferous tubules and they appear early enough in embryonic development, as early as between 41 and 50 days following conception. Spermatogenesis begins in the embryonic stage but is however arrested until the onset of puberty. The seminiferous tubules contain two major types of cells, the germinal and non-germinal cells. The germinal cells are the ones that turn into sperm by meiosis and subsequent specialization, while the non-germinal cells are the nurse-cells for nourishment of the sperm. The interstitial tissues are found between adjacent convolutions of the tubules and they contain the Leydig cells which are the endocrine cells of the testes. These cells secrete testosterone. Secretion of testosterone serves an important function of causing masculinization of embryonic organs. However, following the peak secretion at 12 to 14 weeks, it drops to very low level until the time of puberty.

The testes begin development in the abdominal cavity, but gradually descend unto the scrotum. This descent may not complete till shortly after

birth. The temperature of the scrotum is about 3^0C less than normal body temperature, and this lower temperature is needed for spermatogenesis. Spermatogenesis does not occur in males with undescended testes.
Ovarian follicles which are the functional units of the ovaries in contrast do not appear until the second trimester of pregnancy (about day 105).

3.1.2 Accessory Sex Organs

Various other internal accessory sex organs are needed for reproduction. These are derived from two systems of embryonic ducts, the Wolffian (mesonephric) ducts for the male accessory organs and the mullerian (paranephric) ducts for the female organs. Both male and female embryos have the potential to develop accessory organs of either sex since they both have the two ducts systems between day 25 and 50 of embryonic life. Female accessory sex organs (uterus and uterine tubes) only develop as a result of the absence of testes and its hormone testosterone. As the Leydig cells secrete testosterone the Wolffian ducts are made to develop into male accessory sex organs: the epididymis, vas deference, seminal vesicles and ejaculatory duct. In the male certain cells of the seminiferous tubules (the Sertoli or nurse cells) produce a protein factor that causes regression of the mullerian duct from about day 60.

The external genitalia of males and females also remain identical during the first 6 weeks of development. The secretion of the testes masculinizes the common embryonic structures of the external genitalia to form the penis, and penile urethra, prostate gland and scrotum. The genital tubercles which form the penis in the male become the clitoris in the absence of testosterone. The labioscrotal swellings form the scrotum in the male or the labia majora in the female.

In summary genetic sex is determined by whether an X-bearing or a Y-bearing sperm cell fertilizes the ovum. The presence or absence of the Y chromosome determines whether the gonads will be testes or ovaries. The presence or absence of testes in turn determines whether the accessory sex organs and external genitalia will be male or female.

3.2 Disorders of Embryonic Sexual Development

There are some rare conditions that occur as a result of problems arising in the embryonic stage of sexual development.

Hermaphroditism occurs when both ovarian and testicular tissue are present in the body. In about a third of hermaphrodites, there is an ovary on one side and a testis on the other side. In another 5^{th}, the structure present is ovotestes that is; there is part ovary and part testis on both sides. In the remaining, there may be an ovotestis on one side and either an ovary or testes on the other.

The condition may be caused by the fact that some embryonic cells receive the testis-determining factor while some do not receive.

A commoner disorder is called pseudohermaphroditism; in which the individuals have either testes or ovaries but have incompletely developed accessory organs and external genitalia, or organs that are inappropriate for the chromosomal sex. The commonest cause is congenital adrenal hyperplasia, which results from excessive secretion of androgens from the adrenal cortex.

3.3 Endocrine Regulation of Reproduction

The functions of the testes and ovaries are regulated by gonadotropic hormones secreted by the anterior pituitary. The gonadotropic hormones stimulate the gonads to secrete the sex steroid hormones, and these sex steroids in turn have an unhibitory impact on the ganadotropic hormones. This interaction between the anterior pituitary and the gonads form a negative feedback loop.

3.3.1 Interactions of the Hypothalamus, Pituitary Gland and Gonads

Two hormones secreted by the anterior pituitary gland, the Follicle Stimulating Hormone (FSH) and Lutenizing Hormone (LH) are gonadotropic hormones in that they stimulate the gonads to produce their hormones. The gonadotropic hormones have three effects on the gonads:

(1) stimulation of spermatogenesis or oogenesis,
(2) stimulation of gonadal hormone secretion, and
(3) maintaining the structure of the gonads (the gonads atrophy if the pituitary is removed).

Gonadotropin secretion is on its part, stimulated by gonadotropin B releasing hormone, which is produced by the hypothalamus. This releasing hormone is principally a Lutenizing Hormone Releasing Hormone (LHRH) but is found to stimulate both LH and FSH secretion.

The control of gonadropin secretion is by a negative feed mechanism. This can be demonstrated by the fact that if a male or female animal is castrated, the blood levels of FSH and LH rise to higher levels than the intact animal. This is due to the fact that it is the sex steroids secreted by the gonads oestrogen, progesterone and testosterone that exert the negative feedback. The negative feedback occurs: (i) by the inhibition of GnRH secretion from the hypothalamus and by (ii) inhibition of the pituitary response to a given amount of GnRH.

3.3.2 The Onset of Puberty

The secretion of FSH and LH falls to very low levels a few weeks after birth and remain low until the beginning of puberty - sometime between eight and twelve years. The beginning of puberty is marked by rising levels of FSH and LH secretion and this is supposed to be as a result of two processes:

(1) Maturational changes in the brain that result in increased GnRH secretion by the hypothalamus and
(2) Decreased sensitivity of gonadotropin secretion to the negative feedback effects of sex steroid hormones.

The timing of the maturation of the hypothalamus and other parts of the brain that results in the secretion of GnRH is programmed in each individual before birth such that even children without gonads still show increased FSH secretion at the appropriate time.

Early in puberty, there is pulsatile secretion of GnRH, occurring at night and decreasing during periods of wakefulness. This causes increase in FSH and LH secretions and consequently the sex steroids at night. These pulses of increased gonadotropin secretion during puberty stimulate a rise in sex steroid secretion from the gonads. Increased secretion of testosterone from the testes and oestradiol ITB (the major oestrogen or female sex steroid) from the ovaries during puberty in turn produces changes in body appearance characteristic of the two sexes called secondary sex characteristics. These characteristics are the physical manifestations of the hormonal changes occurring during puberty. These changes are accompanied by a growth spurt and it begins at an earlier stage in girls than in boys.

Summary of secondary sexual characteristics that occur at puberty

Girls	**Age at first appearance**	**Hormones responsible**
Appearance of breast bud	8 to 13	Oestrogen, progesterone, growth hormone, thyroxine, insulin, cortisol.
Pubic hair	8 to 14	Adrenal androgens
Menarche (first menstrual flow)	10 to 16	Oestrogen and progesterone
Axillary (underarm) hair	About 2 years after pubic hair	Adrenal androgens
Endocrine sweat glands and sebaceous glands;	About the same time as Axillary	Adrenal androgens

acne (due to blocked sebaceous glands)	hair growth	
Boys Growth of testes	10 to 14	Testosterone, FSH, growth hormone.
Pubic hair	10 to 15	Testosterone
Body growth	11 to 16	Testosterone, growth hormone
Growth of penis	11 to 15	Testosterone
Growth of larynx (voice changes)	Same as growth of penis	Testosterone
Facial and axillary's hair	About 2 years after pubic hair	Testosterone
Endocrine sweat glands and sebaceous glands, acne (from blocked sebaceous glands).	About same time as facial and axillary's hair growth	Testosterone

The age at which puberty begins appears to be related to the amount of body fat and level of physical activity of the child. In the female child the average age of menarche first menstruation is later (age 15) for very physically active girls than in the general population (age 12 - 16). This also appears to be related to the issue of body fat, whereby a minimum percentage of body fat is required for menstruation to begin. This may also represent a mechanism favored to ensure the ability to successfully complete a pregnancy and nurse the baby.

3.3.3 Function of the Pineal Gland

The pineal gland is a gland located deep within the brain that secretes the hormone melatonin. The production of this hormone is influenced by light dark cycles, with secretion decreasing during exposure to light and increasing when it is dark. Melatonin has been found to exert some regulatory influence on human reproduction though evidence is inconclusive. Melatonin has been shown to inhibit gonadotropin secretion and thus have an antigonadal effect in rats and other vertebrae. However, the overall reduction in the rate of melatonin secretion in humans at puberty, particularly during the night, when the peaks in GnRH secretion first occur, is thought to be one of the triggers for the onset of puberty. Melatonin from the pineal gland is also believed to have a host of other influences on the body that have to do with synchronizing the biological clock for various processes of the body e.g. temperature regulation, anterior pituitary hormone metabolism, fat deposition and immune responses.

4.0 CONCLUSION

Sexual reproduction provides opportunity for genes from two individuals to combine in random and new ways from each new generation to the next. In sexual reproduction, gametes are formed within the gonads by a process of reduction division or meiosis so that the normal number of chromosomes in human cells is halved. When fusion of a sperm cell and ovum eventually occurs, there is restoration of the original number of 46 in the zygote.

