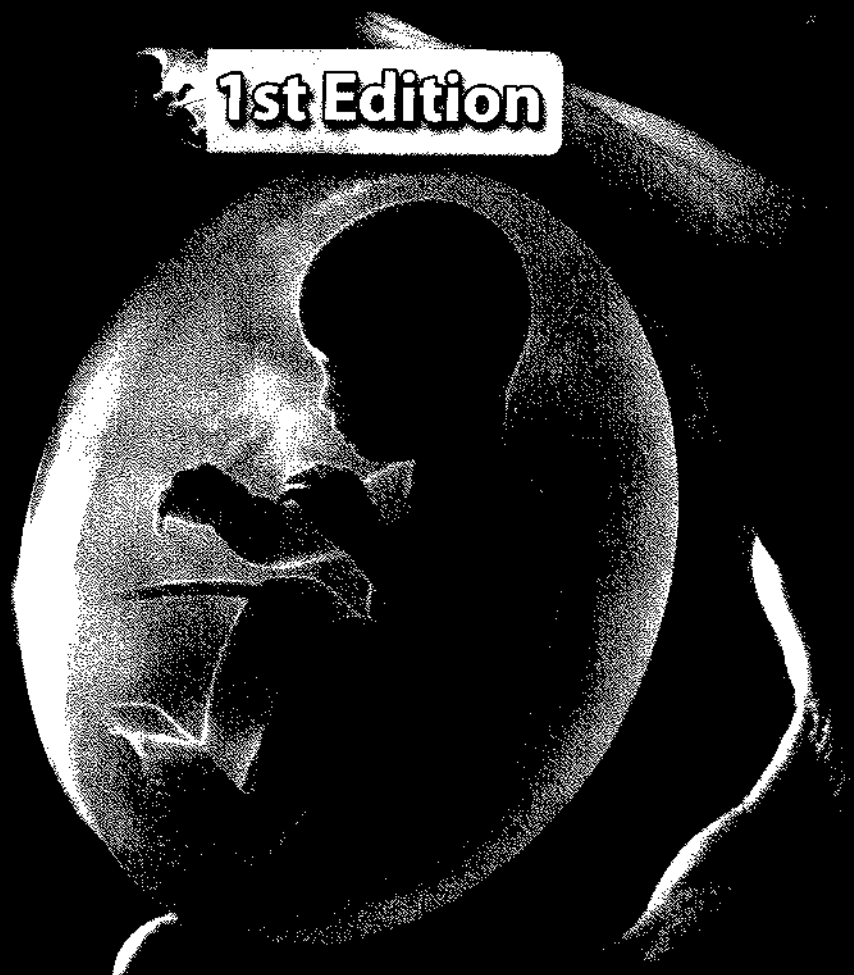
Compact Medical Embryology

1st Edition



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Dedication

Dedicated To My Beloved

With

Love

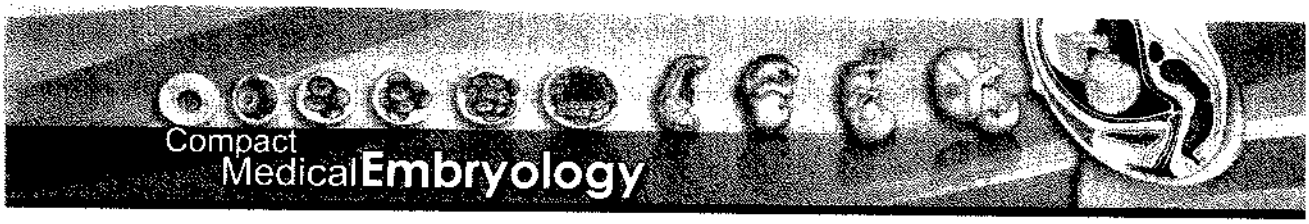
&

Regards!

Mr. Javed Iqbal Arain

&

Mrs. Zahida Javed Arain



PREFACE:

The requisite of having a simple, systematize, pictorial and comprehensive book on embryology has long been felt. The need for such a book has become all the more acute due to lesser time is now available nationwide for learning embryology. The attempt for writing **COMPACT MEDICAL EMBRYOLOGY** has been made with sense to systematize the study of embryology that meet the intellectual demands of medical students. The content has been classified into sections to make it easier for understanding, memorizing and recalling at will. It is adequately illustrated in simple and smooth way with embryological diagrams that assist students to understand the embryological facts which first appear to be defying the intellect of medical students. The important points which are likely to be the part of exams have been tabulated under the heading of embryological tid bits, which makes the book interesting for a photographic memorization. In addition to this tables of various topics have also been drawn in order to facilitate the rapid review. The book has been intentionally divided into four sections (Fundamentals of embryology, General embryology, System based embryology and Pathological embryology) for comprehensive and convenient handling. A significant attempt has been made to put, wherever required, the clinical aspects of the subject. The entire approach is setting to attract and blow the beacon for medical students to dive deep into the world of embryology.

Errors of omission and commission are highly acceptable and will be welcomed for it is mostly the attempt of single hand.

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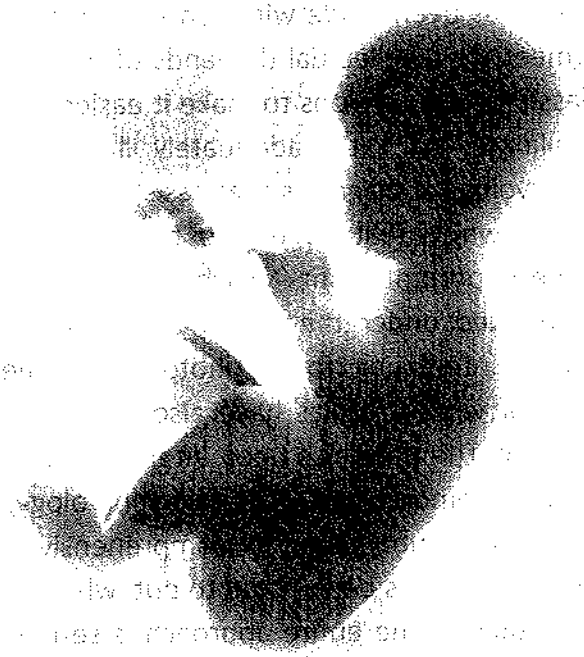

ACKNOWLEDGMENTS

Writing a book is tough job it is more when author doesn't have any support and encouragement. I think many books remain unwritten for these issues. I feel extremely indebted for two of my teachers who have helped me to improve this book over the course of time;

1. **Prof. Dr Anjum Naqvi**
2. **Prof. Dr Muhammad Aslam Channa**

I pay a deep gratitude to my uncle **Dr. Zaheer Saleem Arain** who guided me at various helms during the course of writing this book.

Beside this I am feeling humbled and most grateful to my brotherly seniors **Dr. Bilal Khanzada** and **Dr. Umair Ali Jokhio** for giving me their erudite opinion regarding compilation and boosting my courage to the end of tunnel. They are indeed the generous person. May Allah bestowed them more and more. Long live Medical Arena!

FORE WORD MESSAGE

I am expressing the greatest appreciation for this inspiring book on the subject of Embryology written by my student Saqib Javed Arain. I am fully assured that this book provides a complete guide to Medical Students for enhancing their knowledge and understanding regarding the processes involved in the creation of human being.

May Almighty approves the efforts and hard work of the author.

Prof. Dr. Anjum Naqvi

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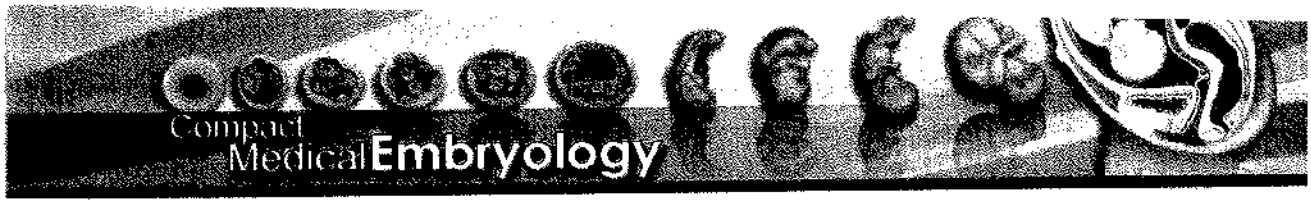
PAQSJIMS, Gambat.



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SECTION – A

THE FUNDAMENTALS OF EMBRYOLOGY

1 INTRODUCTION TO EMBRYOLOGY

LEARNING OBJECTIVES

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- FIELDS OF EMBRYOLOGY
- DEVELOPMENTAL PERIODS
- FUNDAMENTAL DEVELOPMENT PROCESS
- DESCRIPTIVE TERMINOLOGIES
- EMBRYOLOGIC PLANES
- SIGNIFICANCE OF EMBRYOLOGY
- KEY NOTES

DEFINITION OF EMBRYOLOGY:

The branch of developmental anatomy that deals with the study of origin and development of living organism.

Development is all about continuous growth in progressive direction both in structure and function from fertilized ovum to the adult stage.

FIELDS OF EMBRYOLOGY:

Embryology has been categorized into two broad divisions named as;

1. Morphological division
2. Functional division.

1. MORPHOLOGICAL DIVISION:

It is the branch of embryology that deals with the structural aspects of the embryonic development.

2. FUNCTIONAL DIVISION:

It is the branch of embryology that deals with the physiological aspects of the embryonic development.

DEVELOPMENTAL PERIODS:

For the sack of description, developmental periods have been categorized into two periods;

1. Prenatal period
2. Postnatal period.

1. PRENATAL PERIOD:

It is the period of embryonic development which deals with the aspects of life in uterine tube or the life before birth.

Prenatal period has been classified into three sub periods:

a- OVUM PERIOD:

It is the period of development from the time of fertilization up to the first week of development. During this period some minor changes occur.

b- EMBRYONIC PERIOD:

It is the period of development from the second week of development up to the eighth week of development. During this period maximum changes occur like;

1. Placento- maternal relationship.
2. Changes in the shape of conceptus.
3. Growth of various organs primordia.
4. Rapid growth and development.

c- FETAL PERIOD:

This period extends from the third month of gestation up to the tenth lunar month that is till the time of birth. During this period plethora of changes occur like whole host of primordial structures morphed into the systems of an individual both structurally and functionally.

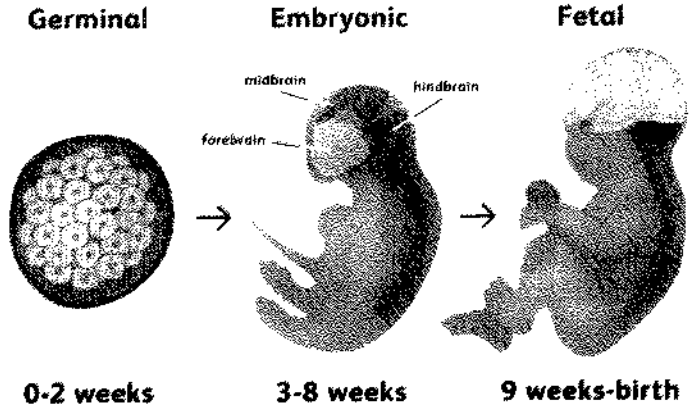


Fig 1.3. Prenatal developmental periods

2. POSTNATAL PERIOD:

It is the period of embryonic development that deals with the aspects of life outside the uterine tube or the life after birth.

Postnatal period has been classified into six sub periods;

a- NEONATAL PERIOD:

Neonatal period extends from the time of birth up to the termination of two weeks of postnatal life. During this phase living body is known as neonate.

b- INFANCY:

It is the period of postnatal development that commences from the 3rd week of postnatal life until the attainment of erect posture and that is the end of first year of postnatal life. In this period living body is known as infant.

c- CHILDHOOD PERIOD:

This is the period of postnatal development that extends from the second year of postnatal life up to the pre pubertal stage. During this period living body is known as child. For the sack of understanding it has been classified into following sub periods;

EARLY CHILDHOOD:

It is the age of milk teeth eruption that extends from the second year of postnatal life up to the sixth year of postnatal development.

MIDDLE CHILDHOOD:

It is the age of permanent teeth eruption that extends from the seventh year of postnatal life up to ninth year of postnatal development.

LATER CHILDHOOD:

This period is known as pre pubertal period. It extends from the ninth year of postnatal life up to the twelfth year of postnatal development.

d- PUBETAL PERIOD:

This period varies in males and females. In males it extends from the thirteenth year of postnatal life up to the sixteenth year of postnatal development while in females it extends from the ninth year to the fifteenth year of postnatal development.

e- ADOLESCENCE:

This is the period of postnatal development during which an individual gets physical, mental and sexual maturity. This period extends from the sixteenth year up to twenty to twenty fifth year of postnatal life.

- ADULTHOOD:
  Following the period of adolescence is the period of adulthood which is further classified as under;

PRIME AND TRANSITION AGE:

This period extends from the twenty fifth year up to the sixtieth year of life.

OLD OR SENILE AGE:

It extends from the sixtieth year of life up to death.

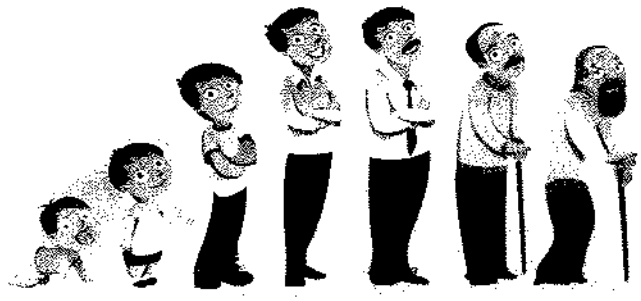


Fig. 2: Postnatal developmental periods

FUNDAMENTAL DEVELOPMENTAL PROCESS:

Fundamentally, the development for the living body commences at the cellular level. It comprises of the following phases;

1. CELLULAR PROLIFERATION PHASE:
   In this phase, cells divide to increase their numbers and size.
2. GROWTH PHASE:
   In this phase, cells adapt the permanent and irreversible increase in both size and mass.

DESCRIPTIVE TERMINOLOGIES:

TERMS	ANATOMICAL RELATIONS
Rostral	Near to the front end
Cranial	Towards head
Cephalic	Towards skull
Caudal	Towards tail end
Dorsal	Near to the back surface
Ventral	Near to the front surface.

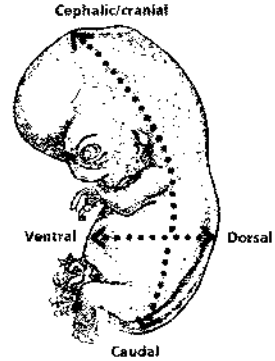


Fig. 3: Anatomical Directions.

EMBRYONIC PLANES:

In order to understand the orientation of the conceptus taking reference is of primary significance. Therefore, for the sack of description following are given types of referral planes;

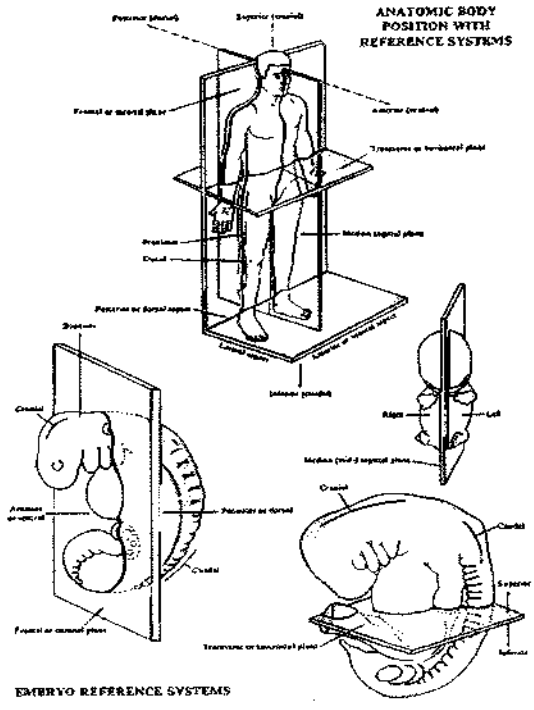


Fig 1.4 Embryonic planes

1. MEDIAN PLANE:
   It is a type of vertical plane that sections the body in two equal halves.

2. SAJITAL PLANE:
   It is a type of vertical plane that sections the body into two unequal halves

3. TRANSVERSE PLANE:
   It is a type of horizontal plane that sections the body in two equal upper and lower halves.

4. CORONAL PLANE:
   It is a type of vertical plane that sections the body into anterior and posterior halves.

SIGNIFICANCE OF EMBRYOLOGY:

Embryology has significance according to the below mentioned lines;

- Firstly it is of practical significance as it provides knowledge for understanding the development of living body.
- It provides knowledge for normal relation and status of the developing body.
- It discusses the causes of congenital malformations that is known as teratology in the developing body.
- It determines the sex of the organism.
- It provides the links of organic evolution.

- It determines the hereditary factors responsible for various developments.
- It also discusses the pattern of growth, differentiation and repair.

KEY NOTES!

a- This chapter deals with the general definitions of embryology. It also discusses the division of embryology.

b- It discusses the both prenatal and postnatal periods of life.

c- For defining the orientation of embryo during prenatal life, various types of planes have been discussed for the sack of understanding.

d- At last significance of embryology has been listed.

2

REPRODUCTION

LEARNING OBJECTIVES

- DEFINITION OF REPRODUCTION
- CONSTITUENTS OF REPRODUCTIVE SYSTEM
- MALE REPRODUCTIVE SYSTEM
- FEMALE REPRODUCTIVE SYSTEM
- REPRODUCTION OF CELLS
- CELL CYCLE AND CELL DIVISION
- TYPES OF CELL DIVISION
  - I. MITOSIS
  - II. MEIOSIS
- GAMETOGENESIS
  - III. SPEMATOGENESIS
  - IV. OOGENESIS
- DISTINGUSIH BETWEEN SPERMATOCYTE AND OOCYTE
- FEMALE REPRODUCTIVE CYCLES
  - V. OVARIAN CYCLE
  - VI. MENSTRUAL CYCLE
- TRANSPORT OF GAMETES
- KEY NOTES.

DEFNITION OF REPRODUCTION:

Reproduction is a process in which male and female gametes unite to form an organism of similar type, this is known as reproduction.

There is a distinct reproductive system in males and females.

CONSTITUENTS OF REPRODUCTIVE SYSTEM:

The male and female reproductive system of human beings consist essentially on the following four components;

1. Gonads
2. Sex glands
3. Genital ducts
4. External genitalia.

MALE REPRODUCTIVE SYSTEM:

Male reproductive system is comprised of the gonads, sex glands, genital ducts and the external genitalia.

1. MALE GONADS:

Testis performs the function of gonads in human males. It is a pair of organs located behind the penis in the pouch of skin known as scrotum. The testis produces and stores the sperm. It is also the major source of male hormones.

There are three main type of cells present in the male gonads, these are;

a. SPERMATOCYTES:

These are the primary cells for the production of sperms.

b. SERTOLI CELLS:

These are regarded as the supporting cells.

c. INTERSTITIAL CELLS:

The tissue layer of cells are present in the seminiferous tubules that is known as interstitial cells or ladic cells. These cells produce testosterone and dihydrotestosterone.

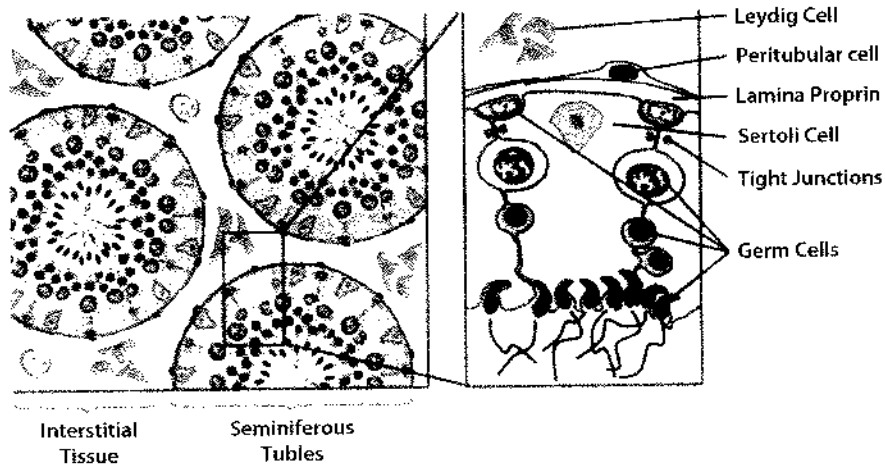


Fig 2.1 : Different cells of male reproductive system

1. SEX GLANDS OF MALE:

Following are given primary sex glands of the male reproductive system.

a. PROSTATE GLAND:

It is the compound tubulo –alveolar gland present at the base of urinary bladder and surrounds the urethra.

b. SEMINAL GLAND:

It is a pair of compact tubular gland present inside the testis. It produces spermy secretion.

c. BULBOURETHRAL GLANDS:

It is also called as Cowper's gland. It is either two pea shaped glands located

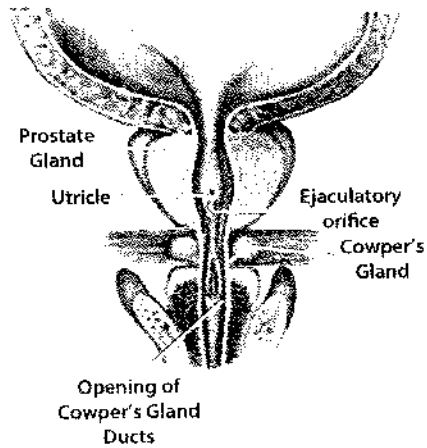


Fig 2.2: Different glands of male reproductive system

beneath the prostate gland at the beginning of the internal portion of the penis. These glands add fluid to semen during the process of ejaculation.

2. MALE GENITAL DUCTS:

Below are given the description of the male genital ducts which are continuous and concerned with the transport and maturation of male gametes.

a. TUBULI RECTI:

These are the straight seminiferous tubules lie in the testicles connecting the convoluted region of seminiferous tubule to rete testis though it differs from the tubuli recti in appearance.

b. RETE TESTIS:

Rete testis is an anastomosing network of delicate tubules located in the hilum of the testicles that carries sperm from the seminiferous tubules to the efferent ducts. It's counterpart in female is rete ovarii.

c. DUCTULI EFFERENTES:

Efferent ducts serves as connecting channel between rete testis and the initial portion of epididymis.

d. EPIDIDYMIS:

It is highly convoluted duct lies behind the testis, along which sperm passes to the ductus deferens.

e. DUCTUS DEFERENS:

It is also known as vas deferens. It is a tiny muscular tube in the male reproductive system that carries sperm from the epididymis to the ejaculatory duct. It is actually a pair of ducts which carries sperms from each testis to left and right ejaculatory ducts.

f. EJACULATORY DUCT:

Each ejaculatory duct is formed by the union of vas deferens with the duct of seminal vesicle. They pass through the prostate and open into the urethra at the seminal colliculus. During ejaculation semen passes through the prostate gland, enters the urethra and exits the body via urinary meatus.

3. EXTERNAL GENITALIA OF THE MALE:

External genitalia of the male consists of the penis, urethra and scrotum.

a. PENIS:

The external male sex organ. The penis contains two chambers, the corpora cavernosa, which run the length of the organ. These chambers are filled with spongy tissue and surrounded by a membrane called the tunica albugenia. The spongy tissue contains smooth muscles, fibrous tissues, spaces, veins, and arteries.

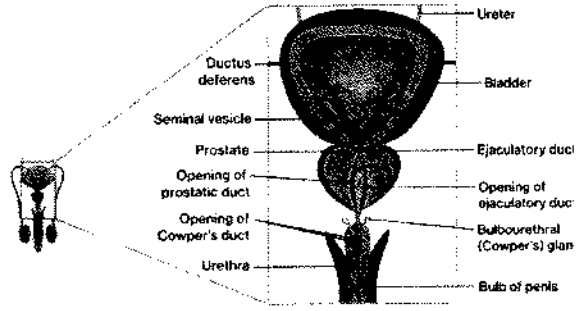


Fig 2.3. Male genital ducts and external genitalia

b. URETHRA:

The urethra, which is the channel for urine and ejaculate, runs along the underside of the corpora cavernosa. The urethra emerges at the glans, the rounded tip of the penis.

c. SCROTUM:

It is a part of the external male genitalia located behind and underneath the penis. It is the small, muscular sac that contains and protects the testicles, blood vessels, and part of the spermatic cord.

FEMALE REPRODUCTIVE SYSTEM:

Like male reproductive system, female reproductive system is also comprised of gonads, sex glands, genital ducts and the external genitalia.

1. FEMALE GONADS:

Female gonads are the ovaries; these are paired almond shaped reproductive organs present close to the lateral pelvic walls on each side of uterus. It serves the function of production of oocytes, progesterone and estrogen that in turn maintain the secondary sexual characteristics and the state of pregnancy.

2. GENITAL DUCTS:

Genital ducts in the females consists of the following three ducts.

a. UTERINE TUBES:

It is approximately 10cm long and 1cm in diameter. It extends laterally from the horns of uterus and ends into the peritoneal cavity. Uterine tube, for the sack of understanding, has been demarcated into four regions;

I. INFUNDIBULUM: It is the funnel shaped upper close part of the uterine tube which is directed towards the ovary.

II. AMPULLA: It is a dilated ad the widest part of uterine tube which serves as the site of fertilization.

III. ISTHMUS. It is the part of uterine tubes which serves the function of connecting link between ampulla and intramural part.

IV. INTRAMURAL PART: It is the small segmented portion of the uterine tubes which opens into the uterus.

b. UTERUS:

It is pear shaped thick walled muscular organ. It ranges approximately 7 to 8 cm in length and 5 to 7 cm in diameter, however it has 2 to 3 cm wall thickness. In order to describe, uterus has been divided into three regions.

I. FUNDUS: It is rounded superior part of the uterus. It extend up to the isthmus. It is only 1 cm constricted region between body and cervix which provides surface for the fetus.

II. BODY: It is the largest part of the uterus lies inferior to the fundus.

III. CERVIX: It is the cylindrical part of the uterus which is projected inside the vagina. The lumen of the cervix s called as cervical canal while it has two openings known as external and internal os which communicates with the vagina and uterine cavity respectively.

WALLS OF THE UTERUS:

The walls of the uterus consist of the following three layers.

a. PERIMETRIUM: It is the thin external layer which serves as peritoneal layer. It is firmly attached to the myometrium.

b. MYOMETRIUM: It is the thick smooth muscular layer present between perimetrium and endometrium.

c. ENDOMETRIUM: It is the thin inner layer having attachment with the wall of uterus.

During the secretory phase of menstruation cycle it is distinguished into following three layers;

1. The thin layer which consists of the densely packed connective tissue around the neck of uterine glands known as *COMPACT LAYER*.
2. The thick layer which is composed of plethora of connective tissues that contain dilated and tortuous bodies of uterine glands known as *SPONGY LAYER*.
3. The thin layer which contains the blind ends of the uterine glands known as *BASAL LAYER*.

EMBRYOLOGICAL TID BITS!
1. Basal layer of endometrium does not sloughed off during menstruation because it has its own blood supply that is spiral arteries.
2. During menstruation cycle, compact and spongy layer which is collectively known as functional layer sloughed off and it disintegrates during parturition.

c. VAGINA.

It is the tubular structure leading from the external genitals to the cervix. It serves as the opening for the copulation.

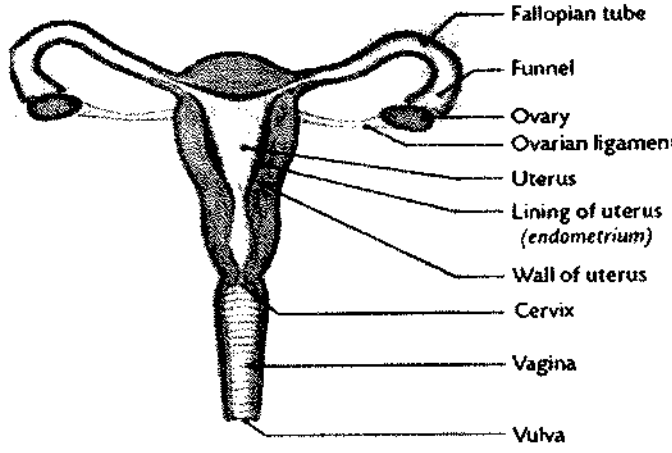


Fig 2.4. Female genitalia

1. FEMALE SEX GLANDS:

Following are given two important female sex glands;

a. BARTHOLIN GLANDS:

These glands are also known as greater vestibular glands. These are two pea sized compound racemose glands located slightly posterior and to the left and right of the opening of vagina. The secrete mucus that lubricates the vagina and these are homologous to the bulbourethral glands in males.

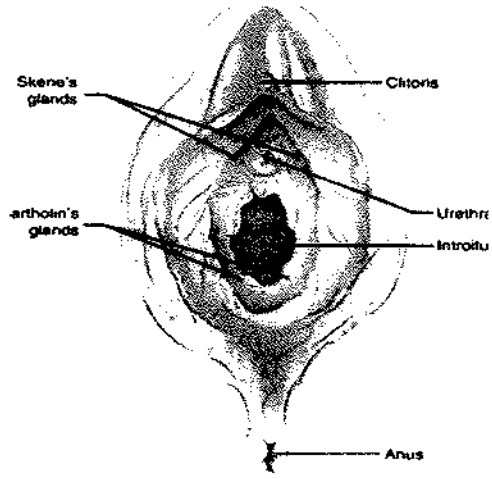


Fig 2.5: Different glands of female reproductive system

a. PARAURETHRAL GLANDS:

These glands are also known as skene's glands or the lesser vestibular glands. These are located on the anterior wall of vagina, around the lower end of urethra. These glands secrete fluid from the openings lies near urethra particularly during orgasm.