5.0 SUMMARY

In this unit you have learnt that

- The sex of an offspring is determined by the fertilizing sperm cell. The 23rd pair of chromosomes in the human cell is the sex chromosomes, which in the male consist of one X and one Y chromosomes and in females there are two X chromosomes. All other pairs from 22 homologous pairs of autosomal chromosomes in the cells look like each other.

- In the formation of testes and ovaries, the embryonic structures that form the gonads have the potential to become either testes or ovaries. It is the substance, testes-determining factor (TDF) that promotes the conversion to testes. The gene for this factor is called the sex determining region of the Y chromosome (SRY) contained in the Y chromosome. This is genetic sex.

- Genetic sex determines gonadal sex i.e. whether the testes or ovaries will develop. Then phenotypic sex i.e. the apparent anatomical sex of an individual depends on the gonadal sex, i.e. the presence or absence of testes determines the accessory sex organs and external genitalia.

- Accessory sex organs of the male and female are needed for reproductive function. The male ones are derived from the Wolffian (mesonephric) ducts while female ones are derived from mullerian (paranephric) ducts. Male and females have both duct systems between day 25 and 50 of intrauterine life that cause the development of male or female accessory organs and external genitalia respectively.

- Sometimes, some disorders of embryonic sexual development occur in the embryo resulting in some abnormalities in the individual. Haermaphroditism and pseudohermaphroditism are examples of such conditions. Some hermaphrodites have an ovary

on one side and a testis on the other, yet others have ovotestes etc. Pseudo hermaphroditism is due to congenital adrenal hyperplasia.

- The functions of testes and ovaries are regulated by gonadotropic hormones secreted by the anterior pituitary gland.

- Gonadotropin Releasing Hormones (GRH) from the hypothalamus stimulates gonadotropin (FSH and LH) from the anterior pituitary. These hormones in turn stimulate spermatogenesis and oogenesis, maintain the structure of the gonads and stimulate gonadal hormone secretion. The interaction is usually mediated through a negative feedback loop.

- Melatonin from the pineal gland influence human reproduction. The overall reduction in its secretion at puberty is thought to be one of the triggers for the onset of puberty.

6.0 TUTOR-MARKED ASSIGNMENT

Explain genetic, gonadal and anatomical sex determination.

7.0 REFERENCES/FURTHER READING

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UNIT 2 MALE AND FEMALE REPRODUCTIVE PHYSIOLOGY

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1.0 INTRODUCTION

The reproductive role of the male is to produce sperm cells and deliver them to the vagina of the female. These functions require four different types of structures the testes, accessory glands, accessory ducts and the penis. The female also produces eggs (ova) to be fertilized by the male, through a more complex and rhythmic process. A wide variety of structures with specialized functions are involved in this complex process. Some of the structures include the ovaries, uterine tubes, uterus, vagina, external genitalia and mammary glands.

This unit will briefly examine the anatomy of some of the structures relevant in male and female reproductive physiology, as well as discuss in some detail the specific functions of the male and female reproductive system.

2.0 OBJECTIVES

At the end of this unit you should be able to:

- briefly describe the structures of the male and female reproductive system
- explain the hormonal control of gonadotropin secretion
- discuss the endocrine function of the testes in spermatogenesis
- explain the processes of erection, emission and ejaculation
- describe the changes in the ovarian cycle
- describe the menstrual cycle
- explain hormonal basis of contraception and menopause.

3.0 MAIN CONTENT

3.1 Brief Description of the Structures of the male Reproductive System

The Testes

Man has two testes which are the male reproductive organs (gonads). The main function of the testes is to produce sperm or spermatozoa. The testes are formed during inter-uterine life, just below the kidneys inside the abdominal pelvic cavity. By the third month, the testes descend from its original site to the inguinal canal and in the seventh month they pass through the inguinal canal on their way to the scrotum. The scrotum is an external sac of skin hanging between the thighs. The descent is completed shortly before birth and the muscular passage for the inguinal canal subsequently gets sealed off. Incomplete closure or rupture of this opening results in inguinal hernia.

One testis (usually the left) hangs slightly lower than the other outside the body. The situation of the testes outside the body enables them to be maintained under a temperature about $3^{o}F$ lower than normal body temperature. This lower temperature is necessary for active sperm product ion and survival. Each testis lies in one of the two compartment of the scrotum, which is divided by a fibrous median septum.

Each testis is oval-shaped, weighs about 10 14gm and measures about 4 - 5cm by 2.5cm in adults. Each testis also contains over 800 tightly coiled seminiferous tubules which produce thousands of sperm per second in any healthy young man. The walls of the seminiferous tubules are lined with germinal tissue which contains two types of cells - the spermatogenic cells which eventually develop into mature sperm and the sustentacular (Certoli) cells that provide nourishment for the sperm as they develop. The sustentacular cells also secrete the fluid that provides the liquid medium

for the developing sperm. Between the seminiferous tubules are clusters of endocrine cells called interstitial endocrinocytes or leydigcells which secrete testosterone. The testes show strict compartmentalization with regard to gonadotropin action. Testosterone secretion by leydig cells is under LH control while FSH controls spermatogenesis.

Spermatozoa (Sperm)

Mature spermatozoa have a head, a middle piece and a tail. The tip of the head has an acrosome, containing several enzymes that help the sperm penetrate an egg. In the centre of the head is the nucleus that contains all the genetic material. The middle pieces contains mitochondria and provide ATP for energy for movement while the tail is responsible for propelling the sperm forward as it beats.

A sperm is very small measuring about 0.05mm long from tip of the head to the tail. Each sperm cell requires over two months for complete development. 300 and 500 million sperm are released during one ejaculation. A man releasing less than 20 million normal sperm is said to be sterile. The seminiferous tubules where sperm are produced always contain sperm at various stages of development. The final maturation of sperm cells takes place in collection tubules on the surface of each testis.

Accessory Ducts

After being produced in the testes sperms are carried to the point of ejaculation by a system of ducts, into the abdominopelvic cavity and finally they join the urethra in the penis.

Epididymis

The seminiferous tubules merge in the central portion of the testes called the mediastinum testis (in the middle of the testis). They straighten to form straight tubules (tubuli recti) which open into a network of tiny tubules called the testis (net) which now drain unto 15 to 20 tubules (efferent ducts) at its upper end. The efferent ducts extend into crescent shaped convoluted mass of tubules which pass over the top of the tests and down along its side. This coiled tube is called the epididymis. The functions of the epididymia include:

(1) To store sperm till they are mature and ready to be ejaculated.
(2) To serve as a duct system for the passage of sperm from the testis to the ejaculatory duct.
(3) It contains circular smooth muscles that propel mature sperm towards the penis by peristaltic contractions. The tightly coiled epididymis is bunched up along a length of about 4cm (1.5in.) but if straightened out, it would extend to about 6 meters (20 feet).

Maturing sperm leave the seminiferous tubules and move into the epididymis. This journey may take from 10 days to as much as 4 to 5 weeks till the sperm are mature, being nourished by the lining of the epididymis. When they mature they enter the ductus deferens. Mature sperm can remain in the epididymis and ductus deferens for about a month after which if they are not ejaculated, they degenerate and are reabsorbed by the body. Ductus deferens (formerly vas deferens). This is the dilated continuation from the tail of the epididymis, about 45cm (18 inches) long to the ejaculatory duct.