2. EXTERNAL GENITALIA OF FEMALE:

These include the perineum, mons pubis, clitoris, urethral (urinary) meatus, labia majora and minora, vestibule, greater vestibular glands, skene's glands, and periurethral area.

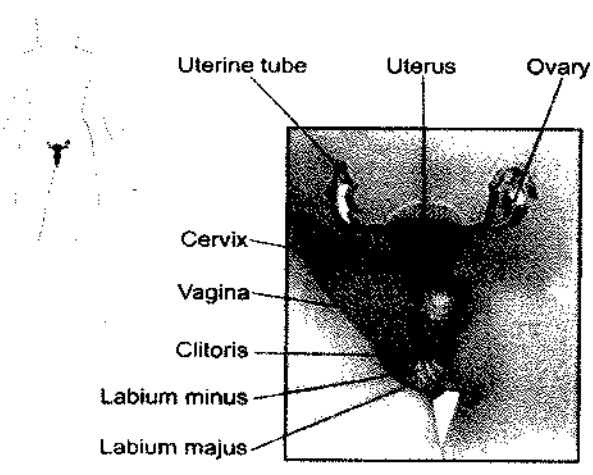


Fig 2.6: External genitalia of female

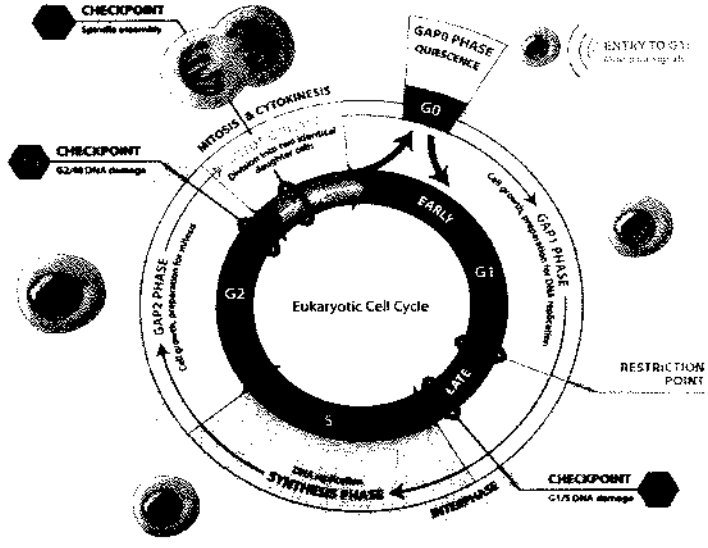
REPRODUCTION OF CELLS:

Below are given some general significant points regarding reproduction of cells;

- Reproduction of cells commence from the embryonic life and it goes on repeating the cell divisions and increases the complexity of body.
- After the process of differentiation cells are unable to undergo further cell division and it is known as differentiated cells.
- Growth and continuous replacement of cells occur in gastrointestinal tract.
- There are two types of stem cells, one with dividing capacity while other devoid of it.
- Sometimes cells abnormally over grow that are known as neoplastic cells.

CELL CYCLE:

It is defined as the sequence of events that occurs in the cells and prepares the cells for division.



Events of cell cycle

MECHANISM OF CELL CYCLE:

Cell cycle consists of the following four phases;

G1 PHASE: In this phase metabolic changes occur in the cells which prepare the cell for division. At some certain point that is known as restriction point, the cell is committed to undo the division and moves into the G_0 phase.

S PHASE: In this phase synthesis of the DNA occur by the replication of genetic material. Each chromatid now consists of two sister chromatids.

G_2 PHASE: In this phase metabolic changes occur which assemble the cytoplasmic materials necessary for mitosis and cytokinesis.

M PHASE: In this phase karyokinesis occurs which is followed by the cytokinesis.

The period between mitotic divisions that is G_1, S, G_2 is known as interphase.

TYPES OF CELL DIVISION:

In eukaryotic cells there occurs two types of cell division;

- Mitosis
- Meiosis

1. MITOSIS:

Mitosis is a type of eukaryotic cell division that produces two daughter cells with the same genetic material as that of parent cells. The chromosomes undergo the process of replication during the S phase and cells divided in such a way as to ensure that each daughter cell have a copy of every chromosomes. It takes about one hour to occur in an actively dividing cells.

The replication of chromosomes are associated with the mitotic apparatus that first align and then separate the sister chromatids in order to produce an even partioning of the genetic material. In mitosis karyokinesis associated with separation of genetic material is followed by cytokinesis and produces two daughter cells. Mitosis plays significant role in cell replacement, wound healing and tumor formation.

Although mitosis is a continuous process but conventionally it is divided into five phases; prophase, prometaphase, metaphase, anaphase and telophase.

THE PHASES OF MITOSIS:

1. PROPHASE:

Half of the mitosis comprises of prophase. During this phase nuclear membrane breaks down and form the number of small vesicles. The nucleolus disintegrates, a structure known as centrosome duplicates itself to produce two daughter centrosomes that migrate to the opposite poles. The centrosomes organize the production of microtubules that gives out the spindle fibers of various kinds and constitute the mitotic spindle. During this phase chromosomes condense into the compact structures. Each replicated chromosome can now be seen as two identical chromatids therefore named as sister chromatids. These are held together by a structure called as centromere.

2. PROMETAPHASE:
   During this phase the chromosomes which are led by the centromeres start to migrate to the equatorial plate in the midline orientation of the cell that is at right angles to the axis formed by the centromeres. The so called name of this region is metaphase plate. The spindle fibers bind to the kinetochore protein of each chromosome. Furthermore chromosomes continue to condense.

3. METAPHASE:
   During this phase chromosomes align themselves along the metaphase plate of the spindle fibers.

4. ANAPHASE:
   This is the shortest phase of mitosis. In this phase the centromeres divide and the sister chromatids of each chromosome pulled a part and start moving in the opposite direction. This is assisted by the spindle fibers which are attached to the kinetochore protein. The separated sister chromatids are now called as daughter chromosomes.

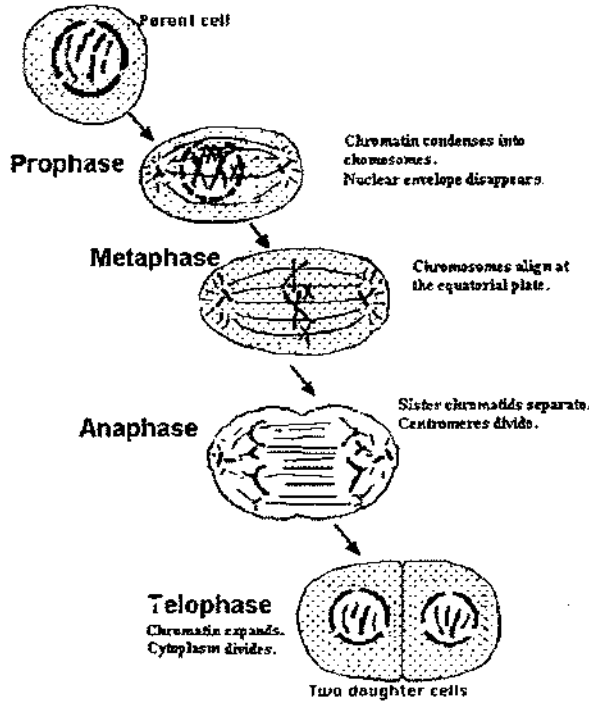


Fig 2.8: Mitotic cell division

5. TELOPHASE:

This is the last stage of mitosis associated karyokinesis. During this phase reversal occurs of many of the processes observed during prophase. The nuclear membrane reforms around the chromosomes. The chromosomes become uncoil and diffuse. The spindle fibers also disappear.

CYTOKINESIS:

It is all about the cytoplasmic division of the cell. During this division cell divides to form the two daughter cells.

MEIOSIS

It is defined as the type of eukaryotic cell division that produce the four daughter cells each with haploid number of chromosomes. It occurs in the gametes. This process takes the form of one DNA replication followed by the two successive nuclear and cytoplasmic divisions known as Meiosis I and Meiosis II. Meiosis, like mitosis, is preceded by a process of DNA replication that converts each chromosome into two sister chromatids.

MEIOSIS I:

It separates the pair of homologous chromosomes. In this type of cell division number of chromosomes reduce to haploid. Following are given the phases of Meiosis I. The first meiotic division is a reduction division (diploid → haploid) in which homologous chromosomes are separated.

PROPHASE I:

Chromosomes condense, nuclear membrane dissolves, homologous chromosomes form bivalents, crossing over occurs. This phase is subdivided into the following sub-phases;

LEPTOTENE:

During leptotene chromosomes start to condense.

ZYGOTENE:

During zygotene homologous chromosomes become closely associated that is to undergo synapsis and form the pairs of chromosomes consisting of four chromatids.

PACHYTENE:

During this phase chiasmata formation occurs by crossing over.

DIPLOTENE

During this phase homologous chromosomes start to separate but remain attached to the chiasmata.

DIKINESIS:

During this phase terminalization occurs.

METAPHASE I:

Spindle fibers from opposing centrosomes connect to bivalents (at centromeres) and align them along the middle of the cell

ANAPHASE I:

Spindle fibers contract and split the bivalent, homologous chromosomes move to opposite poles of the cell

TELOPHASE I:

Chromosomes decondense, nuclear membrane may reform, and cell divides (cytokinesis) to form two haploid daughter cells

Meiosis II

The second division separates sister chromatids (these chromatids may not be identical due to crossing over in prophase I)

PROPHASE II:

Chromosomes condense, nuclear membrane dissolves, centrosomes move to opposite poles (perpendicular to before)

METAPHASE II:

Spindle fibers from opposing centrosomes attach to chromosomes (at centromere) and align them along the cell equator

ANAPHASE II:

Spindle fibers contract and separate the sister chromatids, chromatids (now called chromosomes) move to opposite poles.

TELOPHASE II:

Chromosomes decondense, nuclear membrane reforms, cells divide (cytokinesis) to form four haploid daughter cells.

The final outcome of meiosis is the production of four haploid daughter cells
These cells may all be genetically distinct if crossing over occurs in prophase I (causes recombination of sister chromatids).

EMBRYOLOGICAL TID BITS!
➢ In primary gametes amount of DNA is 4N while chromosome number is 2n.
➢ In secondary gametes amount of DNA is 4N while chromosome number is n.

SIGNIFICANCE OF MEIOSIS:

Following are given some key points of meiosis.

- It provides constancy of chromosome number from generation to generation by reducing the diploid number of chromosomes to haploid.
- It permits random assortment of maternal and paternal chromosomes.
- It relocates the segments of maternal and paternal chromosomes by crossing over which in turn shuffles the genes and produces the genetic diversity.

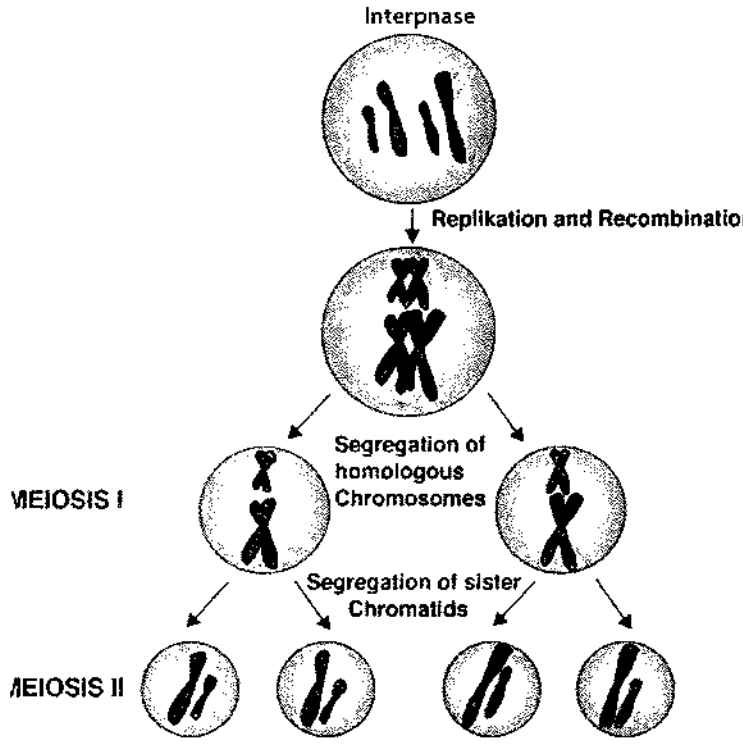


Fig 2.9: Meiosis cell division

GAMETOGENESIS:

It is a specialized process in which bipotential precursor germ cells transformed physiologically as well as morphologically into functional units known as gametes, process is known as gametogenesis.

GENERAL FEATURES REGARDING GAMETOGENESIS:

Following are given some general aspects regarding gametogenesis;

- ✓ During the process of gametogenesis chromosome number is reduced to haploid.
- ✓ During this process the amount of DNA is increased to double.
- ✓ During this process alteration in the shape of cells occur.

✓ The process of gametogenesis takes place through meiosis and cytodifferentiation.

TYPES OF GAMETOGENESIS:

There are two types of gametogenesis;

1. Spermatogenesis
2. Oogenesis

1. SPERMATOGENESIS:

Spermatogenesis is defined as the sequence of events during which primordial germ cells are transformed into mature sperms, it is known as spermatogenesis.

PRODUCTION OF GERM CELLS:

Production of cells have been classified into two phases;

a. Prenatal progression
b. Postnatal progression.

a. PRENATAL PROGRESSION:

Some stages of spermatogenesis occur before birth that is known as prenatal progression of spermatogenesis. At the 4^{th} week of embryonic development germ cells distinguished in the yolk sac, these cells are known as primordial germ cells or spermatogonia. Afterwards, between 4^{th} and 6^{th} week of embryonic development these cells first elongate then move via gut tube through mesentery to the posterior body wall where they settle down on the either side of midline in the developing genital ridges which later on form the male gonads or testis. During this migration primordial germ cells divide solely by mitosis.

b. POSTNATAL PROGRESSION:

Postnatal progression of the germ cell is all about its production during fetal and adult life.

During fetal life two types of reproductive cells present in the body known as spermatogenic and non- spermatogenic cells.

SPERMATOGENIC CELLS:

These are the cells which are the future site for sperm production, these are also known as primordial germ cells.

TYPES OF SPERMATOGENIC CELLS:

There are four types of spermatogenic cells, these are;

1. Primary spermatocyte

2. Secondary spermatocyte
3. Spermatids
4. Spermatozoa.

NON- SPERMATOGENIC CELLS:

These are cells which help in the processes of phagocytosis and nutrition.
During pubertal life, these spermatogenic cells proliferate by mitosis and become the spermatogonia however, by the action of testosterone spermatogonia undergoes mitosis and provide a continuous supply of cells known as primary spermatocyte.

TYPES OF SPERMATOGONIA:

There are two types of spermatogonia;

1. TYPE A:

   Type A is further classified into two named as;

   i. Pale cells which are mitotically active cells.
   ii. Dark cells which serve as stem cells, they divide occasionally as per need. These cells are used for repertoire the cells.

2. TYPE B:

   Type B cells are important category of cells that undergo proliferation to give rise the primary spermatocyte.
   Regarding both type of cells, these cells are interconnected to each other through cytoplasmic bridges. Reorganization of these cells is done by nucleus and nucleolus.

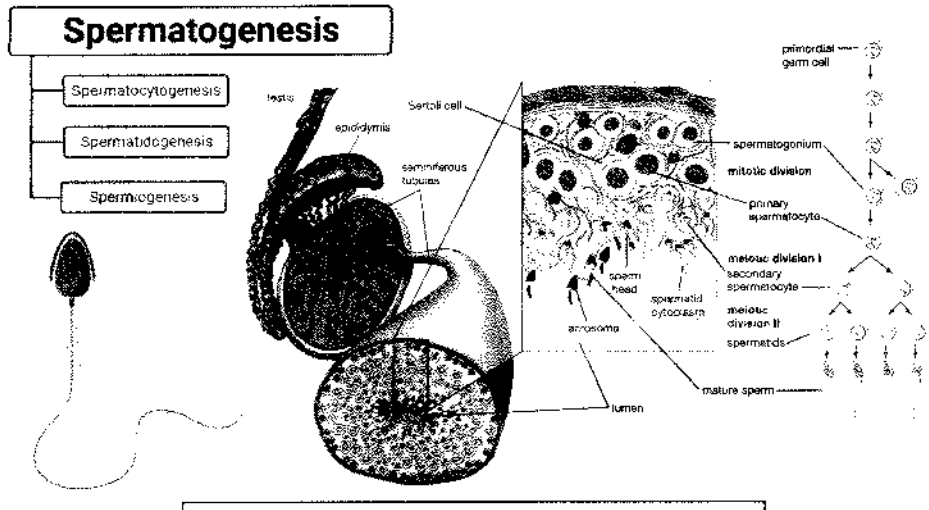


Fig 2.10: The process of spermatocytogenesis

THE PROCESS OF SPERMATOGENESIS:

Spermatogenesis is processed as follows;

- ✓ Primordial germ cells are dormant at fetal and postnatal period.
- ✓ Increase in the number of spermatogonia takes place after the attainment of puberty.
- ✓ Spermatogonia undergoes mitosis and transformed itself into primary spermatocyte, at this stage of spermatogenesis amount of DNA becomes double.
- ✓ Each primary spermatocyte then processed through the meiosis I and ultimately changes its shape and size to become the secondary spermatocyte. However amount of DNA remain same as that of primary spermatocyte.
- ✓ Subsequently the second meiotic division takes place and secondary spermatocyte changes into the spermatids which are approximately half of the size as that of secondary spermatocyte.
- ✓ Afterwards, the process of spermiogenesis takes place and spermatids are transformed into four mature sperms. Then sperms store into the lumen of seminiferous tubules.
- ✓ Later on, sperms are transported from seminiferous tubules to the epididymis where it gets fully mature and this takes no energy.
- ✓ Epididymis is an elongated and highly convoluted tube which has continuation with ductus deferens and it transports the sperm to urethra.
- ✓ There is also a presence of another cells known as sertoli

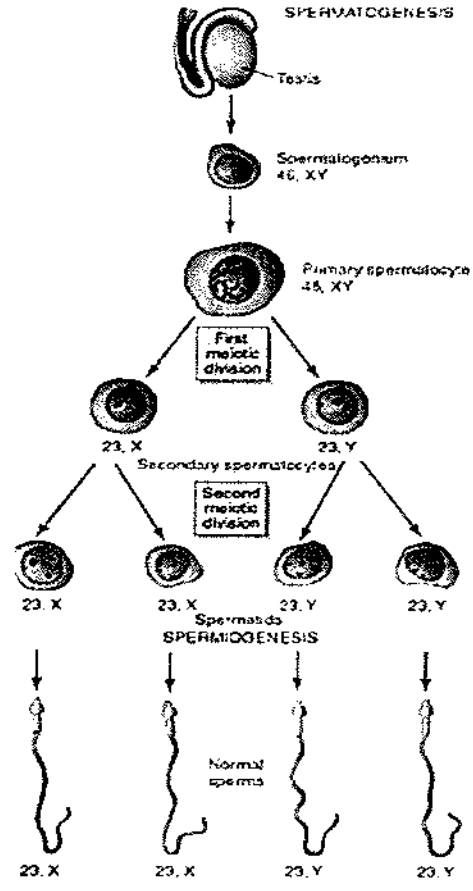


Fig 2.11: The process of spermatogenesis

cells which lines the seminiferous tubules and it does the function of flanking and nutrition of sperms.

- ✓ The entire process of spermatogenesis takes place approximately two months to complete.

SPERMIOGENESIS:

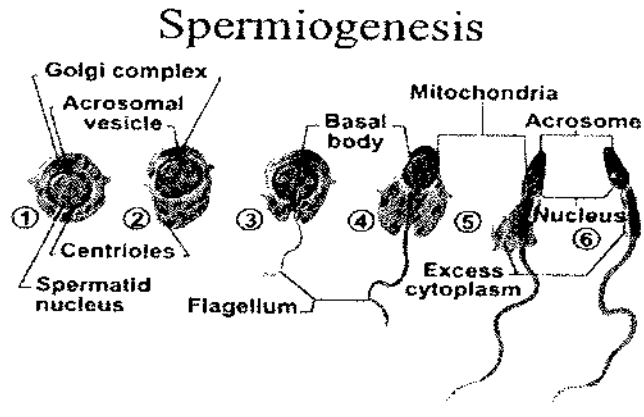
The process of transformation of spermatids into mature sperms is known as spermiogenesis. It involves the following changes;

- ✓ Alteration of the rounded sperms into elongated sperms.
- ✓ Loss of cytoplasm takes place during this process.
- ✓ Formation of the acrosome from the Golgi region takes place that in turn assist the sperm in penetrating the corona radiata and zona pellucida surrounding the secondary oocyte.
- ✓ Development of tail takes place during this process.

SPERM:

It is actively motile male gametocyte consists of the head and tail region. Head of sperm form the bulk of the sperm, neck is the region between head and tail while tail region consists of three compartments; principle piece, middle piece and the end piece. The middle piece is of paramount importance because it contains mitochondria. There are certain factors which play fundamental role in the process of spermatogenesis;

- ✓ BCl-2 family assists in sperm maturation.



- Changes that transform spermatids into spermatozoa

Fig 2.12 The process spermiogenesis

- ✓ HOX genes influence microtubules dynamics and shaping of the head of sperm.

OOGENESIS:

It is an episodic process by which primordial germ cells that is oogonia are transformed into mature oocyte. It involves the following changes;

- ✓ All the oogonia get converted into oocytes before birth.
- ✓ Oogenesis continues until the menopause commences and it is completely arrested at this stage.

PROCESS OF OOGENESIS:

The process of oogenesis has been classified into two phases;

1. Prenatal progression
2. Postnatal progression.

PRENATAL PROGRESSION OF OOGENESIS:

- ✓ During the process of movement from the yolk sac to the posterior body, the germ cells continuously proliferate by mitosis.
- ✓ In the developmental period oogonia increase in number by repeated mitotic divisions.
- ✓ At the eighth week of development they still remain oogonia having 0.02mm diameter and they are 1400 in number during this period.
- ✓ By the third month of gestation the oogonia arranged into clusters and surrounded by the layer of epithelial cells known as follicular cells. The majority of cells still continue to divide by mitosis.

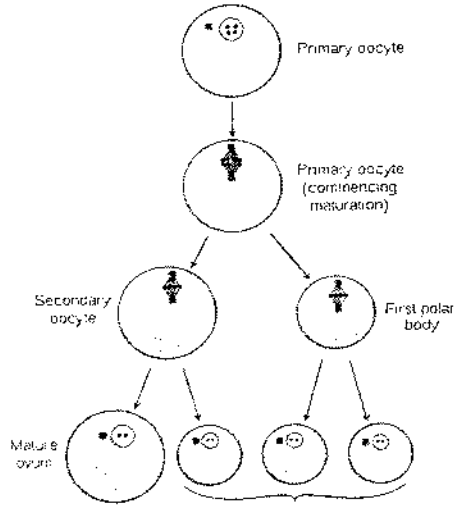


Fig 2.13: The process of oogenesis

- ✓ During 5th or 6th month of fetal life, the primary oocyte become encapsulated by single layer of epithelial cells of primordial follicle. Due to this encapsulation first meiotic division is arrested.
- ✓ Some changes occur in primary oocyte after reaching the pubertal age, these are;

1. Enlargement in the structure of oocyte.
2. Change in the shape of follicular epithelium. Firstly, it changes to cuboidal then transformed into the columnar shape.
3. Formation of primary follicle

4. The primary oocyte soon cloaked with the amorphous acellular layer of glycoprotein material known as zona pellucida.
5. Primary oocyte commences its first meiotic division during fetal life however it does not terminate until adolescence because follicular cells secrete an inhibitor known as oocyte maturation inhibitor which keeps the meiotic division checked.

POSTNATAL PROGRESSION OF OOGENESIS:

- ✓ After attaining the puberty, ovulation occurs every month except the contraceptive ladies.
- ✓ Primary oocyte remains dormant after birth until puberty.
- ✓ As the follicle matures, primary oocyte increases in size and forms the secondary oocyte and a polar body, this happens due to unequal cytodifferentiation.
- ✓ Afterwards, if sperm is present then karyokinesis takes place otherwise it is arrested at metaphase.

EMBRYOLOGICAL TID BITS!

- ➢ Primary oocyte arrests at dictyotene stage while secondary oocyte arrests at metaphase stage.
- ➢ There are 2 million primary oocyte which become 40,000 at adolescence. From these 400 becomes the secondary oocyte.

DISTINGUISH BETWEEN SPERMATOCYTE AND OOCYTE:

SPERMATOCYTE	OOCYTE
1. It is motile cell	It is non motile cell.
2. It is not surrounded by any layer	It is surrounded by two layers namely corona radiata and zona pellucida.
3. It is not so massive compare with oocyte.	Oocyte is a massive cell.
4. Spermatocyte contains two types of chromosomes i.e. X and Y.	It has a single type of chromosome i.e. X

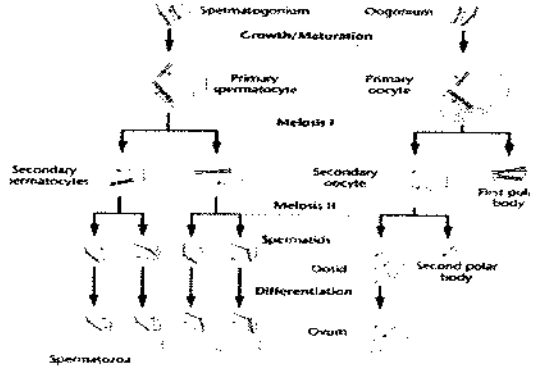


Fig 2.14. Comparison between

FEMALE REPRODUCTIVE CYCLES:

- At the age of puberty (10 to 13 years) females undergo reproductive cycles which involve the activities of the following structures;
  a. Hypothalamus
  b. Pituitary gland.
  c. Ovaries
  d. Uterus
  e. Uterine tubes
  f. Vagina
  g. Mammary glands.
- Neurosecretory cells of the hypothalamus release a factor known as gonadotropin releasing hormone which is carried out through capillaries to the hypophaesal portal system and ultimately it induces the effects on glands.
- Follicle stimulating hormone is a factor which stimulates the development of ovarian follicle and production of the estrogen by the follicular cells.
- Luteinizing hormone is a factor that triggers the process of ovulation and stimulate the follicular cells as well as corpus luteum for the production of progesterone by the induction of embryonic growth and embedment into the endometrium.

OVARIAN CYCLE:

The ovarian cycle refers to the series of changes in the ovary during which the follicle matures, the ovum is shed, and the corpus luteum develops.

Ovarian cycle is under the control of follicle stimulating hormone and luteinizing hormone which are releasing under the influence of gonadotropin releasing hormone. Following changes occur by the action of these hormones and these are regarded as the stages of ovarian cycle;

1. Follicle development
2. Ovulation
3. Corpus luteum formation.

1. FOLLICLE DEVELOPMENT:

Follicle development is associated with the following change

a. Formation of theca folliculi
b. Proliferation of follicular cells
c. Formation of zona pellucida
d. Growth and differentiation of primary oocyte.

a. FORMATION OF THECA FOLLICULI:

As the formation of primary follicle takes place its adjacent cells differentiate to form a capsular layer known as theca folliculi, it soon differentiates to form two layers. The inner one which is glandular as well as vascular called as theca interna while outer one is capsular known as theca externa. These cells have ability to form the factor for angiogenesis which in turn helps in the formation of blood vessels. These vessels continuously assist the follicular cells by providing nutrition.

EMBRYOLOGICAL TID BITS!
➢ Follicle beside the production of estrogen and thecal fluid also produces androgens which later on converts into the estrogen.

b. PROLIFERATION OF FOLLICULAR CELLS:

As the follicular cells proliferate they form a layer of stratified cells around the ovary then the ovarian follicle is shaped into an oval oocyte which is eccentric in position. Later on these proliferated cells approximate towards each other and form a fluid filled cavity known as follicular antrum. At this stage ovarian follicle is named as vesicular or secondary follicle.

c. FORMATION OF ZONA PELLUCIDA:

By the pushing of primary oocyte into one side of antrum the other follicles which lying adjacent to it shackles the oocyte to form a glycoprotein layer that is known as zona pellucida?

d. GROWTH AND DIFFERENTIATION OF PRIMARY FOLLICLE:

As there are many follicles present in the ovary, under the influence of hormones only one grows in size to form the graffian follicle that will later on differentiate into the primary and secondary oocyte. The maturity of the follicle is marked by the formation of swelling at its apex which is known as stigma.

e. OVULATION:

Under the stimulation of FSH and LH growth spurt occurs with swelling at its tip and the cumulus oophorous becomes detached from the interior distended follicle. Ovulation actually commences by the billow of luteinizing hormone that causes the rupture of ovarian follicle and releases out the secondary oocyte with follicular fluid. There are various reasons behind the expulsion of secondary oocyte, these are;

a. Due to intrafollicular pressure
b. Contraction of the smooth muscles of theca externa which in turn is stimulated by the production of prostaglandins.
c. Due to Mitogen Activated Protein 1 and 3 signalling pathway.
d. Rupture of the follicle may occur due to plasma and matrix matelo-proteins because it has controlling capacity to some extent.