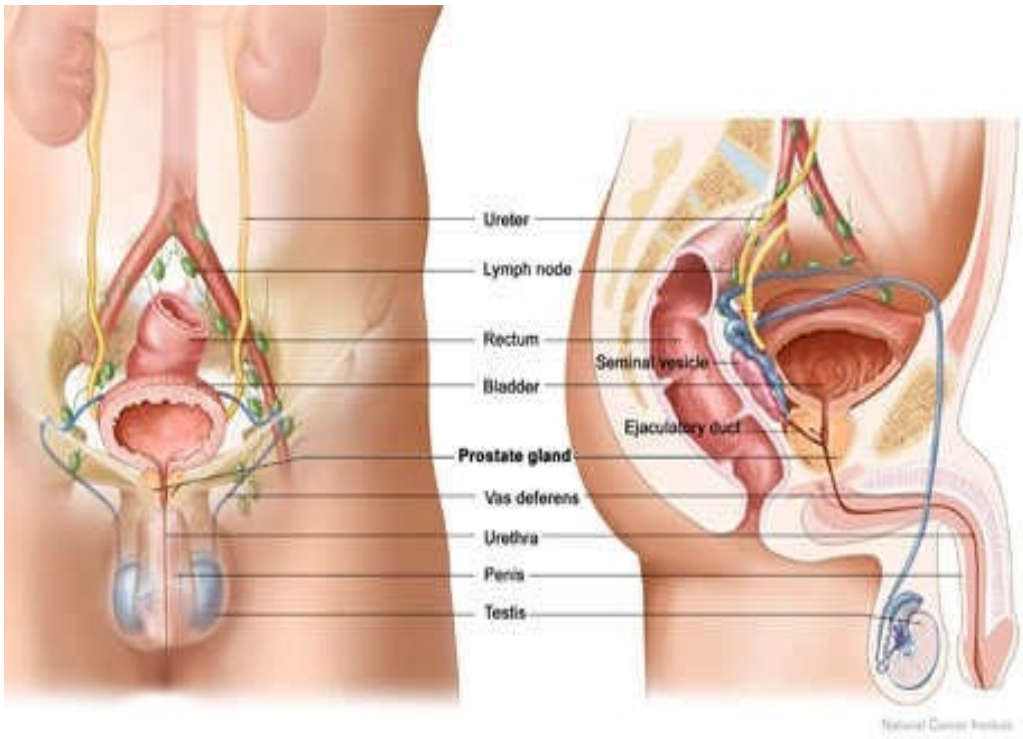


Fig 26: Male Reproductive Organs

Source: http://en.wikipedia.org/wiki/Reproductive

As each ductus deferens passes from the tail of the epididymis, it is covered by the spermatic cord, which also contains the testicular artery, veins, autonomic nerves, cremasteric muscle, lymphatic and connective tissues from the anterior abdominal walls. Leaving the scrotum the ductus deferens pierces the lower abdominal wall by way of the inguinal canal, it then becomes free of the spermatic cord, and passes behind the bladder and comes alongside an accessory gland called seminal vesicle and then continues as the ejaculatory duct. Just before reaching the seminal vesicles it widens into an enlarged portion, the ampulla before it becomes the ejaculatory duct.

This ductus deferens is the main carrier of sperm. It is lined with pseudo stratified columnar epithelium and contains three thick layers of smooth muscle. The sympathetic nerves from the pelvic plexus supply the

muscles. When stimulated the nerves produce peristaltic contractions that move sperm forward to the ejaculatory duct.

The thick smooth muscle coat gives the duct a cord like characteristic such that the initial portion can be felt through the skin of the scrotum, making it easy to locate. Because of this, it is the preferred site to cut during a vasectomy.

Ejaculatory Duct

The ampulla of the ductus deferens joins with the duct of the seminal vesicle and become the ejaculatory duct. Each ejaculatory duct is about 2cm long. They receive secretions from the seminal vesicles, pass through the prostate gland where they receive more secretions and then join the single urethra.

Urethra

The male urethra is the final section of the reproductive duct system. It leads from the base of the urinary bladder, through the prostate gland and into the penis. Its reproductive function is to transport semen outside the body during ejaculation.

The wall of the urethra has a lining of mucous membrane and a thick outer layer of smooth muscle. Within the walls are urethral glands that secrete mucous into the urethral canal.

Accessory Glands

Several accessory glands are present in the genito-urinary system which adds their secretions to the sperm as they are propelled through the ducts. These are located mostly after the ductus deferens has passed around the urinary bladder. The glands include: the seminal vesicles, prostate and bulbourethral glands.

Seminal Vesicles

Two in number, the seminal vesicles, lie next to the ampulla of the ductus deferens. They secrete alkaline secretions which form about 60 percent of the seminal fluid. The secretions which contain water, fructose, prostaglandins and vitamin C are produced by the mucous membrane lining of the glands. Stimulation during sexual excitement and ejaculation causes the seminal fluid to be emptied into the ejaculatory ducts by muscular contraction of the smooth muscle layer, the seminal secretion provides an energy source for the motile sperm as well as helps to neutralize the natural acidity of the vagina.

Prostate Gland: lies inferior to the urinary bladder and surrounds the first 3cm of the urethra. About the size of a chestnut, the rounded mass measures about 4cm across.

The prostate gland is surrounded by a thin fibrous connective tissue capsule and smooth muscle. The lining on the inside of the prostate is made up of many individual glands. The prostate gland is inervated by the sympathetic nerves from the pelvic plexus. When the nerves stimulate the smooth muscles, they contract like a sponge to squeeze out the prostatic secretions through tiny ducts into the urethra. The function of prostatic secretions is to make sperm motile and help neutralize vaginal acidity. The ejaculatory ducts also pass through the prostate gland and receive some of its secretion during ejaculation.

Bulbourethral Glands (Cowper's Glands). They are two in number, about the shape and size of a pea and lie directly below the prostate gland, one on each size of the posterior surface of the urethra. Each gland has a duct that opens into the urethra.

The bulbourethral glands secrete clear alkaline fluids into the urethra with the onset of sexual excitement. The fluid neutralizes the acidity of any remaining urine and also act as a lubricant for the tip of the penis prior to intercourse.

Semen

Semen is composed of secretions from the epididymis, seminal vesicles, prostate gland and bulbourethral glands together with sperm. Sperm make up only about 1 percent of semen. The rest is fluid from the accessory glands which provides fructose to nourish the sperm, an alkaline medium to neutralize urethral and vaginal acidity, and buffering salts and phospholipids that make the sperm motile. Semen contains water, fructose, vitamin like vitamin C and inositol, trace elements like calcium, zinc, magnesium, copper, sulphur plus a high concentration of prostaglandin (highest concentration of prostaglandin in the body is found in semen). The consistency of semen varies from thick to viscous to almost watery.

The average ejaculation produces 3 or 4mls of semen and contains 300 to 500 million sperm on the average.

Penis

The penis has the function of carrying urine through the urethra to the outside during urination. It also transports semen through the urethra during ejaculation.

The penis contains three cylindrical strands of erectile tissue made up of 2 corpora cavernosa (sing: corpus cavernosum) which run parallel on the dorsal aspect. This tissue contains numerous vascular cavities called venous sinusoids. The other tissue is corpus spongiosum which contains the urethra. The corpora cavernosa do not reach the tip of the penis but stops short at a ridged proximal edge of the tip of the penis called the corona. The corpus spongiousum extends beyond the cavernosa and becomes expanded into the tip of the penis called glans penis. The glans penis is a very sensitive area containing many nerve endings and is an important source of sexual arousal.

The penis is normally soft and hangs limply down. With stimulation of the penis, a parasympathetic reflex causes marked vasodilation with arterioles and the sinusoids becoming engorged with blood under high pressure. Distended sinusoids compass the veins that drain blood away from the penis. This dual action prevents blood from escaping and the penis becomes enlarged and firm in erection. Nervous control of erection is from the hypothalamus and from sacral plexus.

3.1.1 Control of Gonadotropin Secretion

The major factor that controls the secretion of the two gonadotropin; LH and FSH is testosterone. This is achieved by a negative feedback mechanism. This means that LH stimulates testosterone secretion by the Leydig cells and testosterone in turn inhibits pituitary secretion of LH. When levels of testosterone are low as may be the case in castrated animals, secretion of LH and FSH rises immediately. An injection of testosterone in the individual will cause the levels of LH secretion to fall to precastration levels.

The second control over the secretion of gonadotropin (especially FSH) is the hormone called inhibin. Inhibin is produced by the Sertoli cells of the testes.

The negative feedback effects of testosterone and inhibin help to maintain a relatively constant (noncyclic) secretion of gonadotropin in the male. This in turn results in relative constant levels of androgen secretion from the testes. This is in contrast to the female where there is cyclic secretion of gonadotropin and ovarian steroids. Also unlike in the female where there is abrupt cessation of sex steroid secretion, there is a gradual decline in androgen secretion to varying levels in men over 50 years of age the cause of this phenomenon however is unknown.

3.2 Endocrine Function of the Testes

The adult testes secrete androgens, the chief of which is testosterone. The hormone and its derivative (5 alpha reduced androgens) are responsible for initiation and maintenance of the body changes associated with puberty in males. Androgens also stimulate the growth of muscles and other structures (bones, larynx, and erythropoiesis) hence they can sometimes be called anabolic steroids. Increased testosterone secretion at puberty also aids in the growth of accessory sex organs like seminal vesicles and prostate.

The testes also produce and secrete small amounts of oestradiol, from both the Sertoli and Leydig cells.

3.2.1 Spermatogenesis

During early embryonic development, germ cells migrate from the yolk sac to the testes and become stem cells called spermatogonia within the outer region of the seminiferous tubules. By spermatogenesis relatively undifferentiated primordial germ cells, the spermatogonia, proliferates and is converted into extremely specialized, motile spermatozoa. Each spermatogonium is a diploid cell (with 46 chromosomes). The process of remodeling or packaging of cellular elements, known as spermatogenesis involves the sertoli cells.