Expelled oocyte is surrounded by two layers. A glycoprotein layer which is known as zona pellucida. This layer is again differentiated into three layers named as; (ZPA, ZPB, ZPC). These layers have multiple pores that give room for the attachment of sperm in fertilization. The other layer is cumulus oocyte complex which is formed after the approximation of follicular cell layer and corona radiata.

2. CORPUS LUTEUM FORMATION:

After the ovulation, the walls of the ruptured follicle and theca folliculi coalesce to give rise a glandular body known as corpus luteum. It is capable of secreting the progesterone hormone that influences the formation of endometrial walls which later on assist in the implantation of blastocyst if fertilization occurs.

Conceivably, there are two fates of corpus luteum;

a. Corpus luteum of pregnancy
b. Corpus luteum of menstruation.

a. CORPUS LUTEUM OF PREGNANCY:

If the oocyte is fertilized then various changes occurs in the corpus luteum as;

a. Increase in the size of corpus luteum
b. Degeneration of corpus luteum is prevented through chorionic gonadotropin hormone.
c. It remains functional until the formation of placenta.

d. CORPUS LUTEUM OF MENSTRUATION:

If the oocyte is not fertilized then there is also some sort of changes occur in the corpus luteum;

a. Firstly, Diminution in the size of corpus luteum.
b. Gradually the degeneration of the corpus luteum takes place.
c. Transformation of corpus luteum into white scar which is called as corpus albicans.

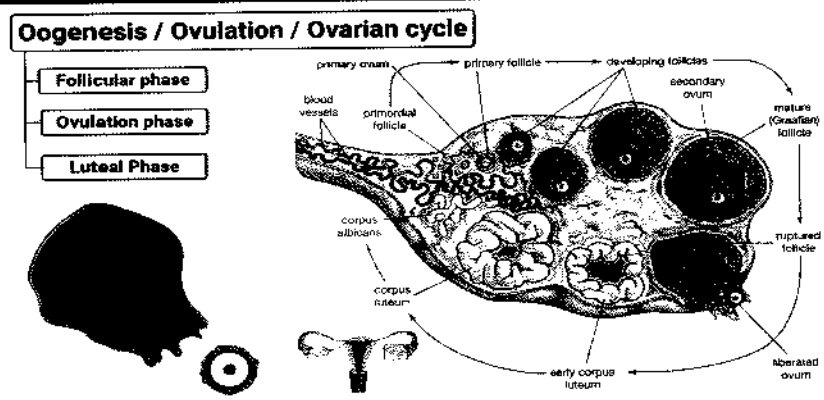


Fig 2.15: Different stages of ovarian cycle

TERMINATION OF OVARIAN CYCLE:

Ovarian cycle is terminated due to the below mentioned reasons;

1. Due to menopause which occurs around 48 to 55 years of age.
2. Ovary failure
3. Due to endocrine contravention
4. Due to somatic structures.
5. Due to psychological alterations.

Termination of ovarian cycle due to endocrine contravention, somatic structures and psychological alterations is known as clinometric termination.

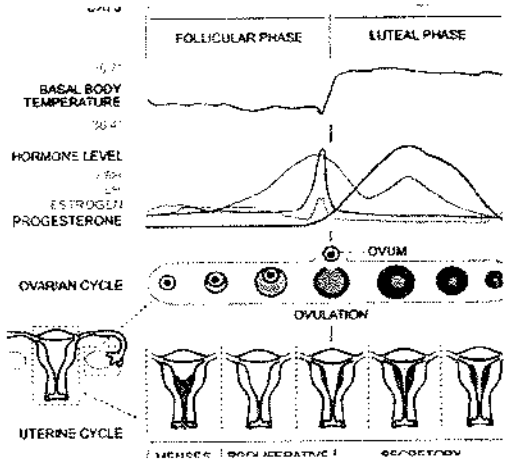


Fig 2.16: Graphical manifestation of various levels such as hormonal & temperature in ovarian & uterine cycles

EMBRYOLOGICAL TID BITS!

Primary indicator for the ovulation to occur is to increase in the basal body temperature.

MENSTRUAL CYCLE:

It is a process which occurs when ovulation takes place and oocyte reaches into the uterine tubes.

- ✓ This process remains under the influence of hormones released from the ovarian follicle and corpus luteum which in turn produces cyclic changes in the endometrial wall.
- ✓ Menstruation is the image of ovarian cycle because it responds in a constant manner to fluctuate the hormone concentration.
- ✓ Average menstrual cycle takes 28 days to complete.

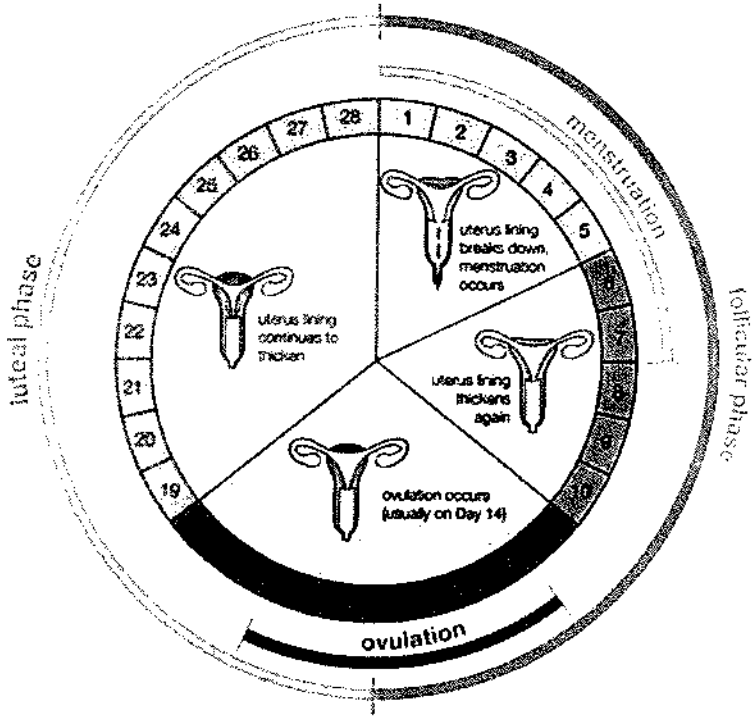


Fig 2.17: Different stages of menstrual cycle

PHASES OF MENSTRUAL CYCLE:

Menstrual cycle comprises of the following four phases;

1. MENSTRUATION PHASE:

   It is the phase in which functional layer of endometrium which consists of spongy and compact layers slough down. This take 4 to 5 days to complete. After this phase of menstrual cycle endometrium is eroded and becomes thin.

2. PROLIFERATIVE PHASE:

It coincides with the follicular phase of ovarian cycle. This take approximately 9 days to complete. During this phase thickness of the endometrium increases two to three folds and number of glands also increases. Spiral arteries become elongated during this phase.

3. LUTEAL PHASE:

This phase coincides with the corpus luteum phase of ovarian cycle. It is the longest phase as it take thirteen days to complete. During this phase progesterone production occurs, glands become saccular and wide and the endometrium becomes thick. Moreover, spiral arteries are clothed into the compact layer and venous network becomes more accomplished. More importantly the formation of arteriovenous anastomosis takes place. If fertilization does not occur corpus luteum soon degenerates to lower the progesterone secretion and menstruation occurs.

4. ISCHEMIA:

It occurs when oocyte does not fertilized. The spiral arteries constricted and hormones does not reach which causes the paleness of endometrial walls. At the end of ischemic period spiral arteries constricted for a long period which causes venous stasis and ischemic necrosis.

However if fertilization occurs cleavage of the zygote and blastocyst implantation occurs.

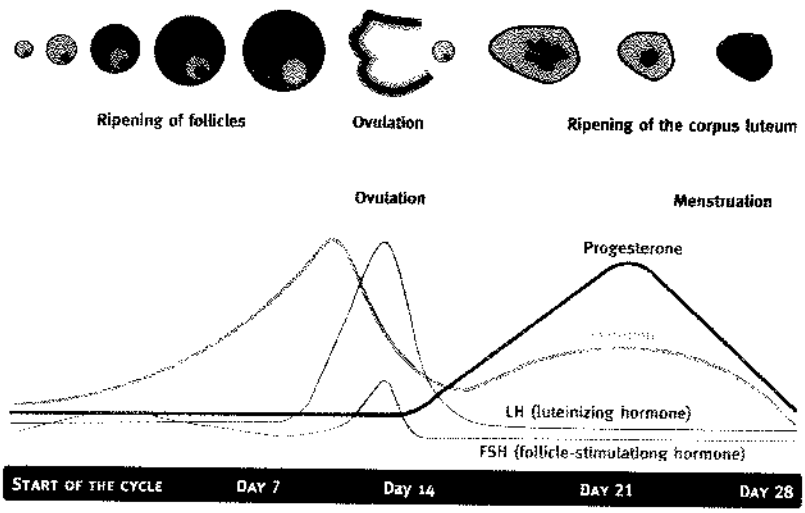


Fig 2.18: graphical representation of role of hormones in ovarian cycle.

TRANSPORT OF GAMETES:

There are two types of gamete transport;

1. Oocyte transport
2. Sperm transport.

1. Oocyte transport:

Expulsion of oocyte takes place at ovulation; by sweeping movement of the fimbriae and the fluid contents produce by the cilia and mucosal cells which cause the secondary oocyte to enter into infundibulum. Afterwards, peristaltic movements occur which moves the secondary oocyte into the site of fertilization known as ampulla.

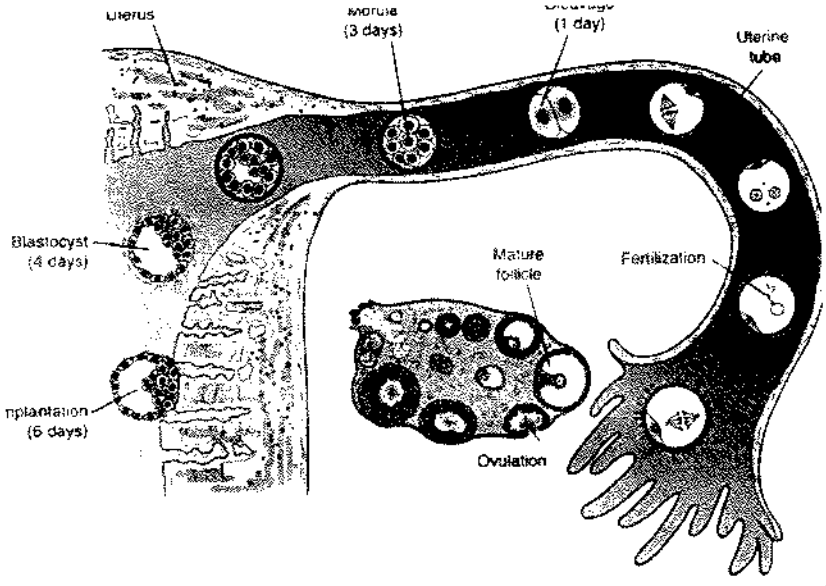


Fig 2.19 the process of oocyte transport and formation of different types of cells i.e zygote, morula and blastocyst.

2. SPERM TRANSPORT:

It takes place by emission and ejaculation. Regarding emission, it is a sympathetic response that carries semen from the prostate part of urethra to ductus deferens through peristalsis. While the ejaculation is the expulsion of semen outside the urethra that takes place by the action of three stimulus.

a. Closure of vesicular sphincter
b. Contraction of urethral muscles
c. Contraction of bulbosponginous muscle.

Rapid transference of sperm occurs across the epididymis to urethra by peristaltic movement from ductus deferens. During this passage of sperm transport three glandular bodies add its secretion to sperm and make it healthier and more motile. These are named as;

a. Seminal vesicle secretes fructose
b. Prostate gland secretes vesiculase enzyme.
c. Bulbourethral gland that adds slimy secretion.

Prostaglandin is a glycoprotein that assists in the sperm transport.

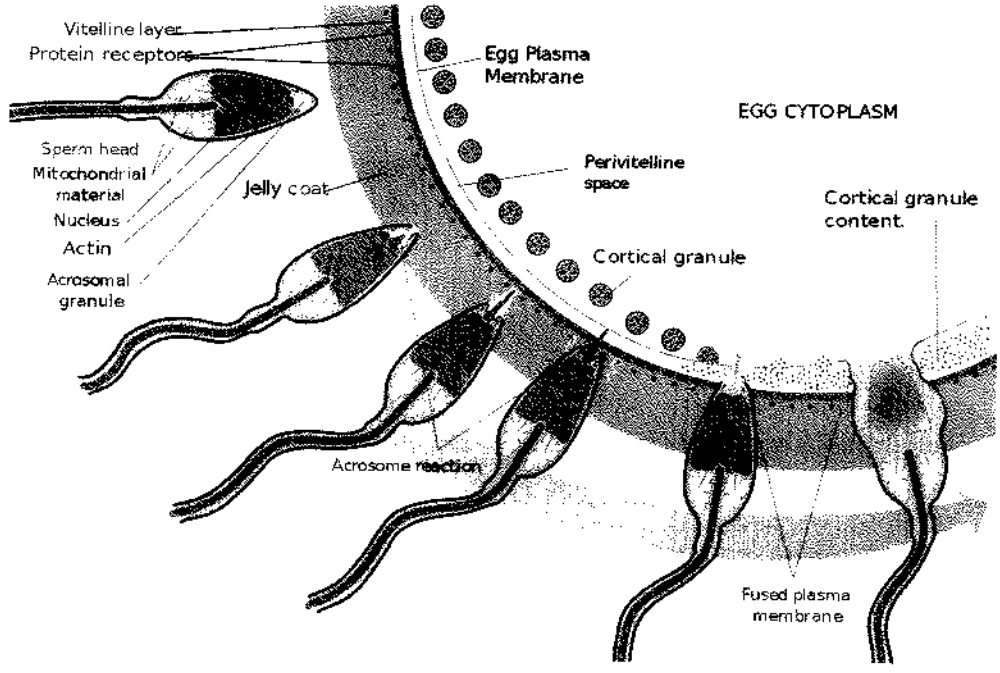


Fig 2.20: Different stages of sperm transport

EMBRYOLOGICAL TID BITS!
a. Count of sperm : 200 to 600 million b. Volume of ejaculation: 2 to 6 ml c. Speed of sperm: 2 to 3 mm/min.

VARIATION IN THE SPEED OF SPERM:

Variation in the speed of sperm occurs due to the changes in the PH of ejaculate. In acidic environment as that of vagina enzyme vesiculase slows down the speed of sperm. However in the basic environment of uterus the speed of sperm is faster.

MATURATION OF SPERM:

Freshly ejaculated sperms are unable to fertilize the oocyte because there is some conditioning process which is required in order to the maturity of sperm.

1. Capacitation
2. Induction of the zona pellucida reactions.

1. CAPACITATION:

Removal of glycoprotein coat and seminal vesicle proteins to induce greater activity in the sperms is called as capacitation.

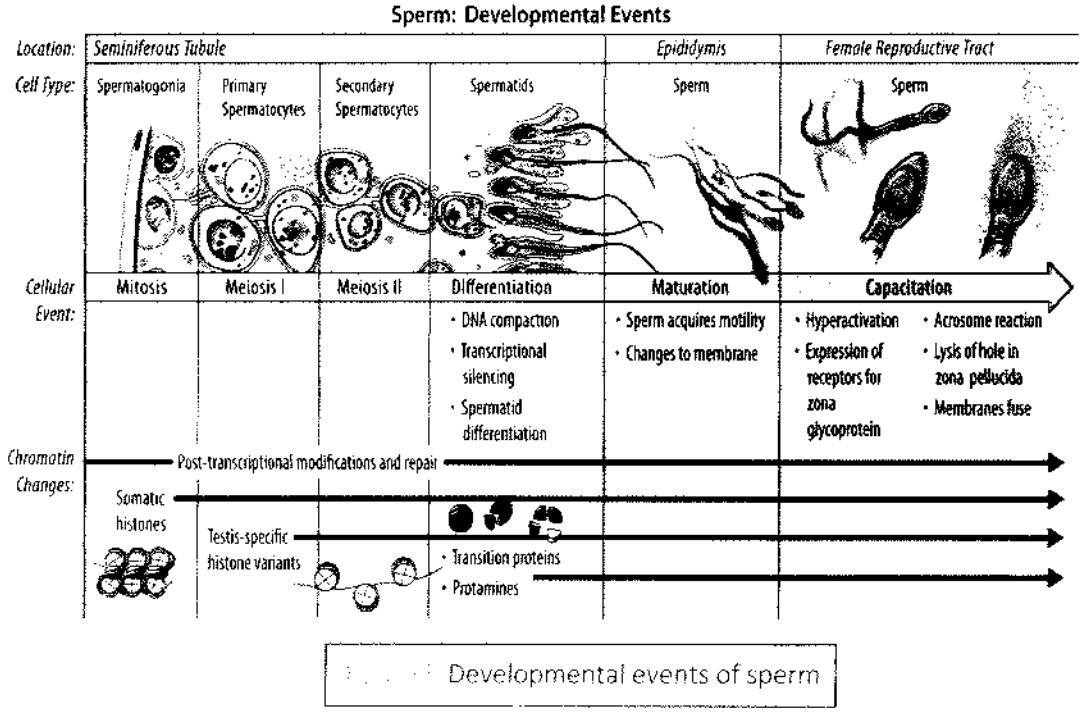
It is an activation process that occurs in the uterine tubes and it lasts for 7 hours. This process consists of enzymatic reactions that consequently remove the glycoprotein coat and certain vesicle proteins present over the acrosome. However there is no morphological change seen during capacitation.

2. ZONA PELLUCIDA REACTIONS:

It is the binding of sperm with ZP^3 proteins of zona pellucida which in turn induces perforation into the acrosomal membrane and breaks the point of attachment between plasma membrane and acrosomal membrane, this is known as zona pellucida reactions.

These reactions occur after the capacitation and it is induced by the hyaluronidase and acrosin.

EMBRYOLOGICAL TID BITS!
Regulation of capacitation and zona pellucida reactions take place through tyrosine kinase.



SURVIVAL OF GAMETES:

- ✓ Human oocyte can survive only for 12 hours after ovulation.
- ✓ Human sperms probably cannot survive more than 48 hours after ejaculation in the female genital tract. However, after ejaculation sperms are stored into the cervical crypts that surges the rate of fertilization.

FERTILIZATION:

Fertilization is a complex series of coordinated molecular reactions that begins with the contact between a sperm and oocyte and ends with the intermingling of maternal and paternal chromosomes at metaphase of first meiotic division which results into the formation of zygote, this is known as fertilization.

The usual site of fertilization is ampulla however it may occur at any place except uterus. If fertilization does not occur then oocyte sweeps down and degenerates.

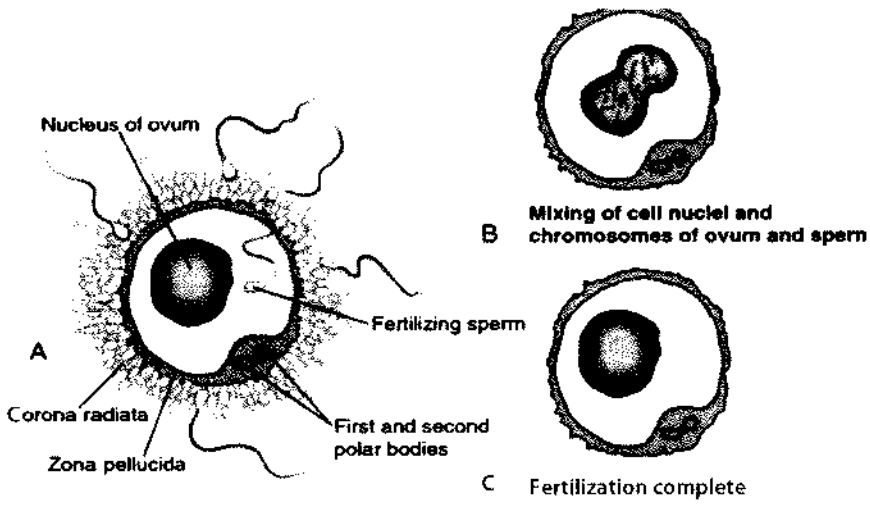


Fig 2.22: The process of fertilization

PHASES OF FERTILIZATION:

Fertilization is the sequence of reactions which is tightly coordinated.

1. AVENUE OF SPERM THROUGH CORONA RADIATA:
   The first stage is the penetration of corona radiata, by releasing hyaluronidase from the acrosome to digest cumulus cells surrounding the oocyte and exposing acrosin attached to the inner membrane of the sperm.

2. PENETRATION OF ZONA PELLUCIDA:
   In this phase sperm enter into the oocyte by the action of esterase, acrosin and neuroamidase enzymes but mostly by acrosin which is a proteolytic enzyme.

3. INDUCTION OF ZONA PELLUCIDA REACTIONS:
   After the penetration of sperm into oocyte zona reaction commences which first alters the properties of zona pellucida and subsequently zona membrane becomes impermeable to the sperms. This is all induced by the lysosomal enzymes released by the cortical granules into the previtelline membrane.

4. FUSION OF THE CELL MEMBRANES OF BOTH GAMETES.
   The plasma membranes of the both oocyte and sperm fuse together and break down into the area of fusion while head and tail region of sperm penetrates into the oocyte while cytoplasm remains in the peripheral region.

5. FORMATION OF THE FEMALE PRONUCLEUS:
   As the sperm penetrates the oocyte, it activates the oocyte to complete the second meiotic division by the production of the second polar body and forms the female pronucleus.

6. FORMATION OF THE MALE PRONUCLEUS:
   Within the cytoplasm of oocyte sperm becomes mature and form the male pronucleus.

7. FORMATION OF THE ZYGOTE:
   Morphologically both pronuclei are indistinguishable. First the male pronucleus replicate its DNA which also contains the two haploid female pronuclei known as ootid. By the fusion of the pronuclei a diploid cell is formed which is known as zygote. Afterwards, chromosomes in the zygote arrange into a cleavage spindle and prepares the zygote for cleavage action. The zygote is actually a foundation of two types of cells one from the maternal side and other from the paternal side which establishes the bipotential variation.

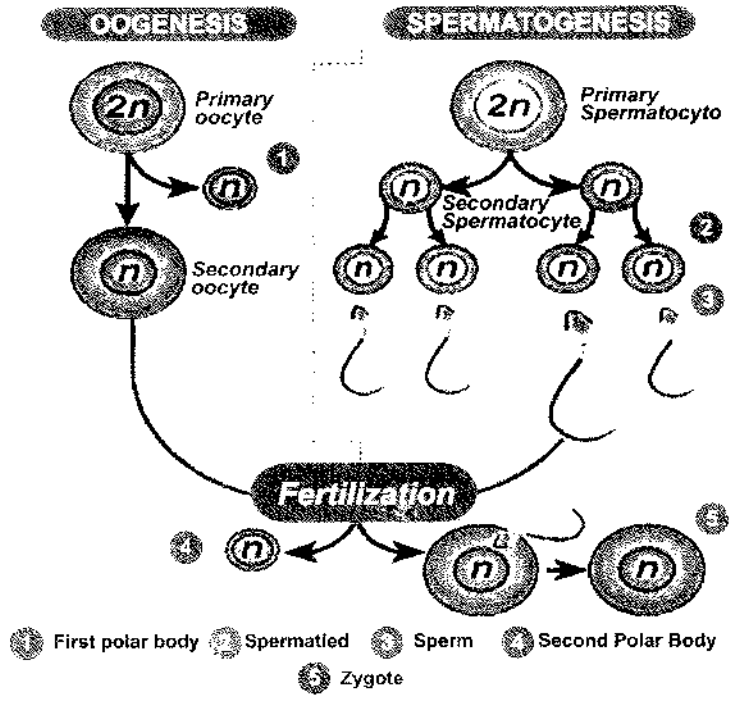


Fig 2.23: Complete view of Fertilization

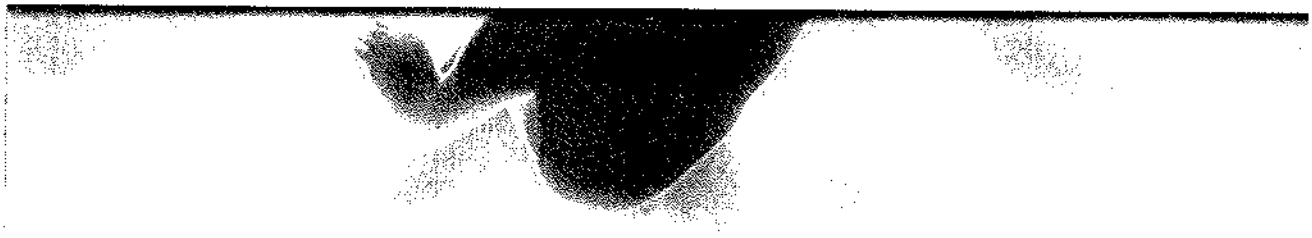
EMBRYOLOGICAL TID BITS!
a. Genetic variability occurs due to; crossing over, random assortment and fertilization. b. Zygote is a totipotent cell therefore it is also known as unicellular embryo. c. Genetic research has find out that X chromosome contains 2.8% more DNA than Y chromosome.

SIGNIFICANCE OF FERTILIZATION:

- ✓ It stimulates the penetrated oocyte to complete the second meiotic division.
- ✓ Restoration of 2n chromosome in zygote.
- ✓ By crossing over variation takes place in individuals.
- ✓ It helps in the determination of sex of the embryo.
- ✓ It induces metabolic activation in the ootid.
- ✓ Due to fertilization zygote is formed which later on undergoes the process of cleavage.

KEY NOTES!
a. This chapter deals with the fundamental concepts of embryology such as the reproduction, male and female reproductive organs and the process of fertilization. b. Reproduction is a process in which parents reproduce the offspring of their own kind. c. Cell cycle is the sequence of changes which divides the cell. There are two types of cell division one is mitosis which occurs in somatic cells while other one is meiosis which occurs in sex cells. d. Fertilization is a process in which male and female gametes fuse to form a diploid cell known as zygote. e. Zygote is regarded as the unicellular embryo.

SECTION - B
THE GENERAL EMBRYOLOGY



3 THE FIRST WEEK OF DEVELOPMENT

LEARNING OBJECTIVES

- GENERAL INTRODUCTION OF THE FIRST WEEK OF DEVELOPMENT
- CLEAVAGE OF ZYGOTE
- BLASTOCYST FORMATION
- BEGINNING OF BLASTOCYST IMPLANTATION
- ABNORMALITIES ASSOCIATED WITH FIRST WEEK OF DEVELOPMENT.
- KEY NOTES

THE FIRST WEEK OF DEVELOPMENT

This chapter deals with the cleavage of zygote, blastocyst formation, beginning of blastocyst implantation and the abnormalities associated with the first week of development.

CLEAVAGE:

It is a process by which unicellular fertilized ovum is transformed into multicellular mass.

GENERAL PRINCIPLES OF CLEAVAGE:

- The speed of cleavage is inversely proportional to the amount of yolk.
- Mitotic spindle occupies the centre of protoplasm.
- The axis of spindle occupies the longest axis of the protoplasmic mass.
- Each new plane intersects the preceding plane at right angle that is the act of maintaining spheroid shape of blastomers.

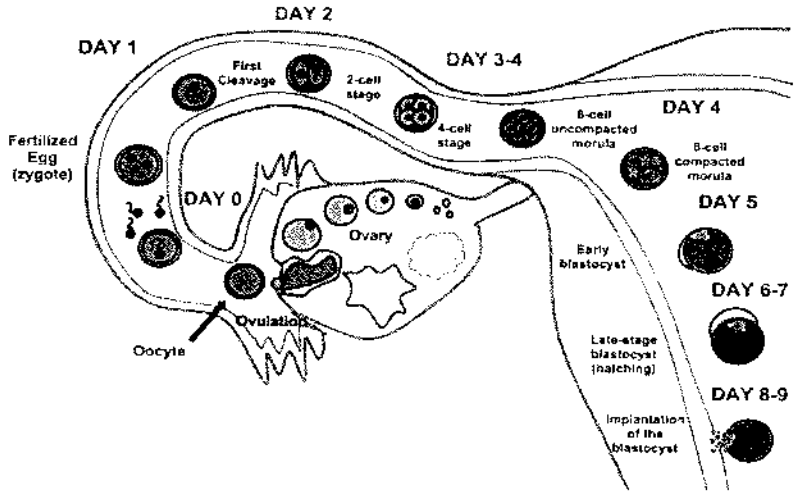


Fig 3.1 Different events of 1st week of development

PROCEEDINGS FROM DAY 1 TO DAY 4:

PROCESS OF CLEAVAGE AND BLASTOCYST FORMATION:

- After the occurrence of fertilization zygote undergoes a series of mitotic cell divisions that consequently give rise to blastocyst.
- Thirty hours after the fertilization, the zygote divides by mitosis into small structures known as blastomers.
- After the first three days of fertilization 12 to 16 solid ball like structures are formed due to continuous division, these solid ball like structures are now called as morula. It remains confine to the zona pellucida. At the 4th day of embryonic development morula enters into the uterine cavity where small cavities appear into it and filled by the uterine fluid. As the fluid increases all the spaces coalesce to form the single cavity and splits into the two group of cells, the one which is laying in the peripheral region is called as outer cell mass or trophoblast while other group which is lying inside is known as inner cell mass or embryoblast. However the central cavity is known as blastocyst cavity or blastocoele while the whole structure is known as blastocyst.