3.2.2 The Function of Sertoli Cells in Spermatogenesis

Sertoli cells are non-germinal cell types in the tubules. Forming a continuous layer around the circumference of each tubule, they form a blood testes barrier such that molecules from the blood pass through the cytoplasm of Sertoli cells before entering germinal cells. The barrier also prevents the immune system from becoming sensitized to antigens in the sperm, thus preventing autoimmune destruction of the sperm. The Sertoli cells also provide nourishment for the developing germ-cells and since they do not have access to blood-borne nutrients, the Sertoli cells perform some phagocytic functions during the remodeling of spermatids to spermatozoa, engulfing the cytoplasm from spermatids and destroying defective germ cells.

- They secrete seminiferous tubule fluid which flushes the released sperm from the tubule into the epididymis for storage and processing.
- They produce the androgen binding protein. This substance by binding to testosterone retains them in the lumen. This maintains a very high level of testosterone in the lumen. The high local concentration of testosterone is essential for sustaining sperm production.

- Finally, the sertoli cells are the final sites of action for control by both testosterone and Follicle Stimulating Hormones (FSH). They secrete the hormone inhibin which acts in negative feedback to regulate FSH secretion.

3.2.3 Hormonal Control of Spermatogenesis

The very beginning of spermatogenesis starting during embryonic development is somehow independent of hormonal action. After this spermatogenesis is arrested. Testosterone is required for the completion of meiotic division that ultimately gives rise to mature haploid gametes by the process of cell division called meiosis. Each of the spermatozoa that is formed now bear a randomly distributed haploid set of 23 chromosomes. When viewed under the microscope, the seminiferous tubule contains layers of germ cells, in different anatomical progression of sperm development. The least differentiated are in the outer layer and moving inward through various stages of division to the lumen where highly differentiated sperm are ready for exit from the testes. It takes 64 days for a spermatogonium to develop to a mature sperm and hundreds of million of sperm mature each day.

Spermatogenesis involves the mitotic proliferation of the germ cells which migrate from the yolk sack. Such proliferation provides a continual supply of new germ cells for spermatogenesis throughout adult life. While half of these germ cells remain at the outer edge of the tubule to maintain the germ cell line, the remaining half start moving toward the lumen where they undergo the various steps of sperm formation beginning in the primary spermatocyte. The process of mitotic proliferation is followed by meiotic division.

The first meiotic division of the primary spermatocyte (46 chromosomes) forms two secondary spermatocytes (each with 23 double stranded chromosomes). This is followed by a second meiotic division which yields four spermatids (each with 23 single strand chromosomes).

Finally the resulting spermatids are remodeled and packaged into spermatozoa; since the four spermatids are still connected with each other and their cytoplasm do not completely pinch off following cell division until puberty when testosterone secretion rises. Testosterone is needed for completion of meiotic division and for the early stages of spermatid maturation. This effect is probably produced by some testosterone derived molecules in the tubules.

The later stages of spermatid maturation during puberty appear to require stimulation by FSH. This FSH effect is mediated by Sertoli cells (as previously discussed).

Testosterone concentration is much higher in the testes than in the blood because a substantial portion of the hormone produced by the Leydig cells is retained in the luminal fluid bound with androgen binding protein secreted by Sertoli cells.

Within the adult testes evidence show that spermatogenesis can be maintained by androgens alone in the absence of FSH. This means that FSH is needed to initiate spermatogenesis at puberty but it may no longer be needed once spermatogenesis has begun.

3.3 Erection, Emission and Ejaculation

Erection is caused by blood flow into the erectile tissues of the penis 2 corpora cavernosa on the dorsal side of the penis and one corpus spongiosum on the ventral side.

Erection is achieved by parasympathetic nerve-induced vasodilation of arterioles that allows blood to flow into the corpora cavernosa of the penis. As the erectile tissues become engorged with blood, and the penis become turgid, venous outflow of blood is partially occluded thus aiding erection. Erection is accompanied by increase in the length and width of the penis.
Emission refers to the movement of semen into the urethra.

Ejaculation refers to the forcible expulsion of semen from the urethra out of the penis. The nervous control of emission and ejaculation is by sympathetic nerves which cause peristaltic contractions of the tubes (ducts), contraction of the seminal vesicles and prostate gland, and contractions of muscles at the base of the penis. Erection is however controlled by the hypothalamus in the brain and sacral portion of the spinal cord. Conscious sexual thoughts originating in the cerebral cortex act through the hypothalamus to control the sacral origin which in turn increases parasympathetic nerve activity to promote vasodilatation and erection of the penis. However sensory stimulation of the penis can more directly activate the sacral region of the spinal cord and cause erection.

3.4 Male Fertility

The volume of semen emitted in each ejaculation is about 1.5ml. 45% to 80% of the fluid is from the seminal vesicles, while 15% to 30% is from the prostate. The concentration of sperm in human males ranges between 40 and 250 million per milliliter of ejaculated semen. A sperm concentration below 20 million per milliliter is termed oligospermia and is associated with decreased fertility. A total count below 50 million per ejaculation is of very clinical significance for male infertility.

3.5 Brief Description of the Structures of the Female Reproductive System

The female reproductive system is more complex than that of the males. It consists of a wide variety of structures with specialized functions:

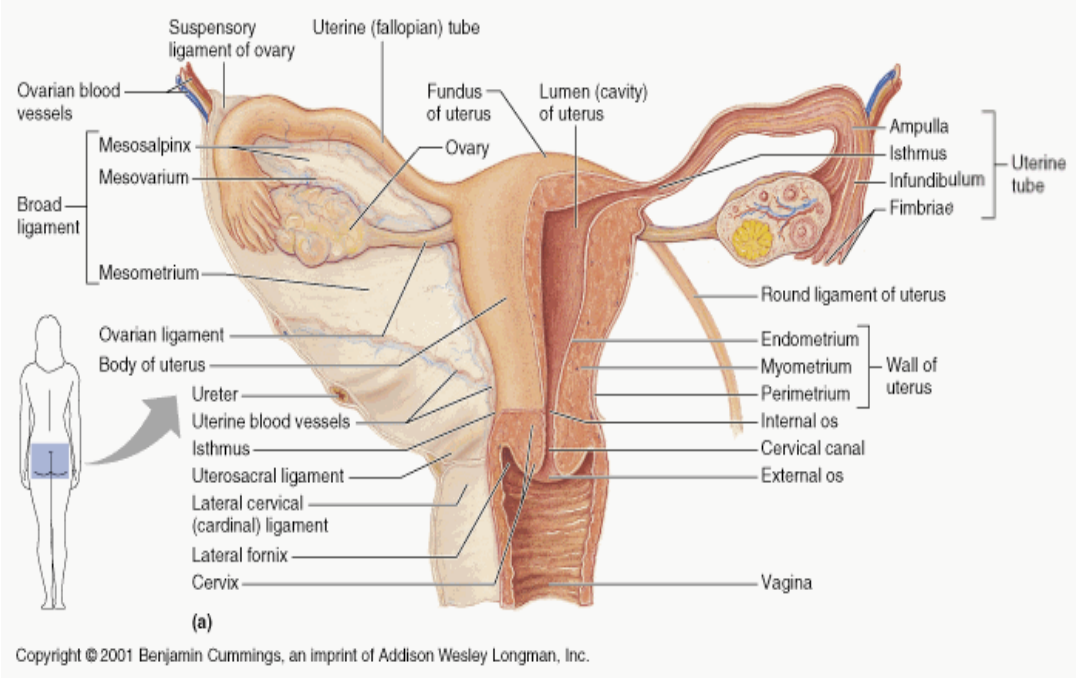
- Two ovaries (which produce ova and female sex hormone)
- Two fallopian (uterine) tubes or oviducts.
- The uterus (houses and nourishes developing embryo)
- The vagina (which receives semen from penis during sexual intercourse)
- The external genitalia and mammary glands.

Ovaries

The ovaries are the female gonads that produce ova and the female hormones. They are about the size and shape of an unshelled almond and are located in the pelvic part of the abdomen one on each side of the uterus. The ovaries are attached by a mesentery called the mesoovarium to the back of the broad ligament. The mesoovarium contains veins, arteries, lymphatic and nerves to and from the hilium (opening) of the ovary.

A cross section of an ovary reveals a cortex and a vascular medulla. The cortex contains young epithelial vesicles called follicles where oogenesis takes place. Each follicle contains an immature ovum called a primary oocyte and follicles are always present in several stages of development. They are classified from primordial follicles (not yet growing) to vesicular (Graafian) follicles (almost ready to release the secondary ooctye by the process of ovulation). As follicles begin to mature, they migrate toward the medulla from the cortex. The medulla consists of layers of soft stromal tissue which contains blood vessels, nerves and lymph vessels.

After the release of secondary oocyte, the lining of the follicle grows inward forming the corpus luteum (yellow body), a temporary endocrine tissue that secretes female sex hormones-oestrogen and progesterone.