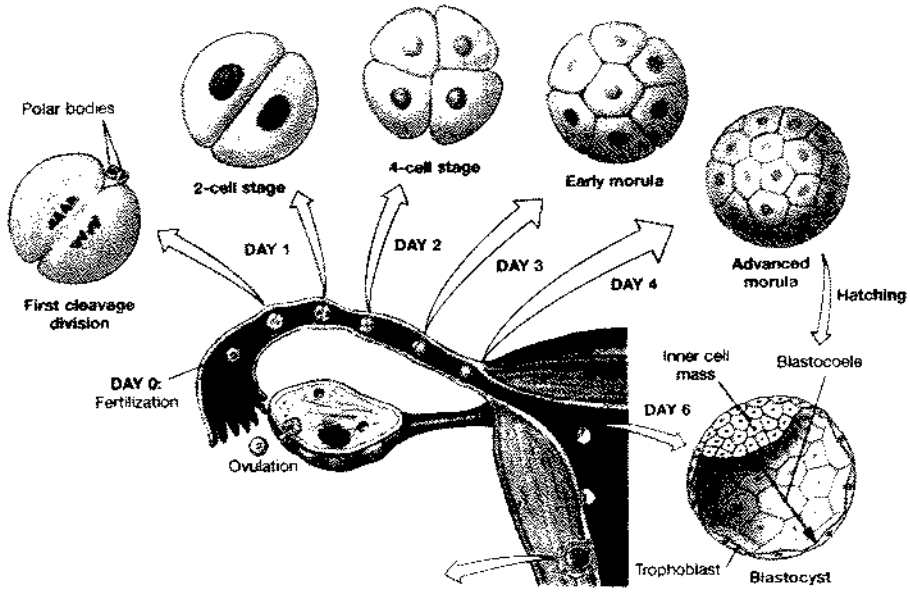


Fig 3.7: The process of cleavage and blastocyst formation

PROCEEDING OF THE 5TH DAY OF DEVELOPMENT:

Mostly during this day the degeneration of zona pellucida occurs and due to this the blastocyst cavity enlarges.

PROCEEDINGS OF THE 6TH DAY OF DEVELOPMENT:

BEGINNING OF IMPLANTATION:

- As blastocyst reaches to the uterine cavity in the secretory phase of uterine cycle, uterine secretions accumulates for two days, in the meantime zona pellucida degenerates and disappears. Later on blastocyst immediately attaches to the endometrial wall from the side of trophoblastic cells.

THE PROCESS OF IMPLANTATION:

As soon as blastocyst adheres with the endometrial wall the trophoblastic cells start proliferation rapidly and subsequently it differentiates into two layers;

1. Outer layer that is syncytiotrophoblast
2. Inner layer that is cytotrophoblast

From the syncytiotrophoblast finger like projections extended and invade the endometrial stroma. By the end of 1st week of development the blastocyst is implanted superficially in the endometrial wall.

PROCEEDING OF DAY 7:

On the day 7th of human development a layer of cuboidal cells is formed on the ventral surface of inner mass cell which is known as hypoblast. It is the precursor of endoderm.

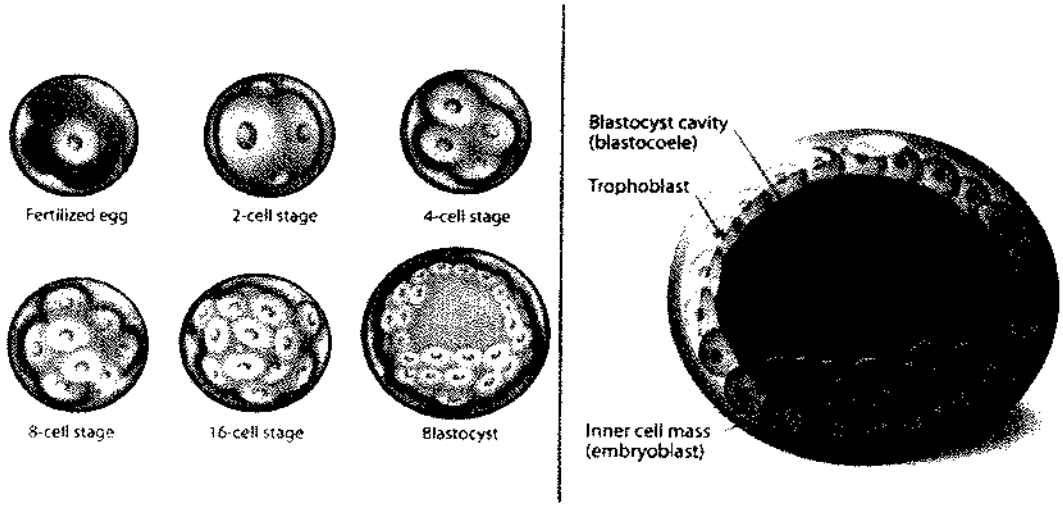


Fig 3.3: blastocyst having embryoblast, trophoblast and blastocoele.

ABNORMALITIES ASSOCIATED WITH FIRST WEEK OF DEVELOPMENT:

1. MOSAICISM:

It occurs when a person has 2 or more genetically different sets of cells in his or her body. Chromosomes are stick-shaped structures in the middle of each cell in the body. Each cell has 46 chromosomes grouped in 23 pairs. A person with mosaicism may have some cells in his or her body with 46 chromosomes.

2. INFERTILTY:

It is defined as not being able to get pregnant despite having frequent, unprotected sex for at least a year for most couples. Infertility may result from an issue with either of the partner, or a combination of factors that prevent pregnancy.

CAUSES OF INFERTILITY:

Infertility can affect one or both partners. In general:

- In about one-third of cases, there is an issue with the man like there is a lesser count of sperms, problems with the delivery of sperm, overexposure to certain environmental factors or damage to the organs related to cancers.
- In about one-third of cases, there is an issue with the woman. These issues include; ovulation disorders, uterine or cervical abnormalities, fallopian tube damage or blockage, endometriosis, primary ovarian insufficiency, pelvic adhesion and cancer.
- In the remaining cases, there are issues with both the man and the woman, or no cause can be found.

KEY NOTES!
a- This chapter includes the events of first week of development which are cleavage, blastocyst formation, implantation and hypoblast formation.
b- Division of cells into 12 to 16 ball like structures is known as morula.
c- Clinical abnormalities associated with this week are infertility and mosaicism.

4

THE SECOND WEEK OF DEVELOPMENT

LEARNING OBJECTIVES

- GENERAL INTRODUCTION OF THE SECOND WEEK OF DEVELOPMENT
- DEVELOPMENT DURING 8TH DAY OF GESTATION
- I. THE DEVELOPMENT DURING BILAMINAR DISC
- II. DIFFERENTIATION OF TROPHOBLAST
- III. FORMATION OF AMNIOTIC CAVITY
- DEVELOPMENT DURING 9TH DAY OF GESTATION
- IV. COMPLETION OF IMPLANTATION
- V. FORMATION OF EXOCOELOMIC CAVITY
- VI. LACUNAE FORMATION
- DEVELOPMENT DURING 9TH TO 12TH DAY OF GESTATION
- VII. DEVELOPMENT OF EXTRAEMBRYONIC MESODERM
- VIII. DEVELOPMENT OF CHORIONIC CAVITY
- IX. DEVELOPMENT OF SECONDARY YOLK SAC.
- DEVELOPMENT DURING 13TH TO 14TH DAY OF GESTATION
- X. DEVELOPMENT OF PRIMARY CHORIONIC VILLI
- XI. DEVELOPMENT OF PRECHORDAL PLATE
- HOW TO TAKE OUT PREGNANCY TEST FROM Hcg?
- ABNORMALITIES ASSOCIATED WITH SECOND WEEK OF DEVELOPMENT.
- KEY NOTES.

(THE WEEK OF TWO'S)

The Second week of gestation is regarded as the week of two's because it is the week when the embryoblast, extraembryonic mesoderm and trophoblast each separate into two distinct layers. Additionally, there is also the development of two cavities within the embryonic unit at this time.

After the occurrence of blastocyst implantation, embryoblast undergoes morphologic changes which morphs the embryoblast into bilaminar embryonic disc comprises of the epiblast and the hypoblast. These layers are precursor for presumptive structures of the embryo. In addition to this trophoblastic layer also divides into the cytotrophoblast and syncytiotrophoblast. However, regarding the extraembryonic structures, it develops the amniotic cavity, amnion, umbilical vesicle, chorionic sac and the connecting stalk during the second week of gestation.

This chapter is sequenced day wise in order to facilitate the readers for getting the clear concept of the individual events. Following are given some key features of this week.

- ✓ This week is regarded for the completion of the blastocyst implantation which later on develops the trophoblastic structures.
- ✓ During this week embryoblast is converted into the epiblast and hypoblast which is precursor for all tissues and organs of the embryonic body.
- ✓ In addition to the aforementioned development extraembryonic parts also develops such as amniotic cavity, yolk sac etc.

THE DEVELOPMENT DURING 8TH DAY OF GESTATION:

There are three distinct events which occur during the eighth day of gestation; the development of the bilaminar disc from the embryoblast, differentiation of trophoblast and the formation of the amniotic cavity.

- ✓ During the 8th day of gestation, the embryoblast differentiates to form the bilaminar embryonic disc remarked by the hypoblast and the epiblast. Hypoblast is the layer of cuboidal cells that lies adjacent to the blastocyst cavity however epiblast is the layer of columnar cells that lies adjacent to the amniotic cavity.
- ✓ Regarding trophoblastic cells, it first forms the embedding into endometrium then differentiate to form the mitotically active mononucleated layer of cells known as cytotrophoblast and mitotically inactive as well as multinucleated layer of cells known as syncytiotrophoblast.
- ✓ Regarding the formation of amniotic cavity, cavity which lies above the epiblastic cells enlarges to attain the shape of dome that is referred as amniotic cavity. Cells involved in forming its roof are amnioblasts.

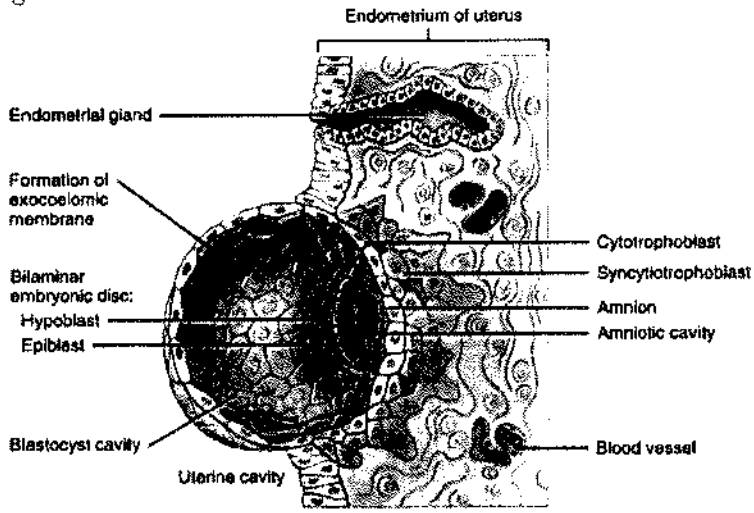


Fig 4.1: The process of implantation and differentiation of cells.

THE DEVELOPMENT DURING 9TH DAY OF GESTATION:

Following are given the events which occur during the 9th day of gestation.

- ✓ During the 9th day of gestation blastocyst acquires deeper embedding into the endometrium and its defect is closed by fibrin coagulum between 9th and 10th day.
- ✓ Regarding the formation of exocoelomic cavity; after the formation of amnion, cells from the cytotrophoblast morphed to form the exocoelomic membrane which is continuous with the hypoblast. It marks the formation of exocoelomic cavity.
- ✓ During the 9th day of gestation after the establishment of amniotic cavity and exocoelomic cavity the syncytiotrophoblast gradually change into the lacunar structure which is first filled with the maternal blood, secretions of uterine glands and ruptured endometrial vessels. Later on maternal blood receives human

chorionic hormone which induces the erosion of endometrial capillaries thus establishes the uteroplacental circulation.

THE DEVELOPMENT DURING 10TH TO 12TH DAYS OF GESTATION:

Below are given some key events which occur during 9th to 12th day of gestation.

- ✓ Regarding the development of extraembryonic mesoderm, the layer of loosely arranged connective tissue is formed by the endoderm of yolk sac. The extraembryonic mesoderm supports the epithelium of the amnion and yolk sac as well as the villi, which arise from the trophoblastic tissue. It is also involved in the development of the fetal blood. The extraembryonic mesoderm of the chorion, chorionic villi, and body stalk originates in the caudal margin of the primitive streak which develops in 9th to 12th day of gestation. As the extraembryonic mesoderm expands it forms spaces which later on fuses to form the extraembryonic coelom. This coelom splits the extraembryonic mesoderm into somatic and splanchnic layers.
- ✓ Regarding chorion and the chorionic cavity; chorion is constituted from the extraembryonic mesoderm and two layers of trophoblast and chorion forms the wall of chorionic cavity in which embryo along with its amnion and yolk sac is suspended by connecting stalk. Therefore the extraembryonic coelom is now known as chorionic cavity.
- ✓ Regarding the development of secondary yolk sac, it is developed after the pinching off and reduction in the size of primitive yolk sac which is also known as exocoelomic cavity. Yolk sac is involved in the transference of nutrients and oxygen to the developing embryo from maternal circulation.

THE DEVELOPMENT DURING 13TH AND 14TH DAY OF GESTATION:

Below is given some description about the 13th and 14th day of gestation;

- ✓ Regarding the formation of chorionic villi, the development of primary chorionic villi occurs during this day. It develops as the budding structures of the trophoblast from the chorion. It consists of the cytotrophoblast covered by the thick layer of syncytiotrophoblast. These villi serve as the precursor for the placental structure.

    - ✓ On the 13th day of gestation formation of the prechordal plate begins as the thickening of hypoblast cells in the cranial region.

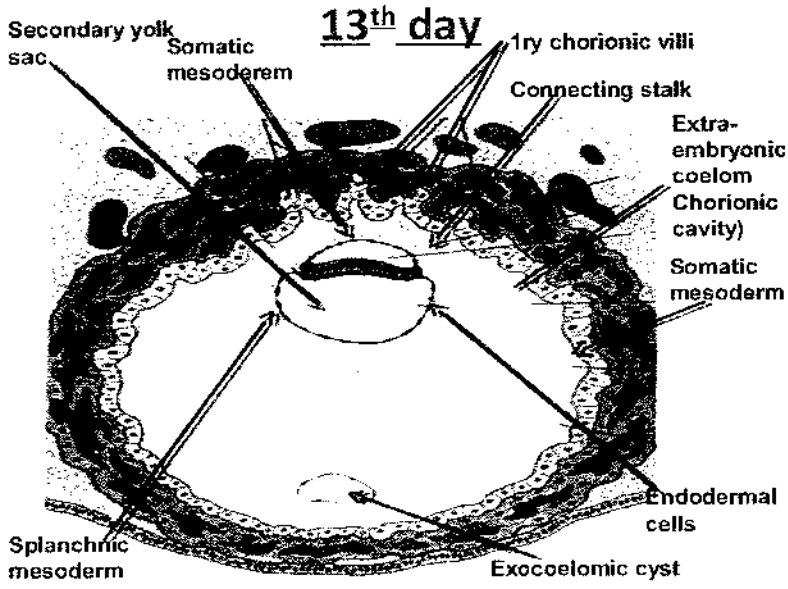


Fig 4.2: 13th day of gestation.

HOW TO TAKE OUT PREGNANCY TEST FROM HUMAN CHORIONIC GONADOTROPIN?

The occurrence of implantation can be misinterpreted as the menstrual flow may also commence. Subsequently most pregnant females may not realize that they are pregnant. However, the pregnancy kits which is employed in homes to determine whether pregnancy occurred or not rely on the presence of β-hCG to determine whether or not the individual is pregnant.

hCG (human chorionic gonadotropin) is a glycoprotein that is made up of alpha and beta subunits. As hCG accumulates in the maternal serum, it is metabolized into the constituent alpha and beta subunits, filtered by the kidneys and excreted in urine. Unlike the alpha subunit, which is homologous to the alpha units in other reproductive hormones (FSH, LH, etc.), the beta (β) moiety is unique to hCG and therefore can be used as the basis of the pregnancy test. Throughout the pregnancy, the β-hCG levels will continue to increase and then decrease as the pregnancy comes closer to term. This can be used to monitor the viability of the conceptus throughout the gestational period.

ABNORMALITIES ASSOCIATED WITH 2ND WEEK OF DEVELOPMENT:

1. ECTOPIC PREGNANCY:

It occurs when a fertilized egg implants itself outside of the womb often in one of the fallopian tubes. The fallopian tubes are the tubes connecting the ovaries to the womb. If an egg gets stuck in them, it won't develop into a baby and your health may be at risk if the pregnancy continues.

2. UTERINE FIBROIDS:

They are the benign tumor occurs mostly in the women of reproductive age. Clinically they develop asymptomatic dysmenorrhea and infertility. Furthermore, they can obstruct the proximal fallopian ostium, preventing the zygote enters in the uterus.

3. ENDOMETROSIS:

It is usually a painful disorder in which tissue similar to the tissue that normally lines the inside the uterus. The endometrium grows outside the uterus. Endometriosis most commonly involves ovaries, fallopian tubes and the tissue lining of the pelvis.

4. HYDROSPLANIX:

It is a condition that occurs when a Fallopian tube is blocked and fills with serous or clear fluid near the ovary that is distal to the uterus. The blocked tube may become substantially distended giving the tube a characteristic sausage-like or retort-like shape.

KEY NOTES!
a- This week is called as the week of twos because it is the week when the embryoblast, extraembryonic mesoderm and trophoblast each separate into two distinct layers. Additionally, there are two cavities that develop within the embryonic unit at this time as well
b- The hatched blastocyst moves along the endometrium towards a favorable point of implantation.
c- The endometrium is converted into an immunologically active site with optimum blood supply.
d- Differentiation of the trophoblast and the endometrial stroma facilitate invasion of the endometrium.
e- Regarding developmental anomalies of this chapter, it includes ectopic pregnancy, uterine fibroids, endometriosis and hydrosplanix.

5

THE THIRD WEEK OF DEVELOPMENT

LEARNING OBJECTIVES

- GENERAL INTRODUCTION OF THE THIRD WEEK OF DEVELOPMENT
- FORMATION OF THE PRIMITIVE STREAK
- FORMATION OF THE NOTOCHORD
- THE PROCESS OF GASTRULATION
- DERIVATIVE OF GERM LAYERS
- ALLANTOIS
- NEURULATION
- SOMITES
- FORMATION OF SECONDARY AND TERTIARY CHORIONIC VILLI
- ABNORMALITIES ASSOCIATED WITH THIRD WEEK OF DEVELOPMENT
- KEY NOTES

(THE WEEK OF GASTRULATION)

The third week of human development is remarked by the progression of trilaminar embryonic disc into three remarkable events;

1. Formation of the primitive streak
2. Formation of the notochord
3. The process of gastrulation.

1. FORMATION OF THE PRIMITIVE STREAK:

✓ The primitive streak is a straight band of thickened epiblast cells that appear first on the caudal end of embryonic disc and then grows cranially. At the cranial end of this

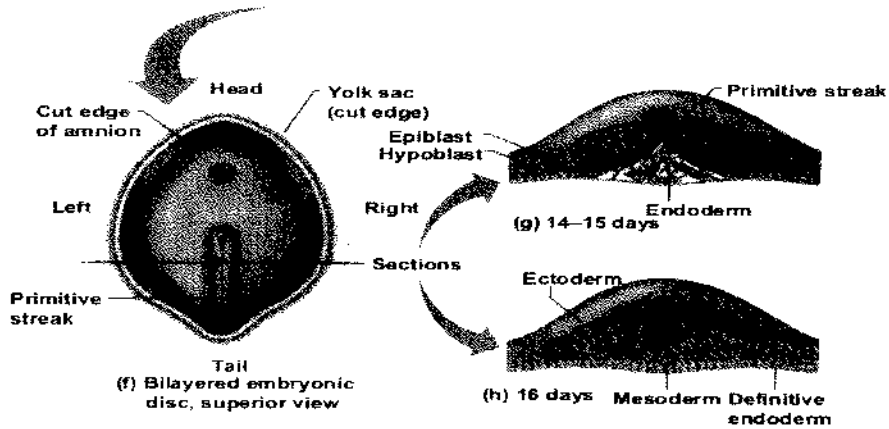


Fig 5.1: The formation of primitive streak

streak cells proliferate to form the primitive node. With the formation of primitive streak cranial and caudal end of the embryo are easily distinct.

- ✓ Concomitantly, a narrow groove and depression called as primitive pit and node develops in the primitive streak. Afterwards the formation of mesenchyme and an embryonic connective tissue take place from the cells which leave the deep surface. These mesenchymal cells later on differentiate into fibroblasts, chondroblasts, and osteoblasts.
- ✓ The fate of primitive streak is the mesoderm formation.

2. FORMATION OF THE NOTOCHORD:

- ✓ Before the formation of notochord there is the formation of notochordal process what happens that, mesenchymal cells migrate from the primitive node to form a cellular cord in the mid line orientation that is known as the notochordal process. Later on, the so called notochordal process grows cranially and it reaches to the prechordal plate that is the future site of the mouth. In this region the ectoderm is directly fused with the endoderm without any intervening mesoderm. This region is known as the oropharyngeal membrane however, later on it will break down to become the mouth. At the opposite end of the primitive streak the ectoderm is also fused directly to the endoderm; this is known as the cloacal membrane that is the future site for anus.
- ✓ The cellular cord which is formed by the modification of notochordal process is known as notochord. During the latter part of embryonic development it eventually develops into the nucleus pulposus of each intervertebral disc.

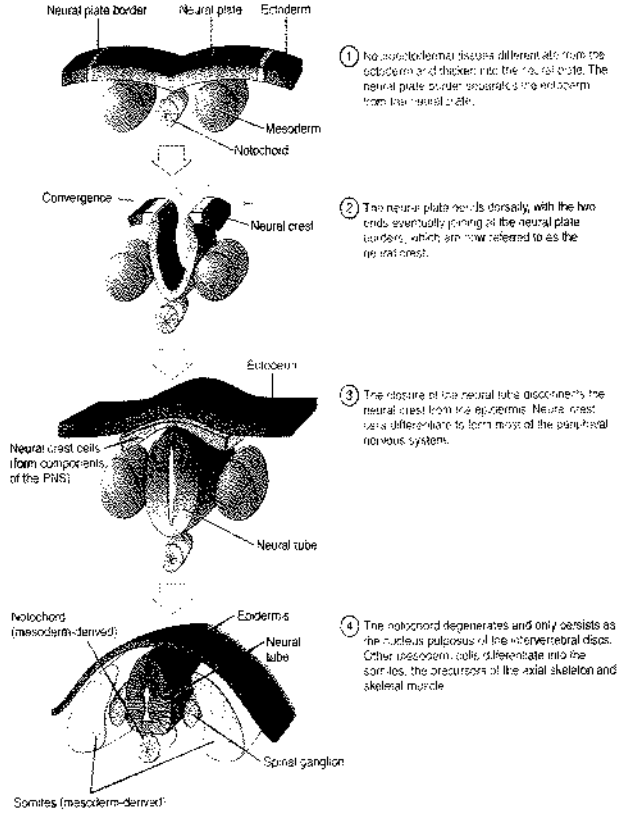


Fig 5.2: The formation of notochord

3. GASTRULATION:

- ✓ Gastrulation is a process by which three germ layers are formed and these layers are the precursors of all embryonic tissues and responsible for the axial orientation of the embryo. By the process of gastrulation bilaminar embryonic disc is converted into trilaminar embryonic disc. During this week embryo is known as gastrula. After the formation of three distinct layers each layer gives rise to specific tissues and organs.
- ✓ Embryonic ectoderm forms the epidermis, eyes, internal layers, neural crest cells, connective tissues of head, central nervous system and peripheral nervous system.
- ✓ Embryonic endoderm forms the internal linings of gastoenteric and respiratory system. It also forms the glandular organs.
- ✓ Embryonic mesoderm forms the blood and lining of the blood vessels, skeletal muscles, visceral smooth muscular coats, serosal linings of all body cavities, connective tissues and most of the cardiovascular system.

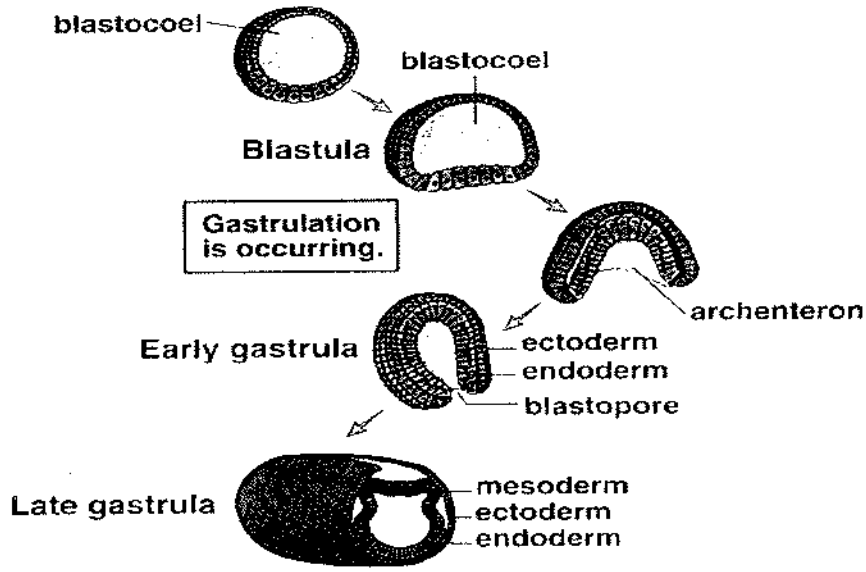


Fig 5.3: The process of gastrulation

DERIVATIVES OF GERM LAYERS:

ECTODERM	ENDODERM	MESODERM
1. SURFACE ECTODERM: a- Lens of eye b- Adenohypophysis (anterior pituitary gland) c- Utricle, semicircular ducts, and vestibular ganglion of CN VIII d- Epithelial lining of external auditory meatus e- Olfactory placodes, including CN I. f- Epithelial lining of: anterior two thirds of tongue, the hard palate, sides of the mouth, ameloblast and parotid glands and ducts. g- Mammary glands h- Epithelial lining of lower anal canal. Epithelial lining of distal penile urethra i- Epidermis, hair, nails, sweat and cutaneous sebaceous glands. 2. NEUROECTODERM: a-All neurons the lies CNS b-All glial cells of the CNS c-Retina d- Pineal gland. 3. NEURAL CREST CELLS: a- Postganglionic sympathetic neurons within the sympathetic chain ganglia and prevertebral ganglia.	a-Epithelial lining of the auditory tube and middle ear cavity b-Epithelial lining of the posterior third of the tongue, floor of the mouth, palatoglossal and palatopharyngeal folds, soft palate, crypts of the palatine tonsil, and sublingual and submandibular glands and ducts c-Principal and oxyphil cells of the parathyroid glands d-Epithelial reticular cells and thymic corpuscles e-Thyroid follicular cells f-Epithelial lining and glands of the trachea, bronchi, and lungs g-Epithelial lining of the gastrointestinal tract h-Hepatocytes and epithelial lining of the biliary tree i-Acinar cells, islet cells, and the epithelial lining of the pancreatic ducts	1. PARAXIAL MESODERM: a-Skeletal muscles of trunk b-Skeletal muscles of limbs c-Skeletal muscles of head and neck d-Extraocular muscles e-Intrinsic muscles of tongue f-Vertebrae and ribs g-Cranial bone h-Dermis 2. INTERMEDIATE ESODERM: a- Dura mater of kidneys b- Testis in males c- Ovaries in females. d- Genital ducts e- Accessory glands. 3. LATERAL PLATE MESODERM:

b- Postganglionic parasympathetic neurons within the ciliary, pterygopalatine, submandibular, otic, enteric ganglia, and ganglia of the abdominal and pelvic cavities. c-Sensory neurons within the dorsal root ganglia, Schwann cells d-Pia mater and arachnoid membrane e-Chromaffin cells of the adrenal medulla f-Melanocytes g-Bony structures of the face and neck: Maxilla, zygomatic bone, palatine bone, vomer, mandible, hard palate, incus, malleus, stapes, sphenomandibular ligament, styloid process, stylohyoid ligament, hyoid bone, frontal bone, parietal bond, sphenoid bone, and ethmoid bone h-Odontoblasts i-Aorticopulmonary septum j-Parafollicular cells of thyroid k-Dilator and sphincter pupillae muscles l-Ciliary muscle m-Carotid body	j-Epithelial lining of the urinary bladder k-Epithelial lining of the vagina l-Epithelial lining of the female urethra and most of the male urethra	a-Sternum, clavicle, scapula, pelvis, and bones of the limbs b-Serous membranes of body cavities c-Lamina propria, muscularis mucosae, submucosa, muscularis externae, and adventitia of the gastrointestinal tract d-Blood cells, microglia, Kupffer cells e-Cardiovascular system f-Lymphatic system g-Spleen h-Suprarenal cortex i-Laryngeal cartilages

ALLANTOIS:

It is defined as the small sac like diverticulum arises from the caudal wall of the umbilical vesicle. It helps in the early formation of the blood and urinary bladder. Allantois becomes the urachus after the formation of urinary bladder however in adults it is morphed into the median umbilical ligament.

NEURULATION:

- ✓ Neurulation is about the development of neural plate, neural folds and neural tube. During this period embryo is known as neurula.
- ✓ Neurulation is the formation of the neural tube from the ectoderm of the embryo. It follows gastrulation. As mentioned above during gastrulation cells migrate to the interior of the embryo, forming the three germ layers: the endoderm, the mesoderm and the ectoderm from which all tissues and organs will arise. After the process of gastrulation a flexible structure is formed which is known as the notochord. It is a rod-shaped body that runs along the back of the embryo and is derived from the mesoderm. During the third week of gestation the notochord sends signals to the overlying ectoderm which induce it to form neuroectoderm. This subsequently results in a strip of neuronal stem cells that runs along the back of the fetus. This strip is called the neural plate, and it forms the entire nervous system.

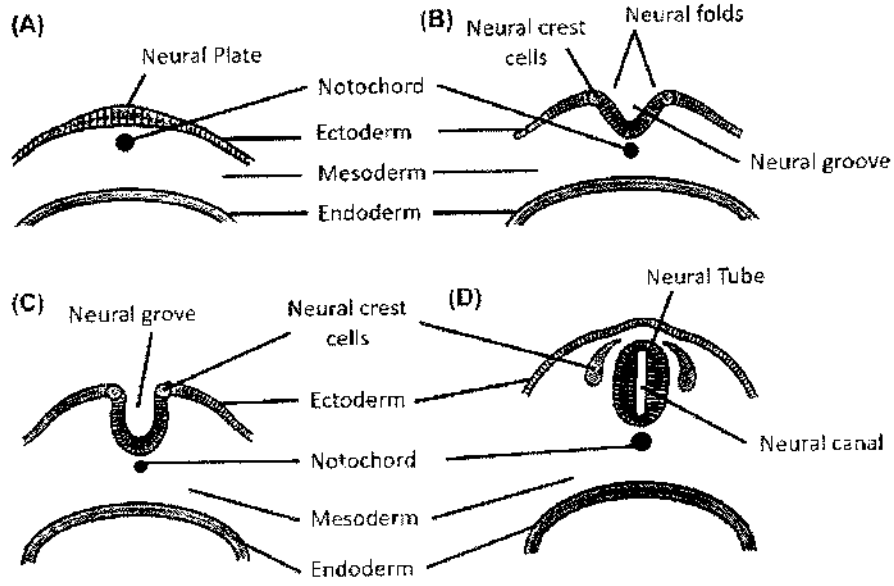


Fig 5.4: The process of neurulation

- ✓ After folding of the neural plate it comes outwards to form the neural groove. The neural folds of the groove close to create the neural tube. The ventral part of the neural tube is called the basal plate while the dorsal part is called the alar plate and the hollow interior region is called as the neural canal. The closure of neuropore occurs after the fourth week of gestation.

NEURULATION?
• The notochord stimulates the process of neurulation in the ectoderm. • The neuronal cells running along the back of the embryo form the neural plate that in turn folds outward to become a groove. • These folds of the groove fuse to form the neural tube. The ventral portion of the tube forms the basal plate while the dorsal portion forms the alar plate however the interior region forms the neural canal. • The ends of the neural tube close at the end of the fourth week of gestation.

SOMITES:

Somites are the cubical bodies formed from the mesoderm lie alongside the notochord and neural tube which first modified into the longitudinal columns known as paraxial mesoderm and then divides into the paired cubical bodies known as somites.

The somites develop in pairs; the first pair develops near the cranial end of the notochord around the end of the third week. Afterwards, the more pairs of somites develop in a caudal direction from days 20 to 30 which is known as the period of somite development and the number of somites is sometimes used as a criterion for determining an embryo's age. The somites form most of the axial skeleton which includes vertebral column, ribs, sternum, and skull base. It also forms associated musculature, as well as the adjacent dermis

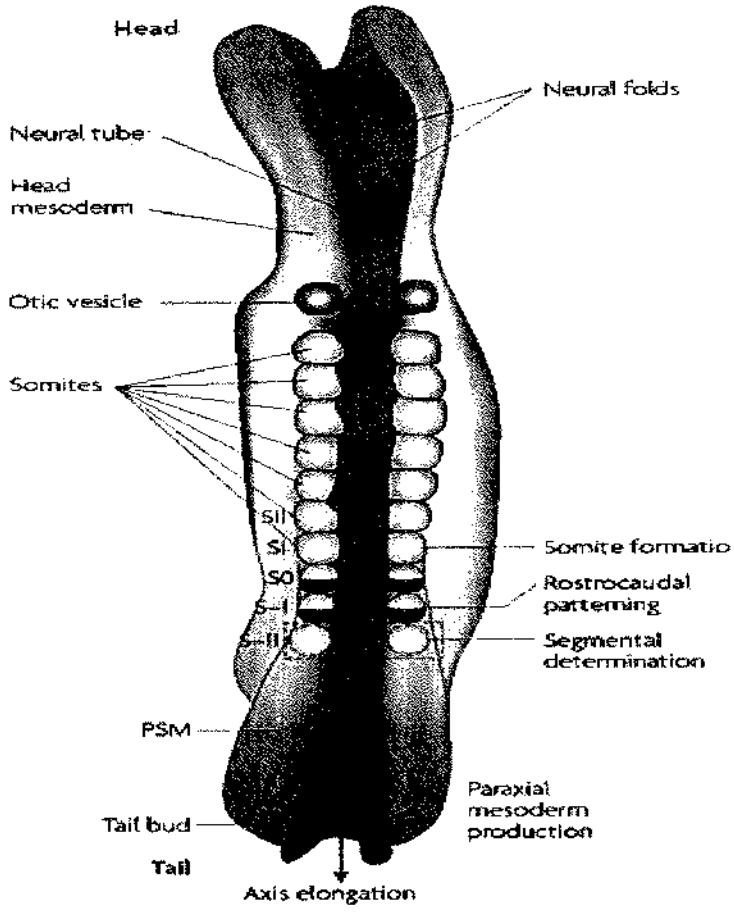


Fig 5.5: Somites

FORMATION OF CHORIONIC VILLI:

The formation of chorionic villi is episodic process as the primary chorionic villi takes place during the 2nd week of gestation. Afterwards, it differentiates into the secondary chorionic villi by mesenchymal infiltration. Soon the mesenchymal cells differentiate to form the blood capillaries which coalesce to form arteriocapillary- venous networks and differentiated into the tertiary chorionic villi.

ABNORMALITIES ASSOCIATED WITH THE THIRD WEEK OF DEVELOPMENT:

1. SACROCOCCYGEAL TERATOMA:

It is a type of tumor known as a teratoma that may be benign or malignant. It develops at the base of the coccyx (tailbone) and is thought to be derived from the primitive streak.

2. ALLANTOIC CYSTS:

It is a rare swelling formed at the base of umbilicus associated with a patent urachus which results from an allantoic remnant.

3. NEURAL TUBE DEFECTS:

Neural tube defects are birth defects of the brain, spine, or spinal cord. They happen in the first month of pregnancy, often before a woman even knows that she is pregnant. The two most common neural tube defects are spina bifida and anencephaly. When caudal neural pore does not close it is known as spina bifida while disclosure of cranial neuropore is known as anencephaly.

KEY NOTES!

a- This chapter is regarded as the week of gastrulation however there is more included in this chapter as the formation of primitive streak, notochord formation, neurulation and the chorionic villi formation.

b- In this week of development bilaminar germ disc converted into the trilaminar germ disc.

c- The formation of primitive streak takes place from the migration of epiblastic cells in the midline orientation of disc.

d- Notochordal process is formed by the mesenchymal cells from the primitive streak between the embryonic ectoderm and endoderm.

e- Neurulation is the formation of neural plates, neural cells, neural folds and neural tube.

f- Formation of the chorionic villi terminates at the end of third week of gestation.

6 THE FOURTH TO EIGHTH WEEKS OF DEVELOPMENT

LEARNING OBJECTIVES

- GENERAL INTRODUCTION OF THE 4TH TO 8TH WEEKS OF DEVELOPMENT
- SALIENT FEATURES OF THE 4TH WEEK OF DEVELOPMENT
- SALIENT FEATURES OF THE 5TH WEEK OF DEVELOPMENT
- SALIENT FEATURES OF THE 6TH WEEK OF DEVELOPMENT
- SALIENT FEATURES OF THE 7TH WEEK OF DEVELOPMENT
- SALIENT FEATURES OF THE 8TH WEEK OF DEVELOPMENT
- ESTIMATION OF THE EMBRYONIC AGE
- COMPARATIVE ANALYSIS OF THE PERIOD OF ORANOGENESIS
- ABNORMATIES ASSOCIATED WITH THE PERIOD OF ORGANOGENESIS
- KEY NOTES.

(THE PERIOD OF ORGANOGENESIS)

The period of human development which extends from the 4th week of gestation to the 8th week of gestation is known as the period of organogenesis because the formation of all major internal as well as external structures take place during this period. In this period the shape embryo is more like human because of the massive changes in the tissues and the organs. Meanwhile there would be the greater chances of the teratogenesis during this period because of the rapid growth and differentiation.

SALIENT FEATURES OF THE FOURTH WEEK OF DEVELOPMENT:

Fourth week is regarded as the week of major changes. For the sack of description it has been classified into three phases;

1. At the onset of 4th week of development:

   The embryo at very onset of 4th week of development is elongated structure having 4- 12 somites that helps in the production of surface elevations which in turn will form the neural tube. During the onset of 4th week of development following changes occur.

   - First and foremost change during the 4th week of development is the closure of the neuropore; what happens that, from the surface elevations neural tube is formed opposite to somites that remain widely open at both cranial and caudal end. During this period closure of these wide openings which is known as

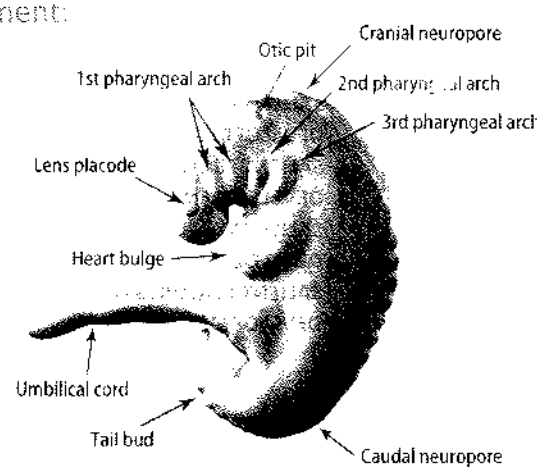
neuropore takes place. Cranial neuropore closes at the 25th day while the caudal neuropore closes at the 27th day.

- Secondly, first and 2nd pharyngeal arches appear during this period of development.
- Thirdly, the yolk sac starts the process of heamopoiesis.

2. At mid of the 4th week of development:

At the middle of 4th week, by the process of median and horizontal foldings embryo almost attains the curvature and becomes cylindrical. Following changes have been observed during the mid of 4th week of development.

- Formation of the upper limb buds on the lateral body wall.
- Formation of the otic and the lens placodes.
- Appearance of three pairs of pharyngeal arches starts.
- Formation of the rudimentary cardiovascular system takes place.

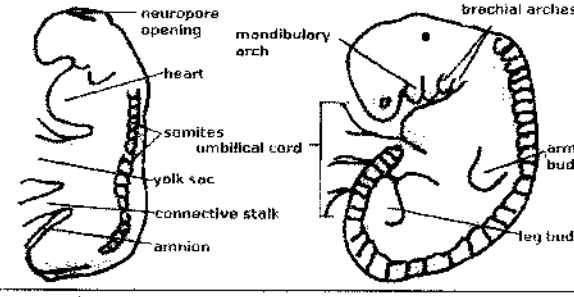


Embryo at mid of 4th week of development

3. Termination of the 4th week of development:

Following changes have been observed at the termination of 4th week of development.

- With the formation of cranial and caudal folds embryo become elongated.
- Formation of the swellings of upper and lower limbs.
- The development of the primordia of lung, liver and pancreas.
- The initiation of gastrointestinal tract formation.
- Appearance of the four pharyngeal arches.

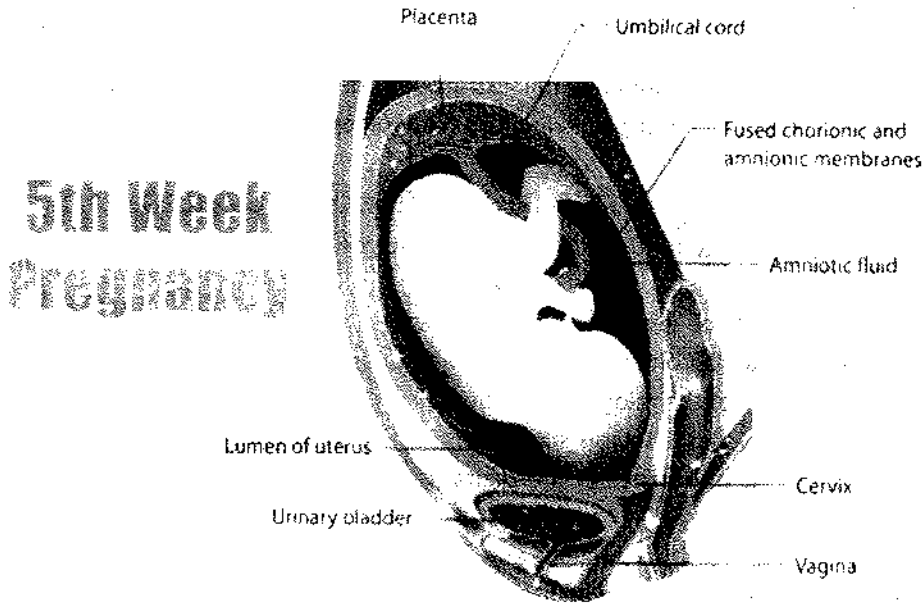


Embryo at the end of 4th week of development

SALIENT FEATURES OF THE FIFTH WEEK OF DEVELOPMENT:

Following changes have been observed during 5th week of development;

- Extensive growth of the head region as compared to the other body parts.
- The beginning of the development of brain and spinal cord.
- During this week the paddling of upper limbs take place.
- The appearance of cervical sinuses take place during this week.
- During this week rotation of stomach and the formation of midgut loop takes place.
- During this week the formation of groove takes place by the growth of 2nd pharyngeal arch over the 3rd and 4th pharyngeal arch.



The 5th week of development

SALIENT FEATURES OF THE SIXTH WEEK OF DEVELOPMENT:

Sixth week of development is characterized as;

- Twitching of the trunk and the developing limbs.
- The development of reflex response to touch during this week.
- The development of ridges on the paddle shaped hand plates is known as the digital rays.
- During this week the development of primordia of ear canals known as external acoustic meatus.
- The development of the auricular hillocks around the first pharyngeal groove.
- The appearance of the foot plates and the recognition of the ankle.

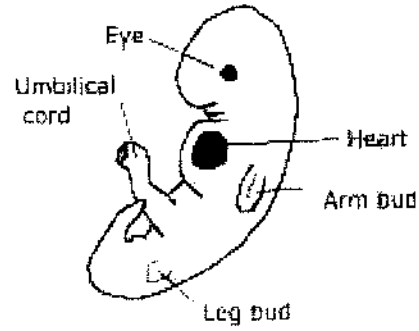


Fig 6.4: The 6th week of development

SALIENT FEATURES OF THE SEVENTH WEEK OF DEVELOPMENT:

Following are the salient features of the seventh week of development;

- The development of disproportional growth regarding the head becomes prominent.
- More prominence of the midgut herniation.
- The reduction of yolk sac to yolk stalk.
- The development of notches in the digital rays and hand plates.
- Webbed notches of the fingers and thumb however gives the appearance of distinct fingers.
- Ossification of the bones of upper limbs take place.

Fig 6.5: The 7th week of development

SALIENT FEATURES OF THE EIGHTH WEEK OF DEVELOPMENT:

Eighth week of development is characterized as;

- Separation of the digits of hands occur by webbing.
- Tail disappear at the end of eighth week of development however it is present at the beginning of 8th week.
- The eyes open during this week.

- During this week the intestine is present in the proximal part of the umbilical cord so that abdomen protrudes.
- The sex identification is oblivious.
- More growth of the cranial region.
- Facial features become more prominent by the formation of distinct nose and the directed eyes.
- Formation of the bands around the head region and appearance of the vascular plexuses around the scalp.

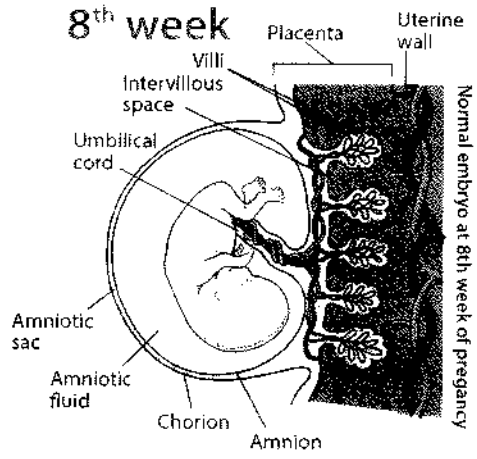


Fig 6.6: The 8th week of development.

ESTIMATION OF THE EMBRYONIC AGE:

The estimation of the embryonic age is done by the measurement of the length and the external features of the embryo. Following is given the procedure to count the length;

1. To measure the length from vertex to the buttocks that is known as crown rump length (CRL).
2. To measure the length from vertex to the heel that is known as crown heel length (CHL).

EMBRYOLOGICAL TID BITS!
a- Normal weight of fetus at the time of birth is 3000-3500g.
b- Crown rump length at the time of birth is 36cm.
c- Crown heel length at the time of birth is 45cm.

COMPARITIVE ANALYSIS OF THE PERIOD OF ORGANOGENESIS:

FOURTH WEEK	FIFTH WEEK	SIXTH WEEK	SEVENTH WEEK	EIGHTH WEEK
1. Curved and elongated body. 2. Appearance of limb buds. 3. Formation of pharyngeal arches	1. Head growth precedes the other body parts. 2. Formation of the facial features.	1. Head growth is more dominant. 2. Confluent oronasal cavities.	1. Formation of yolk stalk. 2. Differentiation of limbs. 3. Distinct fingers and thumb however webbed.	1. Sex identification is oblivious. 2. Facial feature are distinct. 3. Neck is well established. 4. Separation of digits.

4. Beginning of the placental development. 5. Beginning of the cardiovascular system formation. 6. Craniocaudal foldings. 7. Otic and lens placodes formation. 8. Formation of the primary brain vesicles.	3. Formation of limb swellings. 4. Paddling of the upper limb 5. Appearance of cervical sinuses. 6. Rotation of the stomach and midgut loop formation. 7. Paddling of the upper limb.	3. Body becomes straight. 4. Formation of digital rays. 5. Formation of footplates. 6. Finger and toes formation.		5. Retrogression of the tail.

DEVELOPMENTAL ABNORMALITIES OF THE PERIOD OF ORGANOGENESIS:

1. SITUS INVERSUS:

It is a congenital condition in which the major visceral organs are reversed or mirrored from their normal positions. The normal arrangement of internal organs is known as situs inversus.

2. TERATOGENESIS:

Teratogenesis is a prenatal toxicity characterized by structural or functional defects in the developing embryo or fetus. It also includes the intrauterine growth retardation, death of the embryo or fetus, and transplacental carcinogenesis.

KEY NOTES!

a- This period is the period of organogenesis which extends from the 4th week of gestation to the 8th week of development.

b- During this period various changes occur as the median and horizontal folding of the embryo takes place, various organs starts to form and neural pore closes.

c- Estimation of the embryonic age can be done by seeing the external features and measuring lengths of crown rump and crown heel.

7

THE FETAL PERIOD

LEARNING OBJECTIVES

- GENERAL INTRODUCTION OF THE FETAL PERIOD
- SALIENT FEATURES OF 9TH TO 12TH WEEKS
- SALIENT FEATURES OF 13TH TO 16TH WEEKS
- SALIENT FEATURES OF 17TH TO 20TH WEEKS
- SALIENT FEATURES OF 21ST TO 25TH WEEKS
- SALIENT FEATURES OF 26TH TO 29TH WEEKS
- SALIENT FEATURES OF 30TH TO 34TH WEEKS
- SALIENT FEATURES OF 35TH TO 39TH WEEKS
- EXPECTED DATE OF PREGNANCY
- FACTORS AFFECTING THE FETAL GROWTH
- METHODS FOR DETACTING THE STATUS OF FETUS.
- ABNORMALITIES ASSOCIATED WITH THE FETAL PERIOD
- KEY NOTES.

(THE PERIOD OF TRANSFORMATION)

The period which commences from the beginning of the ninth week of development and terminates at birth is marked as fetal period.

Generally speaking, this period is recognized as "the period of transformation" for there are plethora of changes occur in the culmination of embryonic stage to fetal stage. The development of fetus during this period is remarkable as it is basically concerned with the rapid differentiation of tissues, organs and systems as well as the prompt body growth. The striking feature of this period is that during this period the growth of head relative to the body slows down.

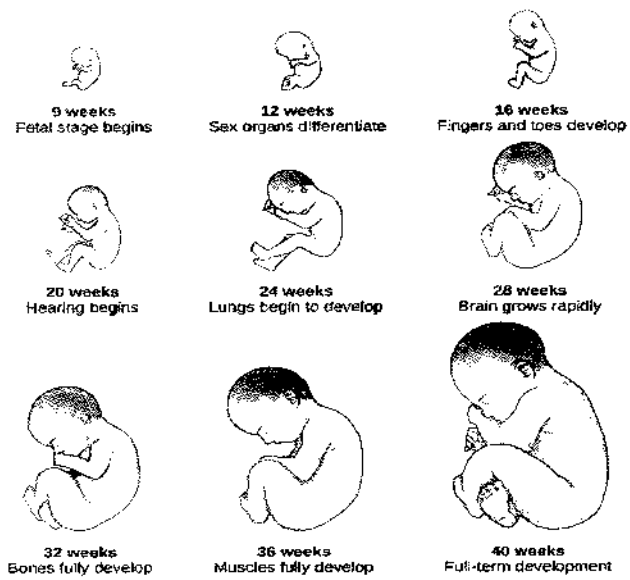


Fig 7.1. Different weeks of fetal

SALIENT FEATURES OF THE FETAL PERIOD:

For the sack of understanding the salient features of fetal period has been classified into four to five weeks' time scale.

SALIENT FEATURES OF NINTH TO TWELVE WEEKS:

Following are given some salient features regarding the development of fetus in between ninth to twelve weeks.

- ✓ During this period body still grows disproportionately as there is remarkable lengthening relative to the growth of head region.
- ✓ During this period remarkable changes appear in the physique of the fetus as the face becomes broad, eyes are placed widely, eyelids approximates and ears come to low set.
- ✓ During this period major change appears in the bones as the primary ossification centres appear in skeleton.
- ✓ One thing that remains the same during this period is that there is no distinction in the male and female genitalia.
- ✓ During this period upper limbs attain their full length and position however lower limbs are relatively short.
- ✓ During the early phase this period erythropoiesis takes place in liver however at the end of this period the liver diminishes this activity and consequently it is done by the spleen.
- ✓ During this period of fetal development intestinal coils are clearly visible proximal to the umbilical cord however during the late in this period it returns to the abdomen.
- ✓ During this period fetus starts to produce urine and this urine is excreted into the amniotic fluid. The fetus first absorb this fluid after swallowing and then excretes it into the placental circulation.

SALIENT FEATURES OF THIRTEEN TO SXTEEN WEEKS:

Following are given some key features of this period.

- ✓ During this stage of development the oogonia become visible after the differentiation of the ovaries.
- ✓ During this period there is rapid growth.
- ✓ The circumference of the head during this period is lesser than the 12^{th} week.
- ✓ During this period of fetal development ossification becomes faster.
- ✓ During this period auricles of the ear are close to attain its definite position.

- ✓ During this period sexuality is easily identified as the external genitalia become fully developed.
- ✓ At this stage of development fetus appears more like human.
- ✓ Eyes are placed anteriorly rather than anterolaterally.

SALIENT FEATURES OF SEVENTEEN TO TWENTY WEEKS:

Below are given some characteristics of fetus related with seventeenth to twentieth weeks of development.

- ✓ During this period the growth of the fetus significantly slows down however limbs continue to grow.
- ✓ The striking feature of this period is that the formation of brown fat occurs which in turn helps in heat production.
- ✓ The heartbeat of the fetus can be heard with stethoscope.
- ✓ During this period quickening are significantly high and felt by the mother.
- ✓ During this period fetus is covered with a mixture of fatty secretions from the fetal sebaceous glands and worn out epidermal cells, this period is known as vernix caseosa.
- ✓ During this period head hairs, eyebrows and eyelashes are very prominent.
- ✓ Body of the fetus during this period is covered by fine hairs known as lanugo hairs.

SALIENT FEATURES OF TWENTY ONE TO TWENTY FIVE WEEKS:

Following are given some key characteristics of these weeks.

- ✓ During these weeks of development body grows substantially and gains the body albeit the growth of body becomes proportionated.
- ✓ Regarding skin, it is usually wrinkled and translucent however it has blood in the capillaries therefore it appears red.
- ✓ During this period of development fingernails are well developed and toenails commence to develop.
- ✓ During this period eyes start to move promptly.
- ✓ The secretory activity by the pneumocytes type two. It secretes surfactant.
- ✓ The risk for neurodevelopmental disability is high in fetuses born before 26th week of development.

SALIENT FEATURES OF TWENTY SIX TO TWENTY NINE WEEKS:

Below are given some key features of the development of these weeks.

- ✓ Gaseous exchange commences during this period as the primitive alveoli and pulmonary vascular structures become fully developed.
- ✓ Eyes become open during this period of development.
- ✓ Toenails are fully developed.
- ✓ During this period of development erythropoiesis commences in the bone marrow because of cessation of erythropoiesis in the spleen.
- ✓ During this period wrinkling of the skin become reduced due to the fat deposition beneath the skin.
- ✓ The body temperature and rhythmic activity is well controlled because of the significant development of central nervous system.

SALIENT FEATURES OF THIRTY TO THIRTY FOUR WEEKS:

Following are given some key features of the aforementioned weeks.

- ✓ At this period the fine hairs which is known as lanugo hairs disappeared from the face.
- ✓ Nails approach the end of finger during this period.
- ✓ During this period pupillary eye reflex elicited.
- ✓ During this period upper and lower limbs have chubby appearance.
- ✓ Fetus can survive if birth occurs during this period.

SALIENT FEATURES OF THE THIRTY FIVE TO THIRTY EIGHT WEEKS:

The prime characteristics of these weeks are given as under.

- ✓ By this period nervous system is significantly mature to take the function of integration.
- ✓ The function of orientation to light is fully established.
- ✓ Lanugo hairs during this period disappear mostly.
- ✓ During this period nails grow beyond the finger fields.
- ✓ During this period testis start to descend into the testis, left testis first appears during the 36th week however at the end of this period both testis reach into the scrotum.
- ✓ During this period relative circumference of abdominal region is greater than the head region.
- ✓ At the end of this period fetus has full grasp.
- ✓ Birth occurs mostly after the 38th week of fertilization or at the 266th day.

EXPECTED DATE OF DELIVERY:

The excepted date of delivery is counted by the Naegele's formula as;
EDD= LMP (LAST MENSTURAL PERIOD) - 3 MONTHS + 7 DAYS.
According to the above mentioned formula the expected date of delivery is 266 days or 38 weeks after fertilization.

FACTORS AFFECTING THE FETAL GROWTH:

There are plethora of factors that affects the fetal growth; they may be maternal, environmental or fetal. Following are given some factors that can affect the fetal growth.

1. Maternal vascular diseases
2. Intrauterine infections
3. Cigarette smoking
4. Alcohol consumption
5. Drug addiction
6. Maternal mainutrition
7. Multiple pregnancy
8. Genetic factors
9. Growth retarding capacities
10. Impaired fetoplacental or uteroplacental blood flow.

METHODS FOR DETECTING THE STATUS OF THE FETUS:

To check the wellbeing of the conceptus after fertilization is of prime importance; following are given some techniques to detect the status of fetus.

1. **Amniocentesis**: It is a technique in which amniotic fluid is removed from the uterus for testing or treatment. Amniotic fluid is the fluid that surrounds and protects a baby during pregnancy. This fluid contains fetal cells and various proteins.

2. **Ultrasonography**: It is a method in which by using echoes of ultrasound pulses to delineate objects or areas of different density in the body.

3. **Spectrophotometry**: It is a procedure for measure how much a chemical substance absorbs light by measuring the intensity of light as a beam of light passes through sample solution. The basic principle is that each compound absorbs or transmits light over a certain range of wavelength. It is employed in the embryology for assessing the erythroblastosis fetalis by examining the amniotic fluid.

4. **Alpha fetoprotein assay**: It is a blood test that measures the amount of AFP present in blood. It's usually part of what's called a triple screen or quad screen in the second

trimester of pregnancy. However, it can also be useful for adults who aren't pregnant.

5. **Chorionic villus sampling Cell culture:** It is a test which is done prenatally that is used to detect birth defects, genetic diseases, and other problems during pregnancy. During this test, a small sample of cells that is taken from the placenta where it attaches to the wall of the uterus.

6. **Non-invasive prenatal diagnosis:** It is a procedure of determining the risk that the fetus will be born with certain genetic abnormalities. This testing analyzes small fragments of DNA that are circulating in a pregnant woman's blood.