Female Reproductive Organs

Uterine (Fallopian) Tubes

These are the two tubes that receive the secondary oocyte from the ovary and convey it to the uterus. The tubes are each 10cm long. The superior end opens into the abdominal cavity, very close to the ovary (but not attached to it) and the inferior end opens into the uterus. The tubes lie in the upper part of the broad ligament. Each tube has 3 distinct portions: the funnel shaped infundibulum near the ovary; the thin walled middle ampulla and the narrow isthmus that opens into the uterus.

The walls of the uterine tube are made up of three layers: the outer serous membrane (part of visceral peritoneum); the middle muscular layer (spiral inner) and the longitudinal outer, (smooth muscle fibers). Contractions of this muscle help move the secondary oocyte towards the uterus. The innermost lining is a mucous membrane which has a single layer of columnar epithelium which alternates as ciliated or secretory cells.

The infundibulum is fringed with thread-like structures called fimbriae which may overlap the ovary so that when a secondary oocyte is released, it is effectively swept across the tiny gap between the tube and the ovary into the infundibulum by the movement of cilia in the fimbriae.

Uterus

The uterus is a hollow muscular organ located in front of the rectum and behind the urinary bladder. It has an inverted pear shape and is also about

the same size (7.5cm long by 5cm wide), but can increase three to six times in size during pregnancy.

The wide upper part of the uterus is called the fundus. The middle portion that tapers down is the body. It terminates in a narrow neck, called the cervix, which is the juncture between the uterus and the vagina. There is a constricted region between the body and the cervix called the isthmus. The non-pregnant uterus is somewhat flattened so that the cavity is just a slit. In this flattened position, the uterus leans forward over the urinary bladder almost at a right angle to the vagina in an antiflexed position.

The uterus has 3 layers of tissue namely:

- The outer serous coat of peritoneum which extends to form the two broad ligaments.
- The middle muscular layer called myometrium made of longitudinal, random, spiral interwoven fibers. These muscles are capable of stretching during pregnancy and they can also contract downwards during labour with more force than any other muscle in the body.
- The innermost layer of specialized mucous membrane is called the endometrium. The endometrium has abundant blood supply and is composed of e layers: the functional layer and the basal layer. Every month, it is the functional layer that is stripped off monthly during menstruation when conception has not taken place.

Vagina

The cervix of the uterus leads downwards into the vagina. The vagina is tube about 8 to 10cm long where semen from the penis is deposited during sexual intercourse. It is also the channel for removal of menstrual blood and the birth canal for the baby during childbirth. The vagina lies behind the urinary bladder and urethra and in front of the rectum and anus. It angles upwards and backwards.

The lining is mostly muscle and fibro elastic connective tissue. The inner-most lining is mucous membrane containing many folds called rugae. The mucous membrane secrete acids that help prevent infection, but which can also create an environment hostile to semen. Ordinarily the opening in the vagina is only a potential space with the walls being collapsed. However the vagina can stretch to accommodate an erect penis during intercourse or the baby during childbirth.

A fold of skin called the hymen partially closes the vaginal entrance. The membrane is usually ruptured during first sexual intercourse or earlier during other physical activities.

Female External Genital Organs

The organs of the female external genitalia are called the vulva. The organs involved are the *mons pubis* a mound of fatty tissue that covers the *symphysis Pubis*. From puberty it is covered with Pubic hair. Labia majora are two longitudinal folds of skin lying just below the mons pubis. It forms the outer borders of the vulva. The skin contains fat, smooth muscle, areola tissue sebaceous glands and many sensory receptors. The outer surface is also covered with hair from puberty.

Labia Minora: Are two smaller folds of skin lying between the labia majora. They contain sebaceous glands and many blood vessels and nerve endings. Together with the labia majora they surround and protect the vagina and urethral orifices. The labia minora merge to form the fore skin or prepuce of the clitoris.

Clitoris: A small erectile organ at the upper end of the vulva below the mons pubis where the labia minora meet. Like the penis it contains many nerve endings being a very sensitive organ, and also has two corpora cavernous which can fill with blood during sexual stimulation, causing it to be enlarged. The clitoris is capped by a very sensitive glans.

Vestibule: The vestibule of the vagina in the space between the labia minora which floor contains the openings of the urethra and vagina. The floor also contain the greater vestibular (Bartholin's) glands and the lesser vestibular (Skene's) glands. These glands secrete alkaline mucus during sexual excitement that provides lubrication and offsets some natural acidity of the vagina.

Mammary Glands: The two breasts rest upon the deep fascia covering the pectoralis major and minor muscles, each extending from the lateral border of the sternum to the middle of the axilla. They contain varying amounts of adipose tissue, and this determines the size of the breast.

However the amount of mammary tissue is fairly constant in females. In children and men the breasts are underdeveloped, but from puberty in the female, they begin their development as potential milk producing organs. Further development takes place under the influence of hormones during pregnancy.

The mammary glands within the breasts are modified sweat glands that produce and secrete milk. Each one has 15 to 20 lobes of areolar gland radiating from the nipple. These clusters look like bunches of groups, with lactiferous ducts that carry milk from the ducts towards the nipple. The ducts join up into larger ducts as they go, and just before a duct reaches the nipple, it dilates to a lactiferous sinus (for temporary storage of milk) then constricts again as it enters the nipple.

The pigmented area around the nipple is called the areola. The nipple consists of dense connective tissue and smooth-muscle fibers, many blood vessels and sensitive nerve endings. The breasts also contain an extensive drainage system made up of many lymph vessels.

3.6 Ovarian Cycle

By 5 months of prenatal life, the ovaries of the foetus contain approximately 6 to 7 million oogonia from the germ cells that migrate into the ovaries during early embryonic development. At this point the production of new oogonia stops and never resumes again. Toward the end of gestation, meiosis begins and by this time the oogonia have become and are referred to as primary oocytes which contain 46 chromosomes each. Oogenesis is arrested during the first meiotic division. Therefore the primary oocytes are still diploid till puberty.

The number of primary oocytes decreases throughout a woman's life. The newborn girl has about 2 million oocytes, by puberty the number reduces to 300,000 to 400,000. Oogenesis ceases entirely at menopause. Before birth each primary oocyte is surrounded by a single layer of granulosa cells to form primary follicles. The pool of primary follicles present at birth (about 2 million) gives rise to an ongoing trickle of developing follicles.

From puberty till menopause, a portion of the resting pool of follicles starts developing into secondary follicles on a cyclical basis. This development is characterized by growth of the primary follicle and expansion and differentiation of the granulosa cells surrounding it. Just before puberty the primary oocyte which has been in a state of meiotic arrest for years completes the first meiotic division to yield two haploid daughter cells. However, these are not two complete daughter cells because only one cell gets almost all the cytoplasm. That one is now called the secondary oocyte. The other cell becomes a small polar body that eventually degenerates. This unequal division ensures that the ovum is large enough to become a viable embryo if fertilization should occur. The secondary oocyte then begins the second meiotic division, but meiosis is again arrested at a stage. This second meiotic division is completed only by an ovum that has been fertilized.

Meanwhile the follicle has developed through the secondary follicle stage to become a Graafian follicle which is a single fluid filled cavity. The granulosa cells of this follicle forms a ring around the oocyte called corona radiata. Between the corona radiata and the oocyte is a gel like layer of protein and polysacchandes called the zona pellucida. Under the stimulation of FSH, the granulosa cells of the ovarian follicles secrete increasing amounts of oestrogen as the follicles grow.

3.6.1 Ovulation

In most females, by about 10 to 14 days after the first day of menstruation, only one follicle continues its growth to become a fully mature Graafian follicle. Other secondary follicles during that cycle regress and become atretic because they fail to rupture. The Graafian follicle gets so large that it bulges on the surface of the ovary. It then ruptures, under proper hormones stimulation, and extrudes the oocyte into the uterine tube this process is called ovulation.

The released secondary oocyte is surrounded by the zona pellucida and corona radiata. If it is not fertilized it degenerates in a few days. If a sperm passes through the corona radiata and zona pellucida and enters the cytoplasm of the oocyte, it will then complete its second meiotic division into two unequal daughter cells. The cytoplasm again remains with the zygote while the other forms another polar body which will disintegrate with time.

Following ovulation the empty follicle under the influence of LH from the anterior pituitary undergoes changes to become the corpus luteum. This yellow body secretes oestrogen and progesterone. Towards the end of a non-fertile cycle the corpus luteum regresses to become a non-functional structure called corpus albicans.

3.6.2 Pituitary Ovarian Hormonal Interactions

The anterior pituitary secretes two gonadotropin hormone Follicle Stimulating Hormone (FSH) and Lutenising Hormone (LH) as has been discussed. These hormones promote cyclic changes in the structure and function of the ovaries. The secretion of this gonadotropin is under the influence of one releasing hormone from the hypothalamus, the Gonadotropin Releasing Hormone (GRH) and by feedback effects of ovarian hormones.