7. **Chromosomal analysis:** It is karyotyping to detect different genetic abnormalities.

8. **Fetoscopy:** It is an endoscopic method during pregnancy to allow surgical access to the fetus, the amniotic cavity, the umbilical cord, and the fetal side of the placenta. A small incision is made in the abdomen, and an endoscope is inserted through the abdominal wall and uterus into the amniotic cavity.

9. **Magnetic resonance imaging:** The magnetic resonance imaging used to detect or treat the fetus.

10. **Percutaneous umbilical Blood sampling:** It is a diagnostic prenatal test. During cordocentesis, an ultrasound transducer is used to show the position of the fetus and umbilical cord on a monitor. Then a fetal blood sample is withdrawn from the umbilical cord for testing.

11. **Fetal monitoring:** It is a procedure in which instruments are used to continuously record the heartbeat of the fetus and the contractions of the woman's uterus during labor.
12. **Fetal transfusion:** It is a method that provides blood to a fetus, most commonly through the umbilical cord. It is used in cases of severe fetal anemia, such as when fetal red blood cells are being destroyed by maternal antibodies.

ABNORMALITIES RELATED WITH FETAL PERIOD:

1. POST MATURITY SYNDROME: It is defined as a fetus whose weight gain in the uterus after the due date has stopped, usually due to a problem with delivery of blood to the fetus through the placenta, leading to malnourishment. After birth, these infants have a distinctive appearance.

2. CONJOINED TWINS: It is a consequence of incomplete division of embryonic disc. Conjoined twins may be of different varieties classified on the basis of region through which these are joined.
   a- Pygopagus: In which twins are joined by back.
   b- Craniopagus: In which twins are joined by heads.
   c- Thoracopagus: In which twins are joined by thoracic region.

KEY NOTES!
a- This chapter deals with the fetal period of development which extends from the 9th week gestation to birth.
b- The factors which affect the fetal growth are broadly classified into placental, environmental and fetal. However smoking, maternal malnutrition, alcohol consumption, blood supply also affects the fetal growth.
c- There are some techniques through which fetal status can be checked these includes; amniocentesis, ultrasonography, alpha fetoprotein assay, chorionic villus sampling etc.

8

THE DEVELOPMENT OF PLACENTA AND FETAL MEMBRANES

LEARNING OBJECTIVES

- GENERAL INTRODUCTION OF THE DEVELOPMENT OF PLACENTA AND FETAL MEMBRANES
- THE DEELOPMENT OF PLACENTA
- DECIDUA
- UMBILICAL CORD
- AMNION
- AMNIOTIC FLUID
- ALLANTOIS
- UMBILICAL VESICLE
- PARTURITION
- MULTIPLE PREGNANCIES
- ABNORMALITIES ASSOCIATED WITH THE DEVELOPMENT OF PLACENTA AND FETAL MEMBRANES
- KEY NOTES

This chapter deals with the formation of placenta, its functions as well as the establishment of placental circulation. It also discusses the process of parturition, the significance and fate of umbilical vesicles as well as the fate of multiple pregnancies.

PLACENTA:

Placenta is a vital organ that serves as the connecting link between fetus and the mother. Fundamentally, it is a blood rich structure which is considered as the lifeline of developing fetus.

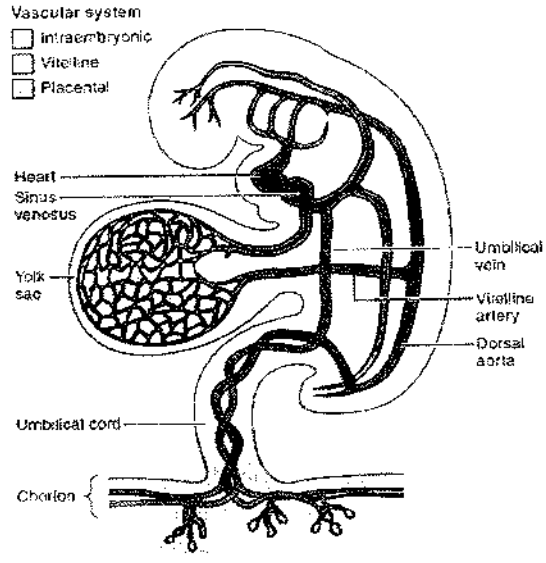


Fig 8.1: Placenta

THE DEVELOPMENT OF PLACENTA:

- The formation of placenta commences when implantation of the blastocyst takes place. The blastocyst contains two differentiated embryonic cell types: the outer trophoblastic cells and the inner cell mass. The trophoblastic cells form the placenta while the inner cell mass forms the fetus and fetal membranes.

- What happens that on the 6th day of gestation when the disintegration of zona pellucida occurs the blastocyst hatches out and permits the implantation to takes place while the trophoblastic cells interact with the endometrial decidual epithelia and enable the

invasion into the maternal uterine cells. However the embryo begins to secretes the proteases that in turn permit deep invasion into the uterine stroma. Normal implantation occurs on the anterior or posterior wall of the body of the uterus. The most common ectopic implantation site is in the ampulla of the Fallopian tube.

- Progressively on the 8th day of gestation the trophoblastic cells distinguishes in outer multinucleated syncytiotrophoblast, which erodes maternal tissues by sending out projections and it starts to secrete human chorionic gonadotropin hormone which is responsible for the pregnancy and the inner one is mononucleated cytotrophoblast that proliferates actively to form the primary chorionic villi. After the establishment of both layers of cell on the 9th day of development lacunae formation begins to take place in the syncytiotrphoblastic cell layer. Later on syncytiotrophoblast erodes the maternal tissues and permits the maternal blood from spiral uterine arteries to circulate the lacunar network. This marks the establishment of primitive uteroplacental circulation. Meanwhile, the other layer of cell that is known as cytotrophoblastic layer of cell commences to form the primary chorionic villi which first penetrates and then extends into the syncytiotrophoblast. In the third week of gestation a core of loose connective tissue forms by the help of extra embryonic mesoderm into these villi. This marks the formation of secondary chorionic villi. Furthermore the vasculogenesis occurs inside the secondary chorionic villi which converts it into the tertiary chorionic villi. Meanwhile, the formation of cytotrophoblastic shell takes place from the growing tertiary villi into the basal layer of decidua that is the functional endometrium. However those villi which connects the cytotrophoblastic shell with the decidua basalis is known as anchoring villi and the villi which grows from anchoring villi in the outward direction into intervillous space is known as branching villi, it increases the surface area for exchange of metabolites.

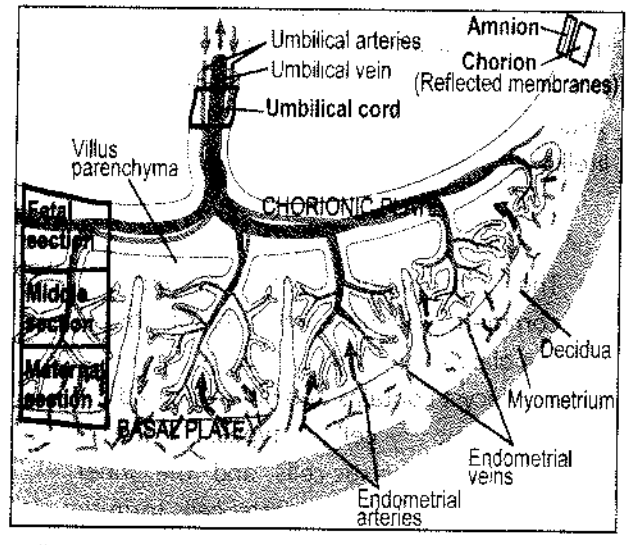


Fig 8.2. Placenta along with different layers, umbilical arteries and viens.

- Regarding the establishment of circulation through placenta; spiral arteries first undergo the process of remodeling and produce the low resistance pathway in order to meet the significant demands of the developing fetus. The reduction of resistance occurs when the cytotrophoblastic cells invade the spiral arteries and the process of replacement occurs

in the maternal endothelium. Then the process of differentiation occurs which increases the diameter of blood vessels and reduce the resistance.

- Regarding the formation of placental barrier, it is relatively a thick temporary barrier which is formed during the first trimester of pregnancy. The placental barrier is not a true barrier as it permits plethora of substances to cross the fetomaternal circulation.
- Human placenta is of hemochorial type as it separates the maternal blood from the foetal blood. During the fourth month of gestation placenta distinctly has the two components one is the maternal component which is known as the decidua basalis and the other is a bushy foetal component known as the chorionic frondosum. On the foetal side the placenta is covered by the chorionic plate while on the maternal side it is intimately bordered by the decidual plate of decidua basalis. However during the 4th and 5th months of gestation the decidua develops the decidual septum which incorporates into the intervillous space albeit it does not coalesce the chorionic plate. The septa are covered by syncytial cells and have a core of maternal tissues. The syncytial cells separates the maternal blood from the foetal in the intervillous space. The function of septa is to divide the placenta into cotyledons and cotyledons easily receives blood supply from the respective spiral arteries.
- The characteristics of the full term placenta are; it is discoid in shape having diameter, thickness and weight of 15-25cm, 3cm and 500-600g respectively. It also have 150ml of maternal blood into it.
- At the end of pregnancy some changes occurs in the placenta to reduce the exchange amongst fetomaternal circulation. These changes are;
  1. Thickening occurs in respiration, the fetal capillaries of the basement membrane.
  2. Fibrous tissue in the core of the villus increases significantly.
  3. Small capillaries start to obliterate.
  4. Some changes occur at the junctional zone and chorionic plate of villi, these changes are marked by the deposition of fibroid tissues and that results into the infarction of the intervillous lake.
- The functions of placenta are; respiration, excretion, nutrition, protection, storage, hormone production, nutrition, oxygen supply and certain storage functions.

EMBRYOLOGICAL TID BITS!

a- Regarding placental membrane which serves as placental barrier, separates the maternal blood from the foetal blood consists of;
1. Syncytiotrophoblast
2. Cytotrophoblast
3. Connective tissues
4. Endothelium of fetal capillaries.

b- Did you know? Placenta is considered as allograft.

DECIDUA:

The decidua is known as functional endometrium. It is a part of endometrium which separates from the uterus after parturition. For the sack of description decidua has been classified into three regions accordingly their relation to the implantation site.

1. Decidua basalis: The part of the functional layer of endometrium which forms the maternal part of placenta and it lies deep to the conceptus.
2. Decidua capsularis: The part of functional endometrium that serves as the superficial covering is known as decidua capsularis
3. Decidua parietalis: The remaining part of functional endometrium other than basalis and capsularis is known as decidua parietalis.

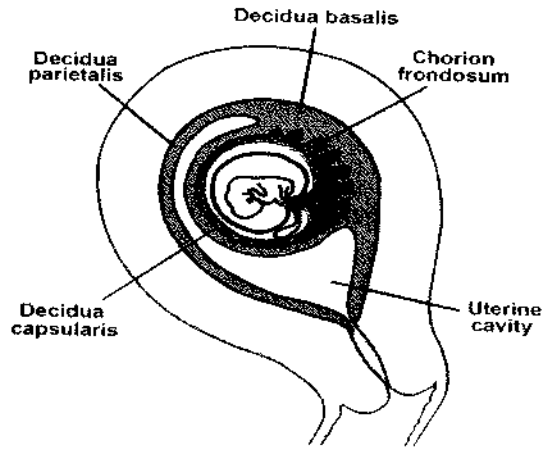


Fig 8.3: Decidua

UMBILICAL CORD:

It is a narrow and elongated tube like structure that connects the conceptus with the placenta. On the ventral surface of the conceptus there exists a patent opening which is known as the primitive umbilical ring. The umbilical cord often has two arteries and a vein which is clothed by the Wharton's jelly.

AMNION:

It is a membrane that covers the embryo closely at very inception of its birth. It is filled with the amniotic fluid which causes the amnion to expand and become the amniotic sac which serves to provide a protective environment for the developing embryo or fetus.

AMNIOTIC FLUID:

The amniotic fluid is a yellowish colored protective fluid contained by the amniotic sac. It is

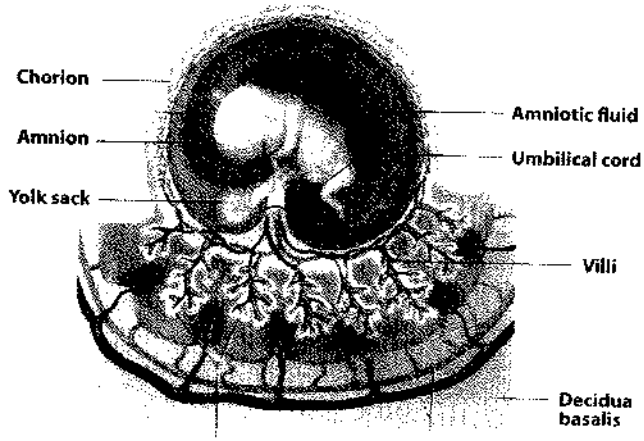


Fig 8.4: The depiction of umbilical cord, amnion and chorion.

made up of carbohydrates, lipids, proteins, hormones, enzymes, fetal cells and fetal urine. Regarding the production of amniotic fluid, it is produced by the dialysis of fetomaternal blood. It increases slowly during the pregnancy and attains its maxim at the 12th week of development. The concentration of amniotic fluid at the 12th of development is 1000ml. Following are given some functions of amniotic fluid.

1. Protection of the fetus
2. Control of the temperature
3. Control of the infection
4. The development of lungs and digestive system
5. Assist in the development of the muscles and bones.
6. Umbilical cord support
7. Lubrication.

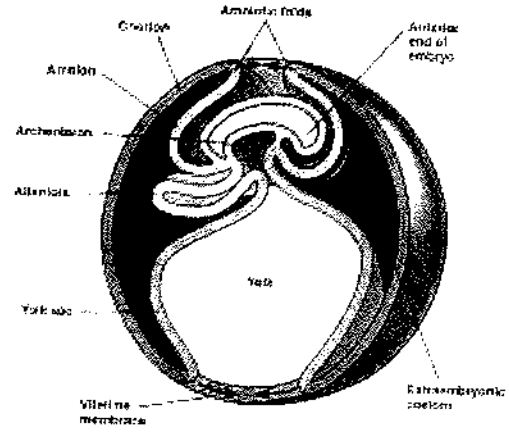


Fig 8.5 Different layers covering embryo.

ALLANTOIS:

It is a sac like hollow structure having the clear fluid covering the conceptus. It assists the conceptus in exchange of gases and clearing the liquid waste. It degenerates to form the median umbilical ligament in adults.

UMBILICAL VESICLE:

It is the fluid filled pouch of the yolk sac having the transitory connection with the digestive system through the ompahaloenteric duct. It has no fate in the postnatal life. Following are given some of its function in the prenatal life.

1. Transfer of nutrients
2. Blood cell development
3. Forms the epithelium of various structures
4. Help in the differentiation of primordial germ cells.

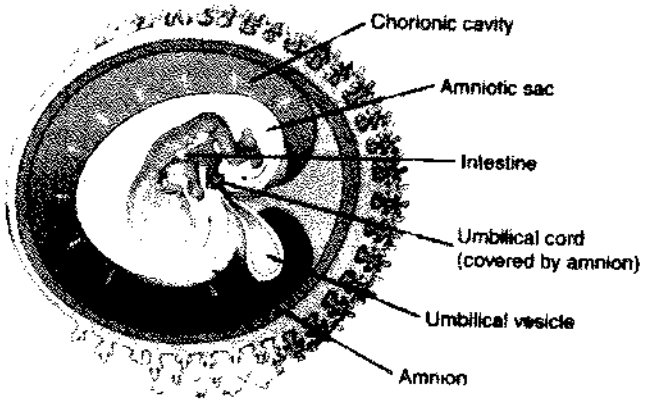


Fig 8.6: Diagram showing chorionic cavity, amniotic sac, amnion and umbilical vesicle.

PARTURITION:

It is the process of the contraction of the uterus at regular intervals that helps in the delivery of the baby at the culmination of pregnancy. The signals that the fully developed fetus sends through the placenta for ejection is called Foetal ejection reflex. These signals induce

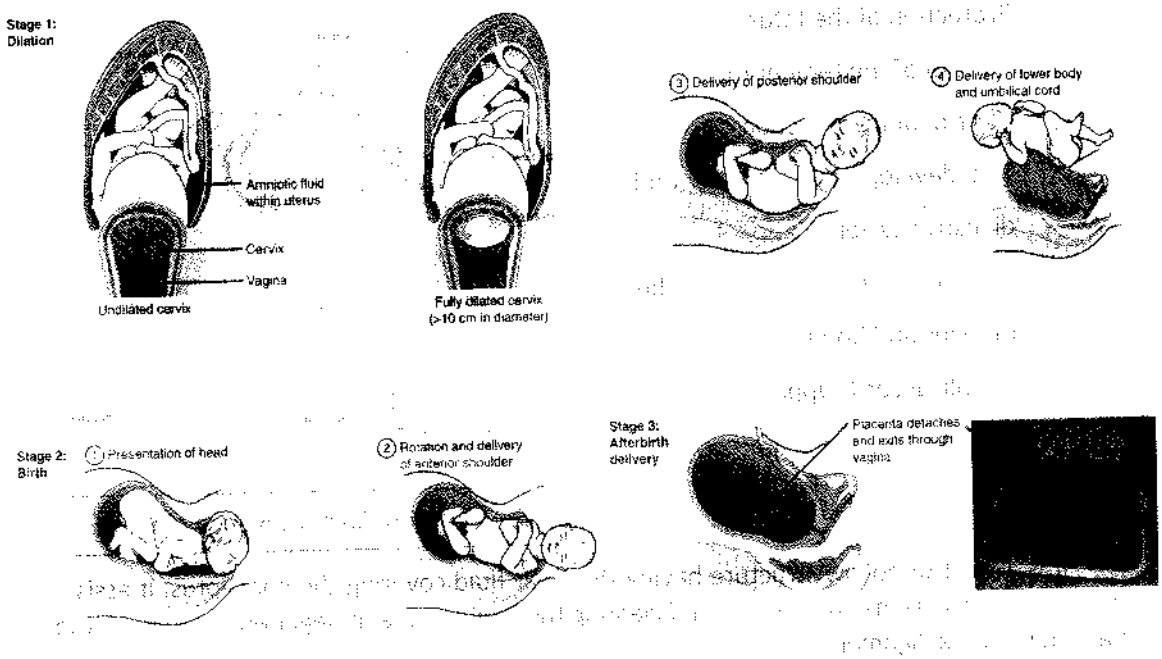


Fig 8.7: The stages of parturition.

muscular contractions. However the sequence of events that leads to the involuntary uterine contractions and subsequently ends up into the delivery of fetus is known as labor. There are four stages of labor which are given as under;

1. DILATION STAGE: This stage lasts for 7 to 12 hours. During this stage there is a progressive opening of the cervix that is induced by the alteration of the circulating hormones and the certain lipid components.
2. EXPULSION STAGE. It lasts for 20 to 50 minutes. During this stage fetus comes outside the uterus or vagina.
3. PLACENTAL STAGE: This stage lasts for 15 minutes. During this stage the placenta and associated structures of the fetus comes outside the maternal body.
4. RECOVERY STAGE: This stage last for two hours. During this stage the constriction of the myometrium occurs which in turn prevent the excessive bleeding.

MULTIPLE PREGNANCIES:

The occurrence of more than one pregnancy is known as multiple pregnancy. It has various causes, it may be due to one zygote or the two.
The proportion of twins are only 1% and 70% of these are dizygotic twins

1. Dizygotic twinning shows racial differences; the incidence of monozygotic twinning, however, is the same in all populations
2. The rate of monozygotic twinning shows little variation with the mother's age; dizygotic twinning increases with maternal age.
3. The anastomoses between blood vessels of fused placentas of human dizygotic twins may occur and result in erythrocyte mosaicism.

Dizygotic twins born as a consequence of fertilization of two oocytes by different sperms. Twins are no more alike genetically having two amnions and two chorion, however placenta and chorions are fused. These twin do not have graft tolerance.

Monozygotic twins formed as the consequence of fertilization of one oocyte. They are morphologically and physiologically identical and of the same sex. They are genetically identical and have identical blood characteristics. They have a tolerance for transplants.

- Conjoined twins formed as a result of incomplete division of embryonic disk and are named by regions of attachment, e.g., Thoracopagus (fusion of anterior thoracic region); Pygopagus (fusion at back); or Craniopagus (fusion at head). One in 400 monozygotic twins are conjoined. Some may be successfully separated surgically.
- Other multiple pregnancies include, triplets, quadruplets, superfetation and superfecundation.

ABNORMALITIES ASSOCIATED WITH PLACENTA AND FETAL MEMBRANES:

1. PLACENTAL ABNORMALITIES:

Following are given some abnormalities of placenta.

a. Placenta previa:
It occurs when a baby's placenta partially or totally covers the mother's cervix that is the outlet for the uterus. Placenta previa can cause severe bleeding during pregnancy and delivery.

b. Placenta accrete:
It is a serious pregnancy condition that occurs when the placenta grows too deeply into the uterine wall. It is the placenta detaches from the uterine wall after childbirth. With placenta accrete, part or all of the placenta remains attached. This can cause severe blood loss after delivery.

c. Placenta abruptio:
It is the premature separation of the placenta from the uterus. Patients with abruptio placentae, also called placental abruption, typically present with bleeding, uterine contractions, and fetal distress

d. Placenta velementous:
It is the placenta in which umbilical vessels travel abnormally through the amniochorionic membrane before reaching the proper placenta

e. Placenta increta:
It is a condition where placenta attaches more firmly to the uterus and becomes embedded in the organ's muscle wall.

f. Placenta percreta:
It is a condition where placenta attaches itself and grows through the uterus and potentially to the nearby organs such as the bladder.

g. Placenta circumvallate:
It refers to the variation in the placental morphology in which, as a result of a small chorionic plate, the amnion and chorion fetal membranes 'double back' around the edge of the placenta.

h. Placenta battledore:
It is a condition in which the umbilical cord is inserted at or near the placental margin rather than in the center. The cord can be inserted as close to 2 cm from the edge of the placenta.

i. Placenta succenturiate:
It refers to the extra placenta from the actual placenta.it is accessory placenta.

j. Placenta bipartite:
Placenta consists of two equal lobes is known as placenta bipartite.

k. Placenta tripartite:
Placenta consists of three equal lobes is known as placenta tripartite.\

2. PREECLAMPSIA:

It is a complication which arises in the pregnancy characterized by the high blood pressure. It can cause the damage of other system as well mostly it harms to the kidneys and liver.

3. TWIN TRANSFUSION SYNDROME:

This is regarded as the prenatal condition which is associated with unequal placental blood supply to the twins resulting in unequal growth.

4. OLIGOHYDRAMINOS:

It refers to the presence of small amount of amniotic fluid usually lesser than 400ml. it is often associated with the renal agenesis of the developing human.

5. POLYHYDRAMNIOS:

it refers to the presence of greater than normal amount of amniotic fluid usually more than 1500 ml.

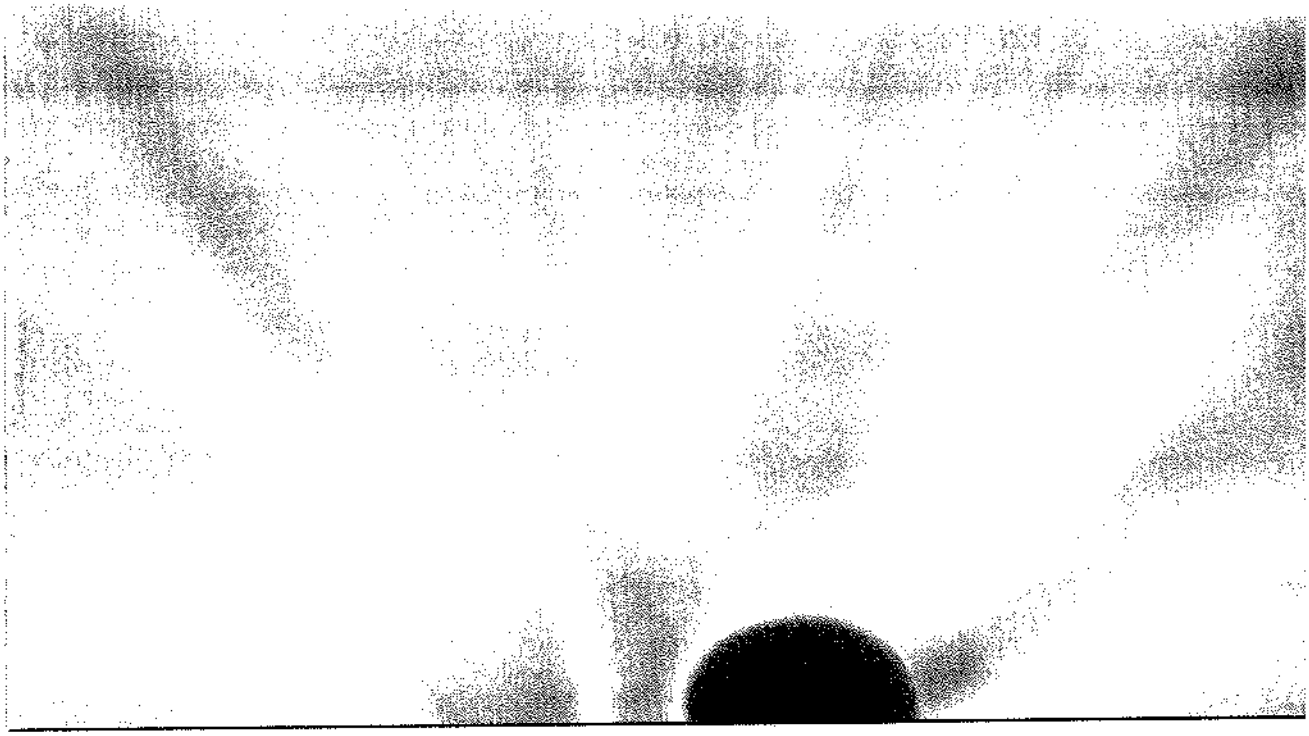
6. AMNIOTIC BAND SYNDROME:

It is a congenital anomaly associated with the development of craniofacial or limb anomalies due to amniotic bands that causes constriction of the various parts of the developing fetus.

7. CHORIOCARCINOMA:

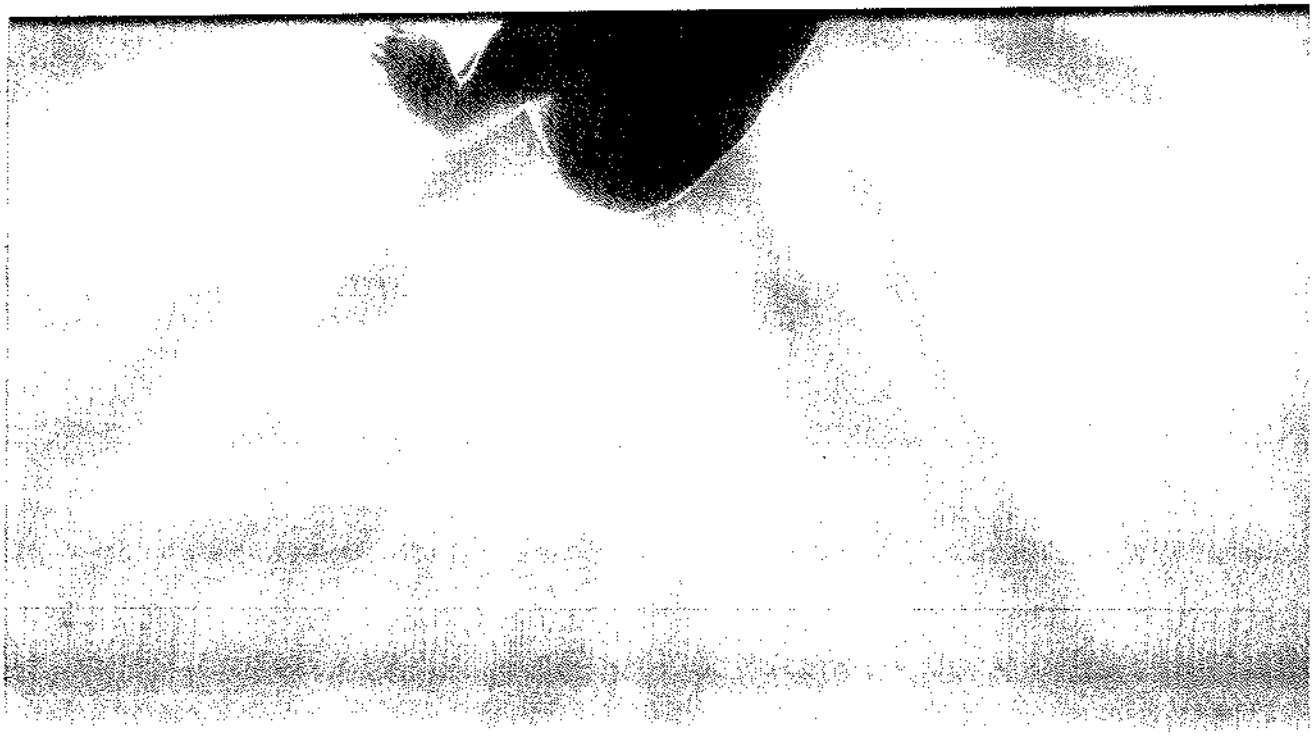
It refers to the formation of carcinoma of trophoblastic layer. It usually occurs due to abortion.

KEY NOTES!
a. This chapter explains the formation of placenta, umbilical cord, allantois, umbilical vesicle, chorion etc. It is also defining the developmental anomalies associated with all these fetal membranes. b. The placenta actually consists of the two parts one is maternal which is smaller and derived from the decidua basalis while the other one is fetal part which is larger and derived from the chorionic villus. c. Placenta is considered as fetal tissue. d. The fetal circulation is separated by the maternal circulation by a thin membrane known as placental membrane. e. The abnormalities of this chapter includes the placental anomalies, oligohydramnios, polyhydramnios, preeclampsia etc.



SECTION- C

THE SYSTEM BASED EMBRYOLGY



9 THE DEVELOPMENT OF HEAD AND NECK

LEARNING OBJECTIVES

- GENERAL INTRODUCTION OF THE DEVELOPMENT OF HEAD AND NECK
- PHARYNGEAL ARCHES
  - I. FIRST PHARYNGEAL ARCH
  - II. SECOND PHARYNGEAL ARCH
  - III. THIRD PHARYNGEAL ARCH
  - IV. FOURTH PHARYNGEAL ARCH
  - V. SIXTH PHARYNGEAL ARCH
- PHARYNGEAL POUCHES
- DERIVATIVES OF THE PHARYNGEAL POUCHES
- PHARYNGEAL CLEFT
- PHARYNGEAL MEMBRANE
- THE DEVELOPMENT OF THYROID GLAND
- THE DEVELOPMENT OF SALIVARY GLANDS
  - I. THE PAROTID GLAND
  - II. THE SUBMANDIBULAR GLAND
  - III. THE SUBLINGUAL GLAND
- THE DEVELOPMENT OF FACE
- THE DEVELOPMENT OF TONGUE
- DEVELOPMENT OF INTERMAXILLARY SEGMENT
- DEVELOPMENT OF LIPS
- DEVELOPMENT OF THE PALATE
- DEVELOPMENT OF NASAL CAVITIES
- DEVELOPMENT OF NOSE
- DEVELOPMENTAL ABNORMALITIES RELATED WITH HEAD AND NECK
- KEY NOTES.

THE DEVELOPMENT OF HEAD AND NECK:

This chapter deals with the development of pharyngeal apparatus, the structures of the face and the structural visceras of neck.

The development of head takes place from the mesenchyme of paraxial and lateral plate mesoderm, neural crest cells and the ectodermal placodes.

- Paraxial mesoderm gives rise to membranous and cartilaginous structure of the skull, all voluntary muscles of skull and face, the connective tissue structures, dermis and the meninges caudal to prosencephalon.
- The laryngeal cartilages and connective tissues derived from the lateral plate mesoderm.
- Neural crest cells after migration into pharyngeal arches, rostral to the prosencephalon and into optic cup forms the face and part of membrano-cartilagenous structures of the skull.
- The ectodermal placodes along with neural crest cells form the neurons of 5th, 7th, 9th and 10th cranial sensory ganglia.
- The most distinguished feature in the formation of the head and neck region is the development of pharyngeal arches, which initially appears as bars of mesenchymal tissues separated by demarcating lines known as pharyngeal clefts having number of outpocketings along the lateral wall of pharynx known as pharyngeal pouches. Pharyngeal arches form not only the neck structures but also play quintessential role in the formation of face. Approximately in the mid of 2nd month of gestation five

mesenchymal elevations named as mandibular, maxillary, frontonasal, lateral nasal and medial nasal appear which differentiate to form different regions of the face.

PHARYNGEAL ARCHES:

There are six pharyngeal arches however, the 5th one regresses soon after its formation. Its development begins early in the 4th week of gestation from the neural crest cells. Each arch

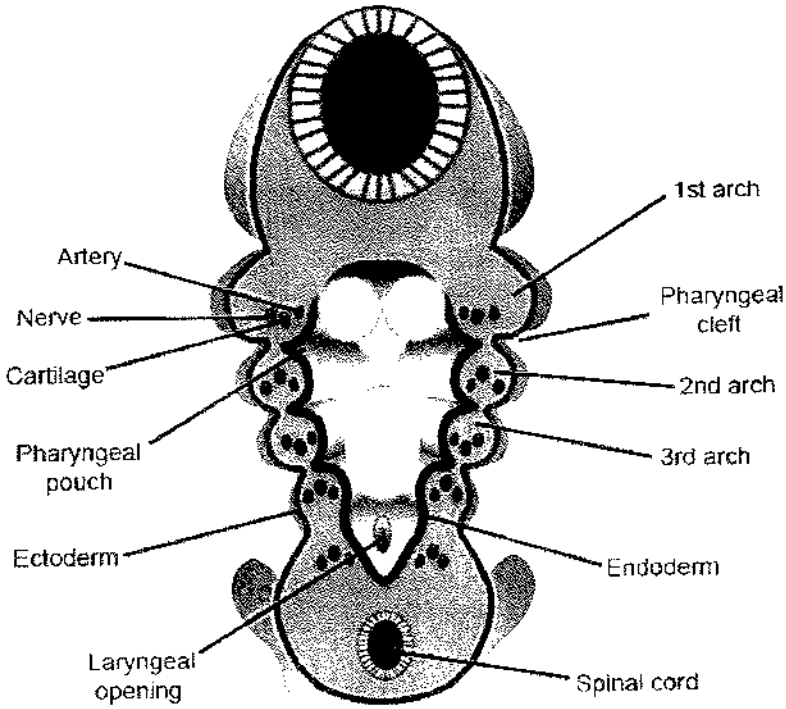


Fig 9.1: Pharyngeal arches

is innervated by an arch-specific cranial nerve and has a muscular component, a skeletal and cartilaginous supporting element as well as a vascular component. In the adult, each pharyngeal arch is associated with specific structures within the head and neck.

FIRST PHARYNGEAL ARCH:

The first pharyngeal arch consists of two parts:

Maxillary prominence: It is dorsal portion of the 1st pharyngeal arch that becomes the future maxilla, zygomatic bone and part of the temporal bone. It is also associated with the maxillary cartilage, which gives rise to the incus.

Mandibular prominence: It is ventral portion of the 1st pharyngeal arch that becomes the future mandible. It is associated with Meckel's cartilage, which gives rise to the malleus and the sphenomandibular ligament.

- ✓ The artery of the first pharyngeal arch becomes the terminal portion of the maxillary artery, which is a branch of the external carotid.
- ✓ The nerve associated with the 1st pharyngeal arch is the fifth cranial nerve known as trigeminal nerve. The first arch gives rise to the muscles of mastication and the mylohyoid, anterior belly of digastric, tensor veli palatani and tensor tympani and all of which are innervated by the branches of the trigeminal nerve.
- ✓ Its sensory field is that of the trigeminal nerve too, namely the skin of the face, the lining of the mouth and nose, and general sensation to the anterior two thirds of the tongue.

SECOND PHARYNGEAL ARCH:

- ✓ Reichart's cartilage is the precursor to the stapes, the styloid process, the stylohyoid ligament and the upper body and lesser horn of the hyoid bone.
- ✓ There are two arteries associated with the second pharyngeal arch:
  - Stapedial artery which connects the embryonic precursors of the internal carotid, internal maxillary and middle meningeal arteries. It regresses before birth.
  - Hyoid artery which gives rise to the corticotympanic artery in the adult.
- ✓ The nerve associated with the second pharyngeal arch is the facial nerve (CN VII). It innervates all the muscular derivatives of the 2nd arch – the muscles of facial expression, stapedius, stylohyoid, platysma and the posterior belly of digastric.
- ✓ The sensory field of the second arch is that of the facial nerve, namely taste sensation to the anterior two thirds of the tongue via the chorda tympani.

THIRD PHARNGEAL ARCH:

- ✓ Its cartilaginous component is less complex than the first two arches and gives rise to only the lower body and greater horn of the hyoid.
- ✓ The artery of the third pharyngeal arch becomes the common carotid artery and the proximal portion of the internal carotid artery.
- ✓ The nerve associated with the 3rd pharyngeal arch cranial nerve is the glossopharyngeal nerve (CN IX).
- ✓ The third arch gives rise to stylopharyngeus, and its sensory function is to provide taste and general sensation to the posterior one third of the tongue.

FOURTH PHARYNGEAL ARCH:

- ✓ The derivatives of fourth pharyngeal arch gives rise to laryngeal cartilages named as the thyroid, corniculate and cuneiform cartilages.
- ✓ The vascular derivatives of the fourth pharyngeal arch differ between the left and right:
  - Right – proximal portion of the subclavian artery
  - Left – aortic arch
- ✓ The nerve associated with the fourth pharyngeal arch is the superior laryngeal branch of the vagus nerve (CN X), which innervates the muscular derivatives of the fourth arch; the constrictors of the pharynx, levator palatani and cricothyroid.
- ✓ Innervation to the root of the tongue is provided by the superior laryngeal branch.

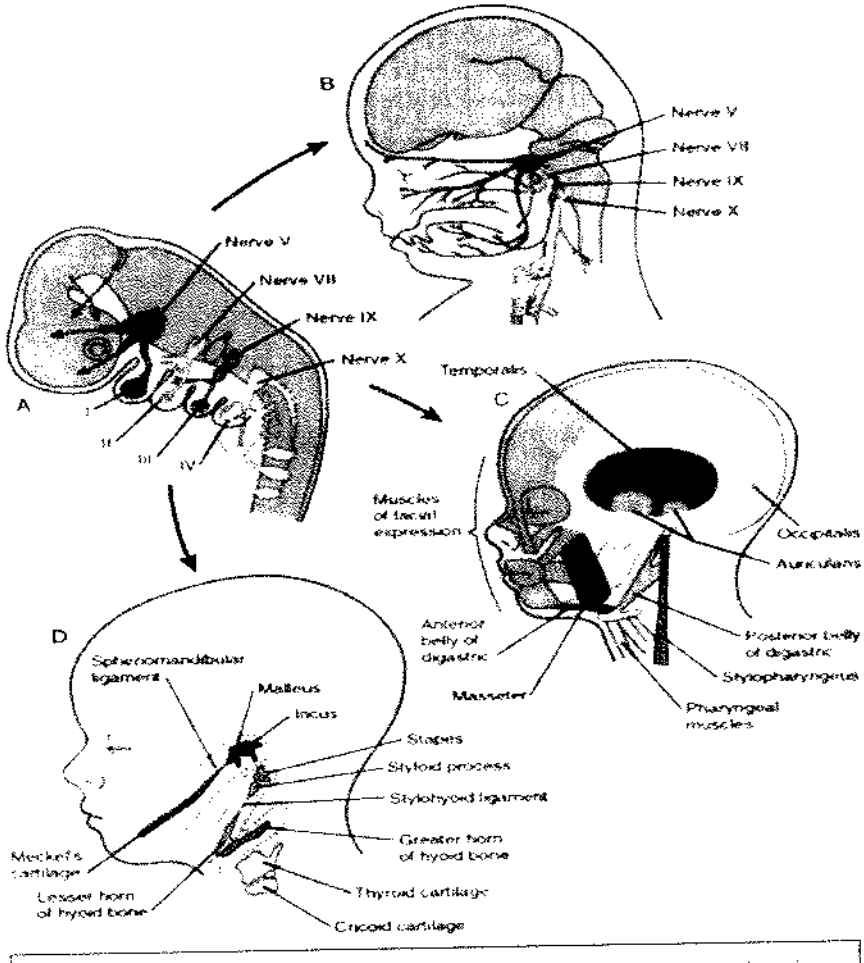
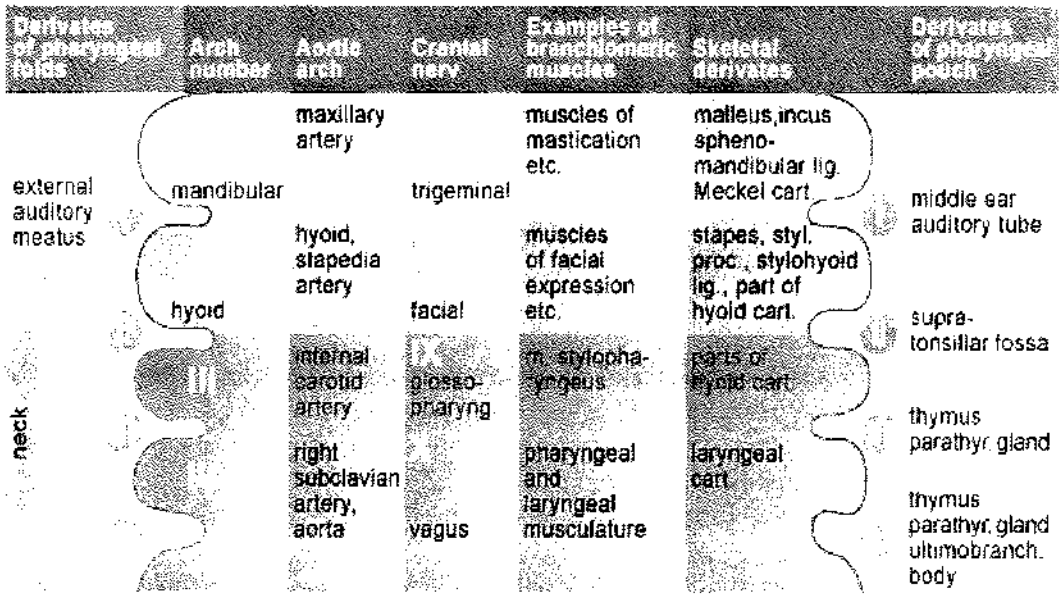


Fig 9.1: Diagram showing different components of pharyngeal arches.

SIXTH PHARYNGEAL ARCH:

- ✓ The vascular derivatives of the sixth pharyngeal arch differ between the left and right:
  - Right – proximal portion of the pulmonary arteries
  - Left – ductus arteriosus
- ✓ The nerve associated with the 6th pharyngeal arch is the recurrent laryngeal branch of the vagus nerve (CN X). It innervates the intrinsic muscles of the larynx (with the exception of cricothyroid), which are derived from the sixth arch.
- ✓ The sensory field of the recurrent laryngeal branch is widespread. It includes taste sensation from the epiglottis and pharynx, general sensation in the pharynx, larynx, esophagus, tympanic membrane, external auditory meatus and part of the external ear. It also provides the efferent limb of the gag reflex, and parasympathetic innervation to viscera.



PHARYNGEAL POUCHES

The development of pharyngeal pouches take place between the pharyngeal arches in the craniocaudal direction. The first pair of pouch lies between the first and second pharyngeal cleft. Four pairs of pharyngeal pouches are well defined in development however the fifth one is formed as rudimentary if it is present. Pharyngeal pouches are demarcated from the pharyngeal clefts by the pharyngeal membranes which is formed by approximation of endoderm and ectoderm of pouches and clefts respectively.

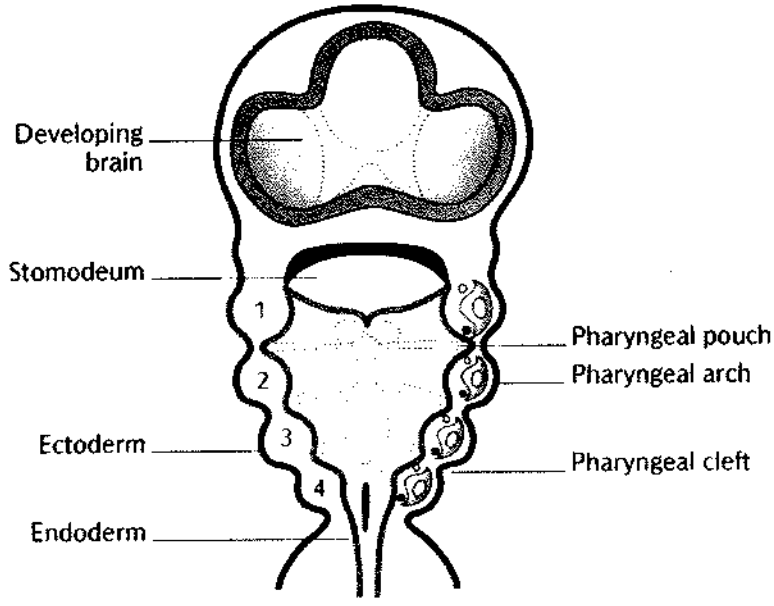


Fig 9.3: Pharyngeal arches and pouches

DERIVATIVES OF PHARYNGEAL POUCHES:

Following are given the important derivatives of the respective pouches which are formed from the ectodermal epithelial lining.

FIRST PHARYNGEAL POUCH:

The expansion and lengthening of the first pharyngeal pouch forms the elongated structure known as tubotympanic recess.

- ✓ The distal part of the tubotympanic recess interacted with the first pharyngeal cleft to form the tympanic membrane.
- ✓ The lumen of the tubotympanic recess modifies into the tympanic cavity and mastoid antrum.
- ✓ However the part of tubotympanic recess which serves as connecting link with the pharynx steadily elongates to become the pharyngotymanic tube.

SECOND PHARYNGEAL POUCH:

The proliferation of the second pharyngeal pouch gives rise to various outgrowths that invade into the surrounding mesenchyme. Afterwards these outgrowths are also penetrated by the mesodermal tissues, consequently forming the primordia for palatine tonsils. However, during the latter weeks these tonsils are infiltrated by lymphatic tissue which soon organizes into the lymphatic nodules of palatine tonsil. Part of it persists during the adult life which is known as tonsilar fossa.

THIRD PHARYNGEAL POUCH:

The development of the 3rd pharyngeal pouch results into a solid, dorsal, bulbar part and a hollow elongated ventral part. The connection of 3rd pouch with the pharynx is reduced during the 2nd month of development.

The epithelium of the dorsal bulbar part soon starts proliferation and differentiate to gives rise to the inferior parathyroid glands.

The ventral hollow part obliterates to form the cavity and comes in the midline orientation to form the thymus gland.

The developing thymus and inferior parathyroid glands lose their connection with the pharynx when brain and associated structures begin to expand rostrally while pharynx and cardiac structures grow caudally. Later on parathyroid glands separate from the thymus and lie on the dorsal surface of thyroid gland.

FOURTH PHARYNGEAL POUCH:

The proliferated epithelium of the dorsal region of the 4th pharyngeal pouch forms the superior parathyroid gland. It remains static when other parts of parathyroid gland loses its connection to the pharynx.

The ventral part of the 4th pharyngeal pouch gives rise to the ultimobranchial body that later on projected into the thyroid gland. Cells of this body forms the parafollicular cells that is also known as C cells which secretes calcitonin- a hormone for calcium regulation in the blood.

Pouch	Derivatives
1st	Eustachian tube and middle ear cavity
2nd	Lining of the palatine tonsils
3rd	• Dorsal – Inferior parathyroid glands • Ventral – Thymus
4th	• Dorsal – Superior parathyroid glands • Ventral – Ultimobranchial body (C cells)

PHARYNGEAL CLEFT:

There are four pharyngeal clefts which appear early in the 2nd month of development and the first of them is manifested in the formation of external auditory meatus however others are congregate with the second pharyngeal arch.

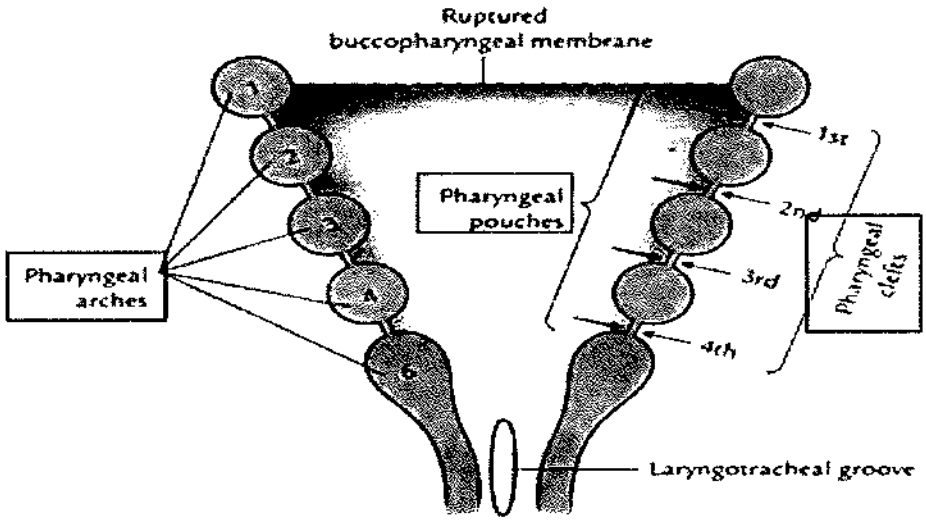


Fig 9.4: Pharyngeal clefts

PHARYNGEAL MEMBRANE:

Pharyngeal membrane is double layered structure which is formed during the 4th week of gestation. It appears beneath the pharyngeal clefts on each side of the neck region of the developing embryo. Only the 1st pharyngeal membrane derives the adult structure that is the tympanic membrane while other becomes regressed.

THE DEVELOPMENT OF THROID GLAND:

The development of thyroid gland begins as median endodermal thickening in the floor of the primordial pharynx. This thickening later on forms a small outpocketings known as the thyroid primordium. With the growth of tongue it travels in the neck in downward direction, passing anterior to the developing hyoid bone and laryngeal cartilages; for this time it is connected to the thyroglossal duct. Initially the thyroid gland is a hollow structure but with the passage of time it becomes solid and divided into two lobes connected by isthmus. Later on the solid cellular aggregation splits into a network of epithelial cords as it is invaded by the surrounding vascular mesenchyme. The lumen soon forms cluster of cells which in turn modifies into the thyroid follicles. By the 11th week formation of colloidal substance starts to appear into the follicle however it becomes fully functional by secreting thyroid stimulating hormone and thyroxin till the 35th week of development.

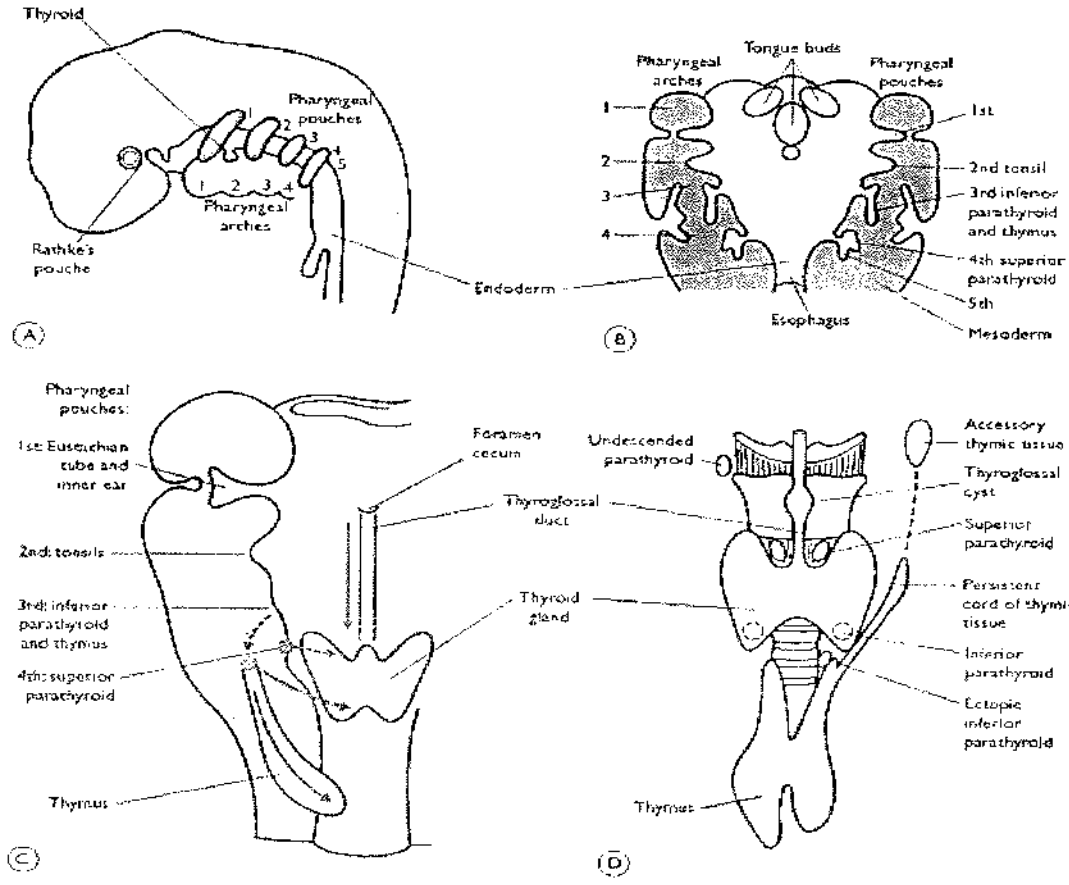


Fig 9.5: The development of thyroid gland.

EMBRYOLOGICAL TID BITS!
The thyroid gland is the first endocrine gland to develop in the embryo.

THE DEVELOPMENT OF MOUTH:

The development of bucal cavity is dual in origin. Initially a surface depression is formed from the ectoderm known as stomodaeum however the cephalic part of the gut is endodermally lined. Both these are separated by buccopharyngeal membrane. It ruptures during the 4th week of development. The structures which lies anterior to the opening of mouth are formed by the ectoderm and those which lies posteriorly are derived from the endoderm.

DEVELOPMENT OF SALIVARY GLANDS:

The salivary glands arise as epithelial buds in the oral cavity between weeks 6 to 7 and extend into the underlying mesenchyme. The adult glands are mucoserous tubuloacinar glands, with secretory acini and the initial part of the duct system also participates in the secretory process.

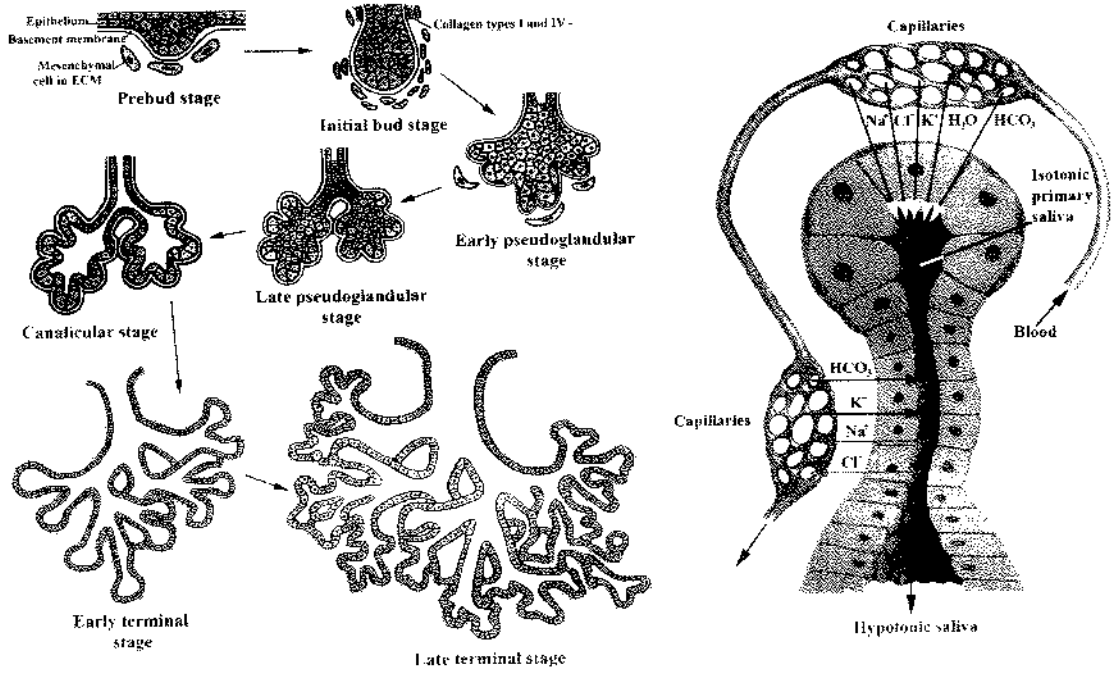


Fig 9.7: The development of salivary gland.

1. THE PAROTID GLAND:

The development of parotid glands begin as outgrowth arising from the oral ectoderm near the angle of stomodaeum at 6th week. The outgrowth grows toward the ears as solid cords but later on these cords undergoes the process of canalization and forms the duct. The connective tissues and capsules are also developed from the surrounding mesenchyme and commences at about 18th week of development.

2. SUBMANDIBULAR GLAND:

The development of submandibular gland begins as the endodermal outgrowth from the floor of stomodaeum. Afterwards, during the 12th week of development acini starts to appear which later during the later weeks start to secrete its secretion.

3. SUBLINGUAL GLAND:

It develops from the multiple epithelial cells of endodermal origin.

THE DEVELOPMENT OF FACE:

During the 3rd week of embryonic development, an oropharyngeal membrane initially appears at the site of the future face. It is comprised of ectoderm and endoderm – externally and internally, respectively.

During the 4th week, the oropharyngeal membrane begins to break down in order to become the future oral cavity, and sits at the beginning of the digestive tract.

The structures of the external face are derived from two sources:

- Frontonasal prominence: It is formed by the proliferation of mesenchymal neural crest cells ventral to the forebrain.
- Mandibular and maxillary prominences: The parts of the 1st pharyngeal arch.

A space lies between the maxillary prominences, covered by the oropharyngeal membrane; this is known as the stomodaeum, the precursor to the mouth and pituitary gland.