However, the effect of the releasing hormone is not always equal on FSH and LH. In the early phase of the menstrual cycle FSH secretion is slightly more but just before ovulation LH secretion greatly exceeds FSH secretion. The differences are supposed to be the result of the feedback effects of ovarian sex steroids which affects the amount of GnRH secreted. These complex interactions result in a pattern of hormone secretion that regulates the phases of the menstrual cycle.

3.7 The Menstrual Cycle

Humans and some mammals have cycles of ovarian activity that repeat at approximately one month interval. The term menstruation is used to

indicate shedding of the functional layer of the endometruim which becomes thickened prior to menstruation under influence by ovarian steroid hormones. This shedding is usually accompanied by bleeding.

3.7.1 Phases of the Menstrual Cycle: Cyclic Changes in the Ovaries

The average menstrual cycle lasts about 28 days. For convenience the first day of menstruation is usually called day 1 of the cycle. The cycle can also be conveniently divided into phases based on changes occurring in the ovaries and in the endometruim. From the first day of menstruation, to the day of ovulation, the ovaries are in the follicular phase. After ovulation to the first day of the next menstruation, the ovaries are in the luteal phase. From the changes that occur in the endometrium the menstrual cycle is divided into menstrual, proliferative and secretory phases.

Follicular Phase

The follicular phase of the ovaries lasts from day 1 to about day 13 of the average 28 days cycle. During this phase the follicle operates to produce a mature egg ready for ovulation at about mid cycle. The ovaries contain only primordial and primary follicles in the early parts of this phase. Some primary follicles therefore grow, develop vesicles and become secondary follicles. Towards the end of this phase, one follicle from one ovary has matured and become a graafian follicle. As the follicles grow, granulosa cells secrete increasing amounts of oestradiol (it reaches maximum concentration in the blood at about day 12).

The growth of the follicles and secretion of oestradiol are controlled by FSH from the anterior pituitary gland. Toward the end of the follicular phase, FSH and oestradiol also stimulate the production of LH receptors in the Graafian follicle. This prepares the Graafian follicle for the next major event in the cycle.

The rapid rise in oestradiol secretion during the follicular phase exerts a positive feedback effect on the pituitary to secrete LH. The result is an increase in secretion of LH in the late follicular phase that culminates in an LH surge that begins 24 hours before ovulation and peaks about 16 hours before ovulation. This surge is what triggers ovulation. There is a simultaneous though smaller surge of FSH since the same mechanism control the release of both of them from the anterior pituitary.

Finally the surge in LH secretion causes the wall of the Graafian follicle to rupture at about day 14. A secondary oocyte, arrested at metaphase II of meiosis is released into a uterine tube. Ovulation occurs therefore as a result of the sequential effects of FSH and LH on the ovarian follicles. By

means of positive feedback effect of oestradiol on LH secretion the follicle in a sense, sets the time for its own ovulation. The reason are that ovulation is triggered by an LH surge; LH surge is triggered by increased oestradiol secretion, which occurs only as the follicle grows.

Luteal Phase

Under the influence of LH, the empty follicle becomes a new structure called corpus luteum following ovulation. The corpus luteum now takes on the function of secreting both oestradiol and progesterone. The levels of progesterone in the blood rise so rapidly to reach a peak in the luteal phase about 1 week after ovulation. The high levels of progesterone with oestradiol inhibit the secretion of FSH and LH by the anterior pituitary through negative feedback for a short while. This ensures that no further ovulation occurs in the same cycle. The levels of oestradiol and progesterone begin to fall about day 22 in the late luteal phase because the corpus luteum starts regressing and eventually stops functioning. LH level remain low during the luteal phase because of negative feedback inhibition from ovarian hormones. Decline in corpus luteum causes oestrogen and progesterone to fall to very low levels by day 28 of the cycle. This hormonal withdrawal causes menstruation and permits new cycle to begin.

3.7.2 Phases of the Menstrual Cycle: Changes in the Endometrium

The cycle can also be described in terms of the changes in the endometrium and three phases can be identified.

The Proliferative Phase of the endometruim occurs in the follicular phase of the ovarian cycle. The increasing amounts of oestradiol produced by the developing follicle causes growth (proliferation) of the functional layer of the endometruim. Spiral arteries develop.

The Secretory Phase occurs when the ovary is in the luteal phase. In this phase, increased progesterone secretion stimulates the development of uterine glands. The combined effect of oestradiol and progesterone causes the endometruim to become thick, vascular and spongy in appearance. The uterine glands become engorged with glycogen. All these serve to prepare the endometruim well to accept and nourish an embryo should fertilization occur.

The Menstrual Phase occurs as a result of the fall in ovarian hormones in the late luteal phase. There is death and sloughing of the functional layer of the endometruim probably as a result of the constriction of the spiral arteries. These arteries also seem to be responsible for the bleeding that occurs. Fluctuating changes in ovarian hormones produce cyclical changes

in cervical mucous that can easily be penetrated by spermatozoa. But after ovulation in the luteal phase high levels of progesterone cause the cervical mucous to become thick and sticky after ovulation has occurred.

3.8 Contraception (Literally Against Conception)

The aim of all contraceptive methods is to prevent pregnancy. This can be achieved by preventing the production of ova or sperm, or by preventing them from meeting or by preventing implantation of the embryo.

Millions of women worldwide use contraceptive pills (hormonal contraception). The pills are usually made of synthetic oestrogen and progesterone taken daily for 3 weeks (after last day of menstrual period). The result is an immediate increase in the blood levels of ovarian steroids throughout the normal duration of a monthly cycle. There is a negative feedback inhibition of gonadotropin secretion, therefore, ovulation never occurs. The entire cycle looks like a false luteal phase.

The ovarian steroids contained in the contraceptives cause the endometrium to proliferate and become secretory just as it does during a normal cycle. Because the pills are stopped after 3 weeks (placebo pills taken in the 4^{th} week); oestrogen and progesterone levels fall and menstruation is permitted.

3.9 Menopause

This refers to the cessation of ovarian activity that occurs in women at about age 50. In the years following menopause the ovaries are depleted of follicles and cease secreting oestradiol due to changes in the ovaries but not in the pituitary. Infact, pituitary gonadotropin (FSH and LH) levels are raised due to the absence of feedback inhibition from oestradiol.

The withdrawal of oestradiol secretion from the ovaries is responsible for the many symptoms of menopause. These include vasomotor disturbances and urogenital atrophy. Vasomotor disturbances produce hot flashes, where a fall in core temperature is followed by feelings of heat and profuse perspiration. Atrophy of urethra, vaginal wall and glands occurs with loss of lubrication. There is increased risk of atherosclerotic vascular changes and increased progression of osteoporosis. These changes can be reversed significantly by oestrogen treatments.

4.0 CONCLUSION

The reproductive physiology of males and females are related in a lot of ways even though a significant variation can be noticed between males and females. Reproductive capacity in both sexes however depends on an

intricate relationship among the hypothalamus, anterior pituitary, reproductive organs and other target cells of the sex hormones.

5.0 SUMMARY

In this unit we have learnt the following:

- the description of the reproductive anatomy of both males and females.

- the major control of gonadotropin secretion in the male is testosterone from the testes and in the female is oestradiol from the ovaries.

- spermatogenesis ensures a continual supply of spermatozoa throughout a man's life. It begins in early embryonic life from primordial germ cells called spermatogonia, which proliferate and through several other processes are converted from diploid cells with 46 chromosomes to extremely specialized mobile and haploid spermatozoa.

- erection, emission and ejaculation are processes that ensure that sperm produced in the male are deposited in the female passage.

- several tens of millions of sperm cells are contained in a millilitre of semen and this several numbers are significant in determining male fertility.

- ovarian cycle begins with germ cells which migrate to the ovary in early embryonic life and develop through the oogonia stage from 5 months of uterine life till they start maturing from puberty till menopause. The ovary contains follicles which house the oocytes in various stages of development from puberty till menopause, when the ovaries are completely depleted of follicles.

- ovulation speaks of the extrusion of the secondary oocyte into the uterus tube. This is brought about by a complex and precisely controlled cycle of hormonal interaction, chief of which is the Luteinizing Hormone from the anterior pituitary.

- the menstrual cycle is concerned with cycles of ovarian activity that repeat at one monthly interval. The changes that take place in the ovaries cause cyclic and dynamic adjustments in the secretion of ovarian hormones. This in turn affects the endometrial lining which responds in anticipation of possible fertilization and implantation. The changes are also reflected in the cyclical changes in the cervical mucus which indicate fertility or non fertility.

- The normal cyclical ovarian activity can be mimicked artificially by synthetic ovarian hormones and the effect used to interrupt normal fertile periods thereby achieving contraception.

- menopause marks the cessation of ovarian activity characterized by the ovaries being depleted of maturing follicles. The signs/ symptoms present are those of withdrawal of oestradiol from female circulation.

6.0 TUTOR-MARKED ASSIGNMENT

Describe the hormonal control of ovulation and spermatogenesis at puberty.

7.0 REFERENCES/FURTHER READING

Carola, R.; Harley, J.P. and Noback; C.R. (1990). *Human Anatomy & Physiology*. New York: McGraw Hill Publishing Company.

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UNIT 3 FERTILIZATION, PREGNANCY AND PARTURITION

1.0 Introduction
2.0 Objectives
3.0 Main Content
3.1 The Process of Fertilization
3.1.1 Cleavage and Formation of Blastocyst
3.1.2 Implantation and Formation of the Placenta
3.2 Endocrine Functions of the Placenta
3.3 Labour and Parturition
3.4 Lactation
4.0 Conclusion
5.0 Summary
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1.0 INTRODUCTION

Once fertilization occurs, the secondary oocyte completes the second meiotic division that was arrested at a stage. It then starts multiplying mitotically to form first a ball of cells and then an early embryonic structure called a blastocyst. The blastocyst secretes the human chorionic gonadotropin that maintains the corpus luteum for the continued production of oestradiol and progesterone. Menstruation is hindered, and the embryo can implant and develop in the uterus and form a placenta. In due time birth takes place as a result of strong contractions of the uterus which are stimulated by oxytocin from the posterior pituitary.

2.0 OBJECTIVES

At the end of this unit you will be able to:

- explain the process of fertilization and initial cleavage of the zygote
- describe the process of implantation and formation of the placenta
- explain the endocrine functions of the placenta
- explain the events of labour and parturition
- explain the process of lactation.

3.0 MAIN CONTENT

3.1 The Process of Fertilization

The act of sexual intercourse between males and females results in the male ejaculation of an average of 300 million spermatozoa in the female vagina. Out of these only about 100 spermatozoa survive to enter each

fallopian tube. The sperm gain ability to fertilize an ovum and the process is called fertilization. A woman on the other hand usually ovulates only once a month during her reproductive years. At ovulation a secondary oocyte enters the fallopian tube, surrounded by its zona pellucida and corona radiata of granulosa cells.

Sperm usually meet the ovum for fertilization in the fallopian tubes. Each sperm has a head that is capped by an organelle called an acrosome. The acrosome possesses trypsin like protein digesting enzyme and hyaluronidase (for breaking down constituents of connective tissues). When the sperm meets the ovum, an acrosomal reaction takes place by which the digestive enzymes are exposed which allows the sperm to penetrate the corona radiata and zona pellucida by digestive reactions.

Once the first sperm cell tunnels its way through the zona pellucida, a chemical change occurs in the zona that prevents other sperm cells from entering. Thus only a single sperm cell is allowed to fertilize an ovum. Fertilization occurs when there has been a successful penetration of an ovum by a sperm. As fertilization occurs, the secondary oocyte is stimulated to complete its second meiotic division. This second meiotic division produces one cell that carries all the cytoplasm, and one polar body which later disintegrates.

The sperm cell then enters the cytoplasm of the large egg cell and within 12 hours the nuclear membrane of the ovum disappears. The haploid number of chromosomes in the ovum is joined by the haploid number of chromosomes from the sperm cell. This forms a fertilized ovum or zygote which contains the diploid number of (46) chromosomes.

A secondary oocyte that has been ovulated but not fertilized does not complete its second meiotic division but rather disintegrates 12 to 24 hours after ovulation. Fertilization therefore may not take place if intercourse takes place later than one day after ovulation. Sperm by contrast can survive up to 3 days in the female reproductive tract making it possible that fertilization can occur if intercourse takes place within 3 days before ovulation.

3.1.1 Initial Cleavage and Formation of Blastocyst

At about 30 to 36 hours after fertilization the zygote divides the first time by mitosis into two smaller cells. A second cleavage occurs about 40 hours after fertilization and produces four cells. A third cleavage about 50 to 60 hours after fertilization produces a ball of eight cells called a ***morula.*** This structure enters the uterus three days after ovulation.

Cleavage continues so that a ball of cells of 32 to 64 cells is produced on the 4th day. The embryo remains unattached to the uterus for the next 2 days during which certain changes occur, converting the ball of cells into a hollow structure the blastocyst. The blastocyst has two parts; an inner cell mass that will form the foetus and a surrounding chorionic layer that will become part of the placenta. The cells of the chorion are called trophoblasts.

On the 6th day following fertilization, the blastocyst attaches to the uterine wall with the side containing the inner cell mass lying against the endometrium the trophoblastic cells produce enzymes that help the blastocyst to eat its way into the thickened endometrium. This is the beginning of the process of implantation. By the 7th to 10th day the blastocyst is completely buried in the endometrium.

3.1.2 Implantation and Formation of Placenta

Withdrawal of sex steroids when fertilization has not taken place results in necrosis and sloughing of the endometrium, following day 28 of the cycle. These events are prevented when fertilization has occurred.

Certain occurrences take place to prevent the blastocyst from being eliminated. First the blastocyst secretes a hormone called Human Chorionic Gonadotropin (hCG) even before the 6thy day when implantation begins. This hormone, produced by trophoblastic cells of the chorion indirectly prevents menstruation. It is identical to LH in action and therefore can maintain the corpus luteum beyond the time it would have regressed. The corpus luteum then maintains its secretion of oestradiol and progesterone and menstruation is prevented. The corpus luteum begins to regress by 5th to 6th week, but by this time the developing placenta would have taken over the secretion of sufficient amounts of steroids to maintain the endometrium and further prevent menstruation. HCG secretion declines by the 10th week of pregnancy.

Another thing that happens is the development of chorionic membranes. The blastocyst is completely embedded in the endometrium by the 7th 12th day. The chorion develops into a 2 cell layer structure; the inner is the cytotrophoblast and the outer syncytio-trophobast layers. The inner cell mass also develops into 2 cell layers; the outer ectoderm (from where the nervous system and skin will form) and the inner endoderm (from where the gut and its related structures will form).

The syncytio trophoblast invades the endometrium and secretes protein-digesting enzymes that create many small blood-filled cavities in the maternal tissue. The cytotrophoblast then forms projections or villi that grow into these pools of venous blood giving a leafy appearance. This is

called chorion frondosum and it occurs only on the side of the chorion facing the uterine wall. As the embryonic structures grow the other side of the chorion bulges into the uterine cavity, loses it villi and gets a smooth appearance.

The cells of the endometrium at the same time undergo changes as the blastocyst is implanted. This change called decidual reaction involves cellular growth and accumulation of glycogen. The part of the maternal tissue in contact with the chorion frondosum is called the deciduas basalis. The chorion frondosum (fetal tissue) and decidual basalis (maternal tissue) together form the unit known as the placenta.

The placenta is a disc-shaped structure continuous on its outer edge with the smooth part of the chorion that bulges into the uterus. The amnion lies immediately beneath the chorionic membrane and envelops the entire foetus, so that the foetus with its umbilical cord lie within the fluid filled amniotic sac.

Amniotic fluid is formed initially as an isotonic fluid. Later the volume increases and the concentration changes by fetal urine. It also contains cells sloughed off from the foetus, placenta and amniotic sac. Since all these cells are derived from the same fertilized ovum they have the same genetic composition. From the 16^{th} week of pregnancy, amniotic fluid can be aspirated in order to examine the cells. This way genetic abnormality can be detected in the foetus before birth.

The glycogen stores in the endometrium are only sufficient to nourish the embryo during the first few weeks. The placenta is rapidly developed to sustain the growing embryo/foetus for the duration of intrauterine life. The placenta is a specialized organ of exchange between the maternal and foetal blood. It is derived from both trophoblastic and decidual tissue. By the 12^{th} day, the embryo is completely embedded in the decidual. By this time the trophoblastic layer is one cell-layer thick and is called the chorion. The chorion continues to grow and expand and forms an extensive network of cavities within the decidual. As decidual capillary walls are eroded by the chorion these cavities fill with maternal blood. Fingerlike projects of chorionic tissue extend into the pools of maternal blood. The developing embryo sends out capillaries into these chorionic projections to form placental villi. Each placental villus contains embryonic/foetal capillaries surrounded by a thin layer of chorionic tissue which separates the embryonic/foetal blood from the maternal blood in the intervillus space. This makes it possible that there is not actual mingling of maternal and foetal blood but the barrier is extremely thin.

It is across this extremely thin barrier that all materials are exchanged between the two blood streams. Throughout pregnancy, foetal blood

continuously passes between the placental villi and the circulatory system of the foetus by means of the umbilical arteries and vein, within the umbilical cord.

The umbilical arteries deliver foetal blood to vessels within the villi of chorion fundosum of the placenta. The blood circulates within the villi and returns to the foetus via the umbilical vein. In the same way maternal blood is delivered to and removed from the cavities within the decidual basal that is located within the placental villi. The two never mix.

The placenta serves as a site for the exchange of gases and other molecules between the maternal and foetal blood. Oxygen diffuses from mother to foetus, and Co_2 (1) diffuses in the opposite direction. Nutrient molecules and waste products (2) also pass between maternal and foetal blood.
The placenta is also involved in protein synthesis. It produces a great variety of enzymes capable of converting hormones and exogenous drugs into less active molecules.

3.2 Endocrine Function of the Placenta

The placenta secretes a number of peptide and steroid hormones essential for maintenance of pregnancy. The steroid and protein hormones are similar in action to some anterior pituitary hormones. These include human chorionic gonadotropic (hCG) and chorionic somatomammaotropin, (hCS). In addition to having LH like effects, hCG also has thyroid stimulating activity like pituitary TSH. Chorionic somatomammotropin has actions similar to two pituitary hormones B growth hormone and prolactin. The placental hormones, hCG and hCS duplicate the actions of four pituitary hormones. There is some evidence that hCG may help in some way, to prevent immunological rejection of the implanting embryo. hCS works together with growth hormone from the mother's pituitary to produce diabetes B like effect in the pregnant woman. They produce effects like stimulating:

1) Lipolysis and increased plasma fatty acid concentration.
2) Decreased maternal utilization of glucose and resultant increased blood glucose levels and,
3) Polyuria thereby producing dehydration and thirst.

The placenta also secretes sex steroids. The placenta becomes the major gland producing the sex steroids after the corpus luteum starts regressing. It secretes oestrogens more than 100 times greater than what exists at the beginning of pregnancy. The placenta also secretes very large amounts of progesterone increasing from early pregnancy levels to almost 100 times its original levels by the end of pregnancy.

The two types of oestrogen produced by the placenta are oestradiol and oestriol. The production of oestriol increases tenfold during pregnancy that by the third trimester oestriol accounts for about 90% of the oestrogens excreted in maternal urine. Measurements of urinary oestriol can be used clinically to assess the health of the placenta.

3.3 Labour and Parturition

At the end of pregnancy powerful contractions of the uterus are required for childbirth to take place. Childbirth also requires dilation of the cervical canal to accommodate passage of foetus.

The uterus remains relatively quiet in the first two trimesters, but during the last trimester the uterus becomes progressively more excitable and mild contractions (Braxton Hicks contractions) are experienced with increasing strength and frequency. Other events that take place near the end of pregnancy include:

1) Softening (ripening) of the cervix as a result of dissociation of its connective tissue fibres;

2) Relaxation of the birth canal by loosening the connective tissue between the pelvic bones. This makes room for the foetus to shift downwards (foetus drops) and the presenting part makes contact with the cervix in preparation for exiting.

Rhythmic co-ordinated contractions, that increases in intensity and frequency as labour progresses begin at the onset of true labour. The contractions forcing the foetus against the cervix results in dilation of the cervix. When this dilation is sufficient for the passage of the foetus, the foetus is pushed out by the contractions.

The uterine contractions are known to be stimulated by oxytocin, a polypeptide hormone of the hypothalamus secreted by the posterior pituitary and prostaglandins a class of cyclic fatty acids with autocrine function produced in the uterus.

The factors that lead to the initiation of parturition in humans remain unclear. It appears that both oxytocin and prostaglandins are required in humans since oxytocin induced contractions in the absence of prostaglandins may not lead to dilation of cervix and progressive labour. It has been demonstrated that the sensitivity of the pregnant uterus to oxytocin is up to 100 times that of the non-pregnant uterus. This is due to the increased concentration of myomentrial oxytocin receptors; although the blood level of oxytocin remains constant. The increase in oxytocin receptors and sensitivity may result from the effects of oestrogen that

occur during gestation. Furthermore, more recently it has been suggested that the foetus and the uterus itself synthesize oxytocin therefore the local concentration of oxytocin is higher than blood levels.

This local oxytocin may then stimulate prostaglandin production in the decidual. Prostaglandins diffusing into the myometrium from the decidual may act together with the increased myometrial oxytocin sensitivity to stimulate the onset of labour.

Labour is divided into three stages:

1) Progressive to full dilation of the cervix;
2) Delivery of the baby and
3) Delivery of the placenta

The First Stage is the longest, lasting from a few hours to as long as 24 hours. The membrane surrounding the amniotic sac may rupture during the stage. There is increasing frequency and intensity of uterine contractions accompanied by progressive cervical dilation till maximum dilation is achieved.

The Second Stage is the actual birth of the baby which begins as soon as cervical dilation is complete. Abdominal contraction, uterine contractions and efforts from the mother all combine to push the baby through the birth canal. The infant is still attached to the placenta by the umbilical cord at birth until the cord is tied and severed. The stump shrivels up in a few days to form the umbilicus (navel).

After the delivery of the baby a second series of uterine contractions causes the placenta to separate and be expelled which is the third stage of labour. After the placenta is expelled, continued contractions of the myometrium constrict the uterine blood vessels supplying the site of placental attachment to prevent bleeding.

After delivery the uterus shrinks to its pre-pregnancy size in a process known as involution. It takes 4 to 6 weeks to complete. During involution any remaining endometrial tissue that was not expelled after delivery gradually disintegrates and sloughs off and is expelled in a vaginal discharge called lochia that continues for 3 to 6 weeks. After this period the endometrium is restored to non-pregnant state.

3.4 Lactation

After parturition, when the placenta is expelled, declining levels of oestrogen are accompanied by an increase in the secretion of prolactin and this stimulates milk production. The production of milk proteins; casein

and lactalbumin is stimulated after parturition by prolactin - a hormone of the anterior pituitary gland.

Changes occur in the mammary gland during pregnancy in preparation for lactation, under the influence of some hormones. The high concentration of oestrogen in pregnancy promotes extensive duct and tubular development, whereas the high level of progesterone stimulates abundant development of mammary alveoli. All these require the permissive actions of insulin, cortisol and thyroid hormones.

The secretion of prolactin during pregnancy is inhibited by prolactin inhibiting hormone (PIH) from the hypothalamus which is stimulated by high levels of oestrogen. In addition the high levels of oestrogen act directly on the mammary glands to block their stimulation by prolactin and hCS. During pregnancy therefore the high levels of oestrogen prepare the breasts for lactation but prevent prolactin secretion and action.

The act of nursing helps to maintain high levels of prolactin secretion via a neuroendocrine reflex. Sensory nerve endings in the breast activated by suckling relay impulses to the hypothalamus and inhibit the secretion of PIH. Suckling therefore results in reflex secretion of high levels of prolactin which promotes the secretion of milk from the alveoli into the ducts. Another hormone is required for the baby to get the milk.

Suckling stimulus also results in the reflex secretion of oxytocin from the posterior pituitary. The secretion of oxytocin results in milk-ejection reflex. It stimulates contraction of the lactiferous ducts as well as the uterus.

Breast feeding causes reflex inhibition of GRH secretion and so hinders the secretion of gonadotropins from the mother's anterior pituitary. This inhibits ovulation. This way breast feeding acts as a natural contraceptive that helps to space births.

4.0 CONCLUSION

The act of fertilization marks the beginning of a new life. It first of all results in restoration of the original chromosome number of 46 in the zygote. From this point the zygote can grow into an adult member of the next generation through a series of complex processes which proceeds through a 38 week gestation and results in the birth of a newborn.

5.0 SUMMARY

In fertilization the sperm undergoes acrosomal reaction which enables it to penetrate the corona radiata and zona pellucida to unite with the ovum. The secondary oocyte immediately completes its second meiotic division producing a second polar body. A diploid zygote is formed which

undergoes cleavage to form a morula and then a blastocyst after which the blastocyst is implanted into the endometrium between the 5th and 7th day of fertilization. The trophoblastic cells of the blastocyst secrete hCG which maintains the corpus luteum for the first 10 weeks of pregnancy. The trophoblasts later become the foetal contribution to the placenta while the adjacent material tissue contributes the other part. Oxygen, nutrients and wastes are exchanged by diffusion between foetal and maternal blood. The placenta secretes hCG and steroid hormones. The major steroid hormone from the placenta is oestriol. Contraction of the uterus in labour is stimulated by oxytocin from the posterior pituitary and prostaglandins produced within the uterus leading to expulsion of the foetus at the end of pregnancy. The high levels of oestrogen during pregnancy work together with other hormones to stimulate the growth and development of the mammary gland. Prolactin and hCS stimulate the production of milk proteins but it can only stimulate milk production after birth when oestrogen level falls. The stimulus of suckling causes reflex secretion of oxytocin which stimulates contractions of the lactiferous ducts and the ejection of milk from the nipples.

6.0 TUTOR-MARKED ASSIGNMENT

List the protein hormones and sex steroids secreted by the placenta and explain their functions.

7.0 REFERENCES/FURTHER READING

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