Frontonasal prominence: Nasal development is instigated by the appearance of raised bumps called nasal placodes on both sides of the frontonasal prominence. These then invaginates to form nasal pits, with medial and lateral nasal prominences on either side. As the maxillary prominences expand medially, the nasal prominences are 'pushed' closer to the midline. The maxillary prominences then fuse with the nasal prominences – and soon after fuse in the midline to form a continuous central structure.

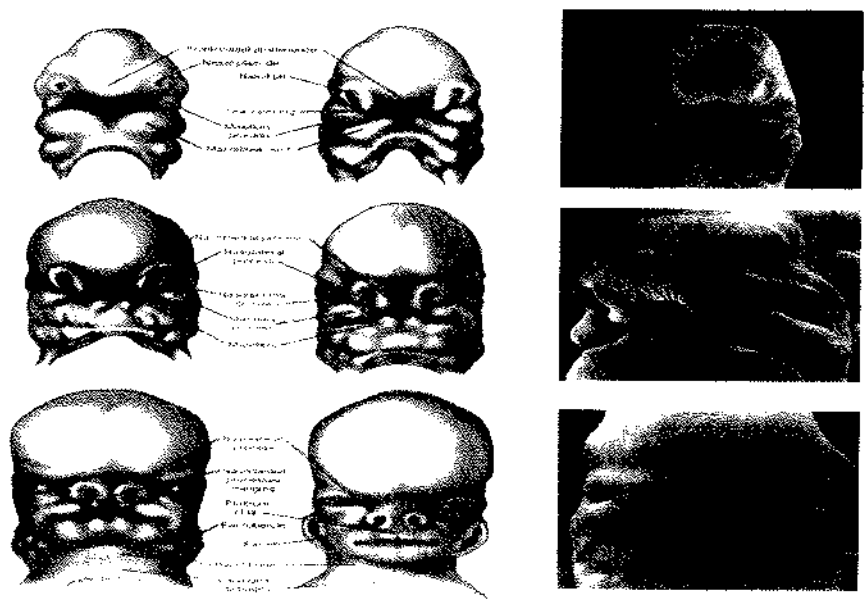


Fig 9.7: The development of face.

THE DEVELOPMENT OF TONGUE:

The development of tongue begins in the 4th week of gestation. It is derived from pharyngeal arches 1-4 (forms the mucosa of the tongue) and the occipital somites (forms the musculature of the tongue).

In the first stage of development, lingual and medial swellings appear:

Lateral lingual swellings: - It is derived from the 1st pharyngeal arch. Contributes to the mucosa of the anterior two thirds of the tongue.

Medial swellings:

Tuberculum impar: It is derived from the 1st pharyngeal arch. Contributes to the mucosa of the anterior two thirds of the tongue.

Cupola (hypobranchial eminence): It is derived from the 2nd, 3rd and 4th pharyngeal arches. Forms the mucosa of the posterior one third of the tongue.

Epiglottal swelling. It is derived from the 4th pharyngeal arch. Forms the epiglottis.

During the 4th week, the lateral lingual swellings overgrow the tuberculum impar and merge together - forming the mucosa of the anterior two thirds of the tongue. Their line of fusion is marked by the median sulcus of the tongue.

Within the cupola, the 3rd pharyngeal arch component overgrows the 2nd arch, and forms the mucosa of the posterior 1/3 of the tongue. The anterior two thirds and posterior one third fuse - forming a V shaped groove known as the terminal sulcus. At the center of this groove is the foramen cecum, a pit which represents the place of origin of the thyroid gland.

As the tongue forms, it is initially is tethered to the floor of the oral cavity. A process of carefully programmed cell death known as sculpting apoptosis releases the tongue, leaving in place the lingual frenulum to anchor the tongue in the mouth.

The intrinsic and extrinsic muscles of the tongue are derived from occipital somites, which are segments of mesoderm in the region of the upper neck. The somites migrate from the neck anteriorly to give rise to the muscles of the tongue.

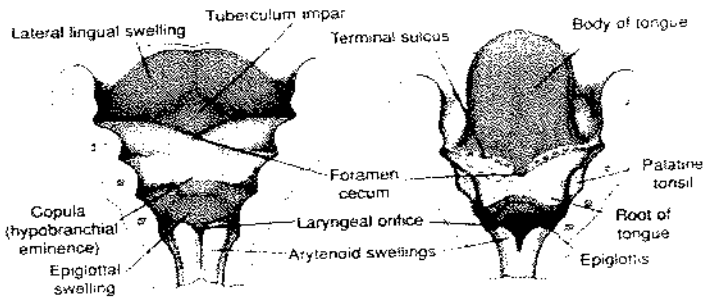


Fig 9.8: The development of tongue.

DEVELOPMENT OF INTERMAXILLARY SEGMENT:

It is formed by the merging of two medial nasal prominences in the midline. This is composed of;

1. Philtrum
2. Upper jaw compartment
3. Palatal component.

DEVELOPMENT OF LIPS:

The upper lip is formed by the approximation of maxillary process with the medial nasal process.

The lower lip is formed by the mandibular process which grows medially inferior to the stomodaeum and merging into the midline orientation to form the entire lower lip.

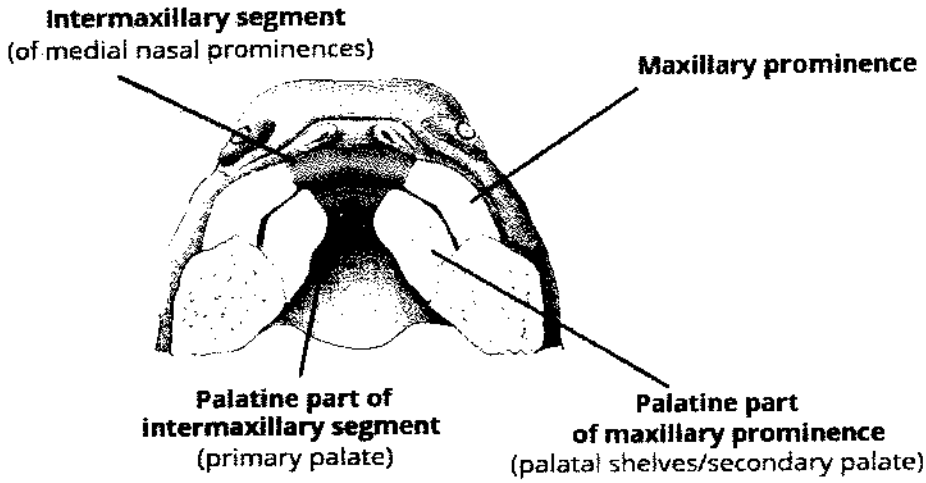
Prominence	Derivatives
Frontonasal	Forehead, bridge of nose, medial and lateral nasal prominences
Medial nasal	Philtrum, primary palate, upper 4 incisors and associated jaw
Lateral nasal	Sides of the nose
Maxillary (1st pharyngeal arch)	Cheeks, lateral upper lip, secondary palate, lateral upper jaw
Mandibular (1st pharyngeal arch)	Lower lip and jaw

DEVELOPMENT OF THE PALATE:

Initially, the nasal cavity is continuous with the oral cavity. A series of steps lead to their separation, and the establishment of the palate.

As the nose forms, the fusion of the medial nasal prominence with its contralateral counterpart creates the intermaxillary segment – which forms the primary palate (becomes the anterior one third of the definitive palate). The intermaxillary segment also contributes to the labial component of the philtrum and the upper four incisors.

The maxillary prominences expand medially to give rise to the palatal shelves. These continue to advance medially, fusing superior to the tongue. Simultaneously, the developing mandible expands to increase the size of the oral cavity; this allows the tongue to drop out of the way of the growing palatal shelves. The palatal shelves then fuse with each other in the horizontal plane, and the nasal septum in the vertical plane, forming the secondary palate.



DEVELOPMENT OF NASAL CAVITIES:

The development of nasal cavities is formed by the nasal placodes which appear during the 6th week of gestation. These nasal placodes invades to form the nasal pits and later on it modifies to form the nasal sacs. Concomitantly, the proliferation of the surrounding mesenchyme forms the medial and lateral prominences that later on separated by the oronasal membrane. However, the presumptive conchae is formed by the approximation of oral and nasal cavities. Moreover the budding in the lateral wall of nasal cavity forms the various conchae known as superior, middle and inferior.

DEVELOPMENT OF NOSE:

Nose is developed by the three prominences named as frontonasal, medial and lateral nasal prominences respectively which form the bridge of nose, crest and tip of nose and alae of the nose.

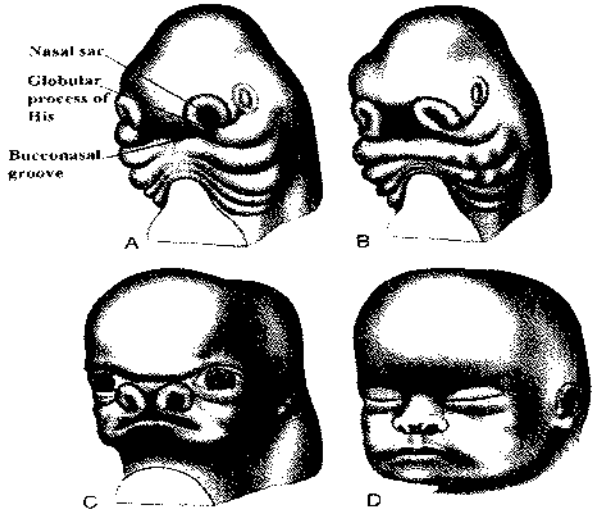


Fig 9.3: The development of nose.

however, they do not follow the appropriate path and end up in other areas of the neck and/or chest. This is known as ectopic parathyroid gland.

7. ECTOPIC THHYROID GLAND:

It is defined as any thyroid tissue not located in its usual position (i.e., anterior and lateral to the second, third, and fourth tracheal rings). During development, the thyroid gland descends from the foramen cecum at the base of the tongue to its location at the front of the trachea.

8. THYROGLOSSAL DUCT CYSTS:

It is a fluid-filled pocket in the front of the neck, just above the voice box. The cyst forms in tissue that is sometimes left over from the development of the thyroid gland. Thyroglossal cysts are present at birth and often occur in children.

9. CONGENITAL HYPOTHYROIDISM:

It is thyroid hormone deficiency present at birth. If untreated for several months after birth, severe congenital hypothyroidism can lead to growth failure and permanent intellectual disability.

10. ANKYLOGLOSSIA:

It is a condition in which an unusually short, thick or tight band of tissue (lingual frenulum) tethers the bottom of the tongue's tip to the floor of the mouth. If necessary, tongue-tie can be treated with a surgical cut to release the frenulum.

11. MICROGLOSSIA:

It is an abnormal smallness of the tongue.

12. MACROGLOSSIA:

Macroglossia is the medical term for an unusually large tongue. Severe enlargement of the tongue can cause cosmetic and functional difficulties in speaking, eating, swallowing and sleeping. Macroglossia is uncommon, and usually occurs in children.

13. GLOSSOSCHISIS:

It is a tongue with a groove or split running lengthwise along the tip of the tongue. It is the result of incomplete fusion of the distal tongue buds. A bifid tongue may be an isolated deformity and has also been reported to be associated with maternal diabetes.

14. ATRESIA OF THE NASOLACRIMAL DUCT:

It is obstruction, or dacryostenosis, occurs when the lacrimal duct has failed to open at the time of birth, most often due to an imperforate membrane at the valve of Hasner. Lacrimal sac massage has been proposed as helping to open the duct, though this is not always successful.

DEVELOPMENTAL ABNORMALITIES RELATED WITH HEAD AND NECK REGION:

1. FIRST PHARYNGEAL ARCH SYNDROME:

First arch syndromes are congenital defects caused by a failure of neural crest cells to migrate into the first pharyngeal arch. They can produce facial anomalies.

1a. TEACHER COLLINS SYNDROME:

It is a type of fist pharyngeal arch syndrome occurs due to genetic manifestations characterized by deformities of the ears, eyes, cheekbones, and chin. The degree to which a person is affected, however, may vary from mild to severe. Complications may include breathing problems, problems seeing, cleft palate, and hearing loss.

1b. PIERRE ROBIN SYNDROME:

It is a condition in which an infant has a smaller than normal lower jaw, a tongue that falls back in the throat, and difficult breathing. It is present at birth.

2. DIGEORGE SYNDROME:

It is caused by the deletion of a small segment of chromosome 22. While the symptoms can vary, they often include congenital heart problems, specific facial features, frequent infections, developmental delay, learning problems and cleft palate.

3. GOLDENHAR SYNDROME:

It is a rare congenital condition characterized by abnormal development of the eye, ear and spine. Also known as oculo-auricular-vertebral spectrum or OAV, Goldenhar syndrome was first documented in 1952 by Maurice Goldenhar, an ophthalmologist and general practitioner.

4. RANULA:

A ranula is a fluid collection or cyst that forms in the mouth under the tongue. It is filled with saliva (spit) that has leaked out of a damaged salivary gland. Salivary glands are small structures around the mouth which make saliva.

5. ACCESSORY THYMIC TISSUE:

Accessory thymic tissue may occur anywhere along the path of descent (thymopharyngeal duct) as the result of failure of descent, sequestration, or failure to involute. It may be found in the vicinity of the superior vena cava, brachiocephalic vessels, and aorta.

6. ECTOPIC PARATHYROID GLAND:

When a baby is developing in the womb, the four small parathyroid glands move from the head down to the neck during different stages of fetal development. Sometimes,

15. CONGEITAL PREAURICULAR SINUSES:

Preauricular sinus is a common birth defect that may be seen during a routine exam of a newborn. It generally appears as a tiny skin-lined hole or pit, often just in front of the upper ear where the cartilage of the ear rim meets the face. It may occur on one side (unilateral) or both sides (bilateral) of the ear.

16. CLEFT PALATE:

It is an opening or split in the roof of the mouth that occurs when the tissue doesn't fuse together during development in the womb. A cleft palate often includes a split (cleft) in the upper lip (cleft lip) but can occur without affecting the lip.

17. CONGENITAL MICROSTOMIA:

It is the term used to describe a congenital reduction in the size of the oral aperture that is severe enough to compromise cosmesis, nutrition, and quality of life.

18. FACIAL CLEFTS:

It is an opening or gap in the face, or a malformation of a part of the face. Facial clefts is a collective term for all sorts of clefts. All structures like bone, soft tissue, skin etc. can be affected. Facial clefts are extremely rare congenital anomalies.

19. VANDER WOUDE SYNDROME:

It is a genetic form of cleft lip and palate. Baby born with this syndrome have a gap in lip (cleft lip) or the roof of their mouth (cleft palate) or both. Small mounds of tissue or pits on lower lip are also present.

KEY NOTES!
a- This chapter deals with the formation of pharyngeal apparatus, structures of the neck and head. The remarkable event of development regarding this chapter is the development of pharyngeal arches which gives various structures of head and neck. In addition to this pharyngeal clefts and pouches also forms various structures.
b- Regarding the development of face which is developed from the five prominences named as maxillary, mandibular, frontonasal and nasal.
c- Thyroid gland originates from the epithelial proliferation in the floor of the tongue.
d- There are various developmental anomalies associated with the head and neck region development like first pharyngeal arch syndrome, cleft palate, digeorge syndrome etc.

10

THE DEVELOPMENT OF RESPIRATORY SYSTEM

LEARNING OBJECTIVES

- GENERAL INTRODUCTION OF THE DEVELOPMENT OF RESPIRATORY SYSTEM
- THE FORMATION OF PRIMIITIVE RESPIRATORY STRUCTURES
- THE DEVELOPMENT OF LARYNXX
- THE DEVELOPMENT OF TRACHEA
- THE DEVELOPMENT OF BRONCHI AND LUNGS
- MATURATION OF LUNGS
- ABNORMALITIES RELATED WITH THE DEVELOPMENT OF RESPIRATORY SYSTEM
- KEY NOTES

The respiratory system comprises of the upper respiratory organs and the lower respiratory organs. Upper respiratory organs have been discussed in the head and neck section. Lower respiratory organs (larynx, trachea, bronchi, and lungs) are discussed here.

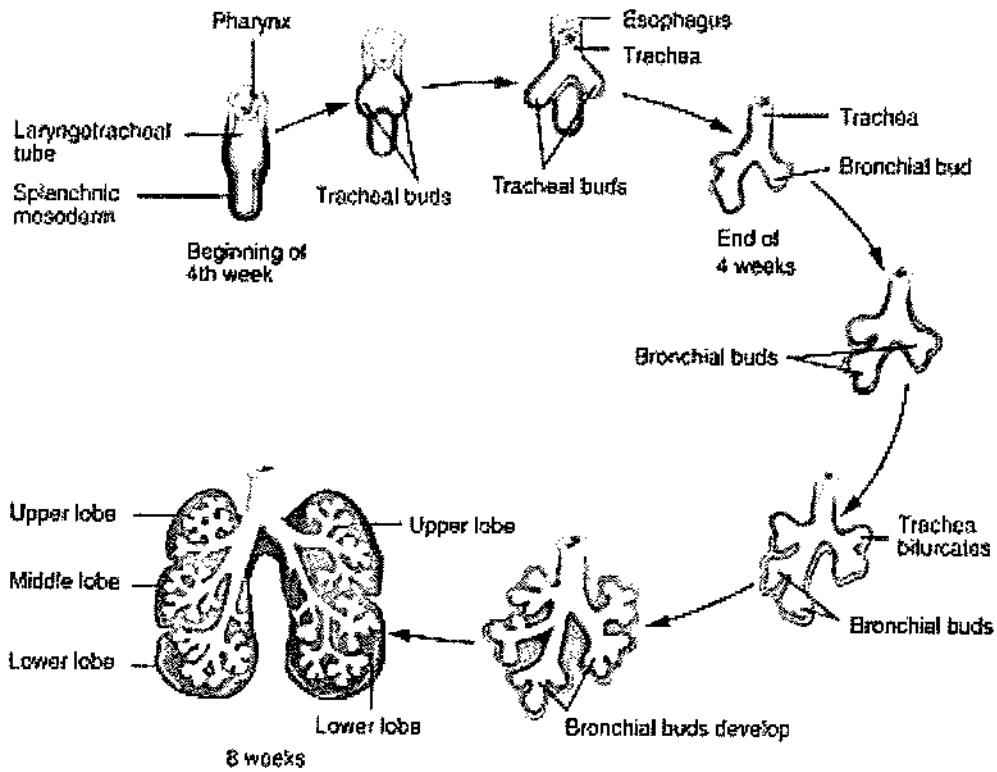


Fig 10.1 The development of respiratory system.

THE FORMATION OF PRIMITIVE RESPIRATORY STRUCTURES:

- ✓ The development of respiratory system commences at about the 3rd week of gestation as a median respiratory bud known as laryngotracheal groove which become visible at the caudal portion of ventral foregut. Meanwhile, the portion of pharynx caudal to fourth pair of pharyngeal pouches develops into tracheobronchial tree.
- ✓ The pulmonary epithelium and glands of the various lower respiratory organs are formed by endodermal lining of the laryngotracheal groove. However, the splanchnic mesoderm surrounding the foregut give rise to the other structures like smooth muscles, cartilaginous structures and connective tissues.

- ✓ At the age of the 4th week of gestation a budding structure protruded from the ventral wall of foregut which is known as "RESPIRATORY DIVERTICULUM". As respiratory diverticulum lengthens, it is invested by surrounding splanchnic mesoderm that soon differentiate to give rise to the frame work to developing respiratory system. In addition to this, the internal lining of the lower respiratory organs such as larynx, trachea, bronchi and the lungs is formed by endoderm.

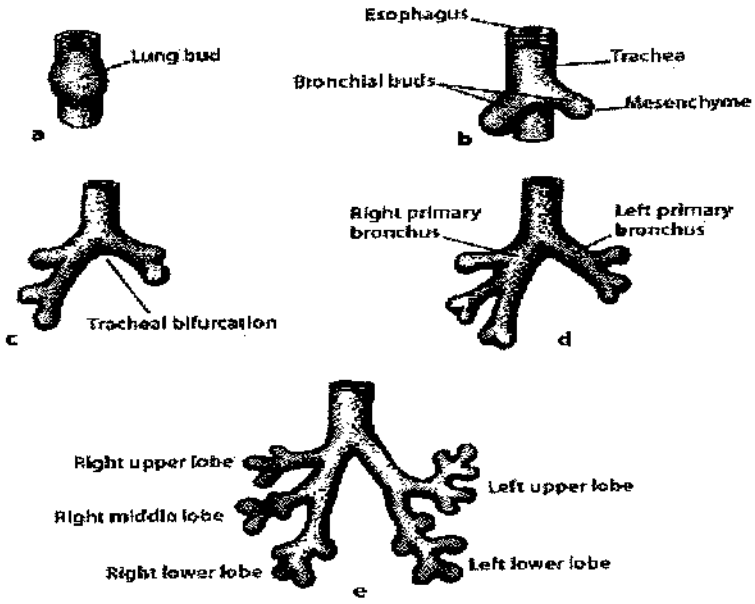


Fig 10 2: Primitive respiratory development.

- ✓ The respiratory diverticulum elongates in the caudal direction, albeit it is separated from the foregut by the formation of longitudinal ridges that is known as tracheoesophageal ridges. These tracheoesophageal ridges soon approximated to form a septum called as tracheoesophageal septum, this in turn partitions the foregut into ventrally lying

laryngotracheal tube and dorsally lying oesophagus. The laryngotracheal tube is the primodia for the formation of lower respiratory organs.

The laryngeal inlet is formed by the opening of laryngotracheal tube which opens into the pharynx.

THE DEVELOPMENT OF LARYNX:

- ✓ Development of the larynx consist of the formation of epithelial lining of the larynx, the cartilages of the larynx, structures associated with the larynx and the muscles of the larynx.
- ✓ Regarding the epithelial lining of the larynx, it develops from the endoderm of the cranial portion of the laryngotracheal tube.
- ✓ Regarding the cartilages of the larynx, generally it develops from the fourth and sixth pairs of pharyngeal pouches however it is mesenchymal in origin as it derived from the neural crest cells.
- ✓ Regarding structures associated with the larynx;

1. The arytenoid swellings: The mesenchyme of the cranial portion of laryngotracheal tube proliferates to form the arytenoid swellings.

2. Laryngeal inlet: The arytenoid swellings grow toward the tongue, converting slit like orifice, the primordial glottis into laryngeal inlet.

3. Vocal folds: The laryngeal epithelium proliferates promptly and occlude the laryngeal lumen. By the 10th week recanalization occurs which results into the formation of laryngeal ventricles. These ventricles are bounded by the folds of mucous membrane that become the vocal cords or vestibular folds.

4. Epiglottis: It develops from the caudal end of hypopharyngeal eminence, it is a prominence that is produced by proliferation of mesenchyme in the ventral ends of 3th and 4th pharyngeal arches.

   - ✓ Regarding the development of laryngeal muscles, it develops from the myoblast in the 4th and 6th pairs of pharyngeal arches. Laryngeal muscles are supplied by laryngeal branches of vagus nerve.

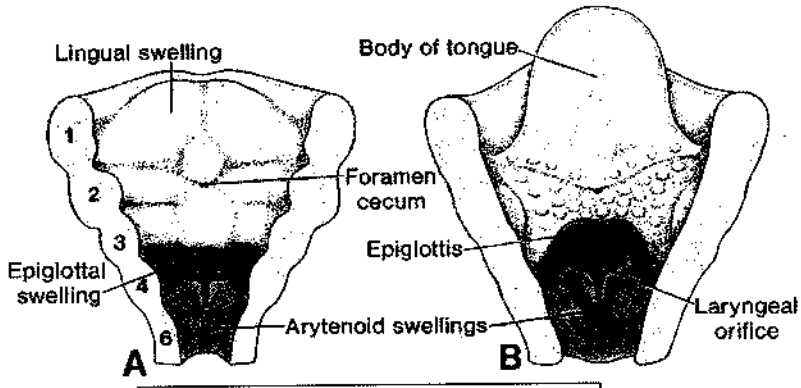


Fig 10.3 The development of larynx

THE DEVELOPMENT OF TRACHEA:

- ✓ Trachea is formed during the separation of foregut into ventrally lying trachea and dorsally lying oesophagus by tracheoesophagal septum.
- ✓ The epithelial lining and glands of trachea develop from the endoderm of the caudal end of the laryngotracheal tube.
- ✓ The formation of the cartilage, connective tissue and muscle of the trachea takes place from the splanchnic mesenchyme of the surrounding laryngotracheal tube.

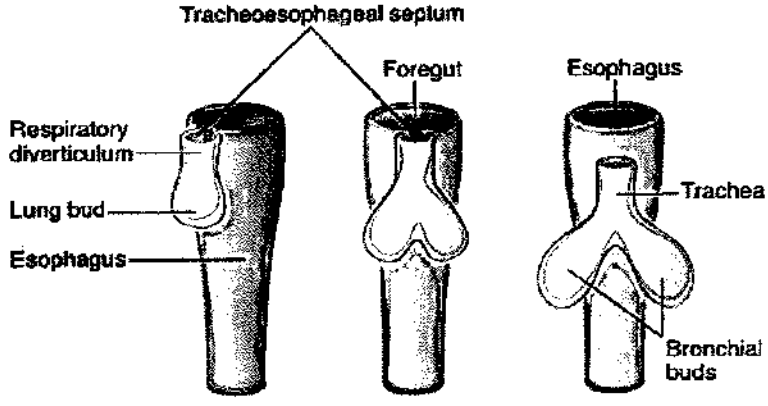


Fig 10.4 The development of trachea.

THE DEVELOPMENT OF BRONCHI AND LUNGS:

- ✓ During the 4th week of gestation, respiratory bud appears the caudal end of tracheoesophageal diverticulum which soon proliferates to form to outpocketings that are known as primary bronchial buds. These primary bronchial buds have propensity to

expand laterally into the primordia of the pleural cavity where they will differentiate into secondary and tertiary buds.

- ✓ During the early 5th week, mesenchyme along with buds differentiae into bronchi and having there ramifications into the lungs. Consequently, the enlargement of trachea forms the connection with bronchial buds and form the primordia for main bronchi. The right main bronchi is slightly larger than the left one and its vertical orientation explain the prominent occurrence of infection in right lung.
- ✓ Later on the main bronchi subdivide into secondary, lobar, segmental and intersegmental branches. In the right lung, the superior lobar bronchus divides to supply upper and median lobe while inferior bronchus supply to inferior lobe. On the other hand, left lung is supplied by two bronchi to their respective upper and lower lobes.
- ✓ As the bronchi develops cartilaginous plate develops from the associated splanchnic mesenchyme.

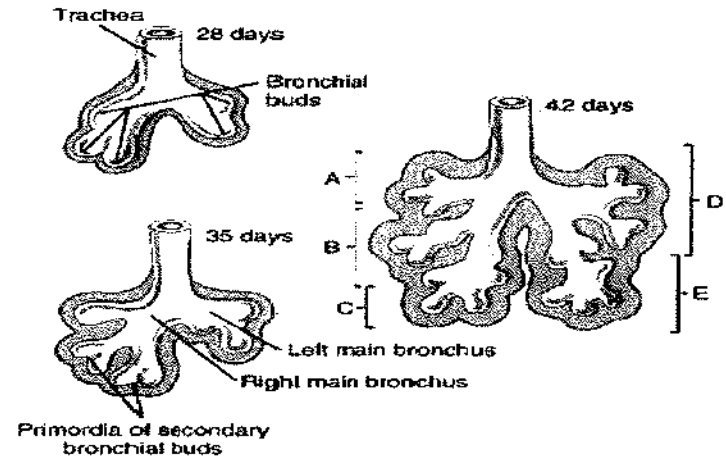


Fig 10.5 The development of bronchi and lungs.

- ✓ Regarding the connective tissue, cartilages and smooth muscles of the bronchi and lungs, it develops from the differentiation of the splanchnic mesenchyme. In addition to this, visceral pleura also formed from it while thoracic body wall becomes the parietal pleura.

EMBRYOLOGICAL TID BITS!
There are 10 segmental bronchi in the right lung while 8 in the left lung.

MATURATION OF LUNGS:

On the basis of histologic changes maturation of lungs have been classified into four phases;

- THE PSEUDOGLADULAR PHASE: (5^{th} – 16^{th} week)
  - ✓ It is the phase during which rapid branching of the bronchi occurs and subsequently the formation of bronchioles take place. This phase is named so because in which pulmonary structures has exocrine glands like appearance. Physiologically, respiration cannot takes place during this phase. Therefore, child born during this phase has immature pulmonary system and cannot survive

- THE CANALICULAR PHASE:(16^{th} – 25^{th} week)
  - ✓ This is the phase during which terminal bronchioles divide to form respiratory bronchioles along with alveolar ducts.
  - ✓ Internal lining is of cuboidal variety.
  - ✓ Respiration is possible at the end of this phase because of terminal sacs and well vascularization. Still there are high chances of the death of neonate in this period if intensive care is not provided.

- THE TERMINAL SAC PHASE:(24th week to birth)
  - ✓ During this phase terminal sacs become fully saturated with squamous epithelial cells known as type 1 pneumocytes which forms blood air barrier and type 2 pneumocytes which form surfactant.
  - ✓ During this phase formation of the primitive alveoli takes place. Gaseous exchange is possible in primitive alveoli.

- THE ALVEOLAR PHASE:(29th week- 10 years of age)
  - ✓ During this phase there is the increase in the size of lungs and functionality of the pneumocytes. Pulmonary maturation continues after birth until ten years.
  - ✓ Terminal sacs develop into mature ducts and alveoli.

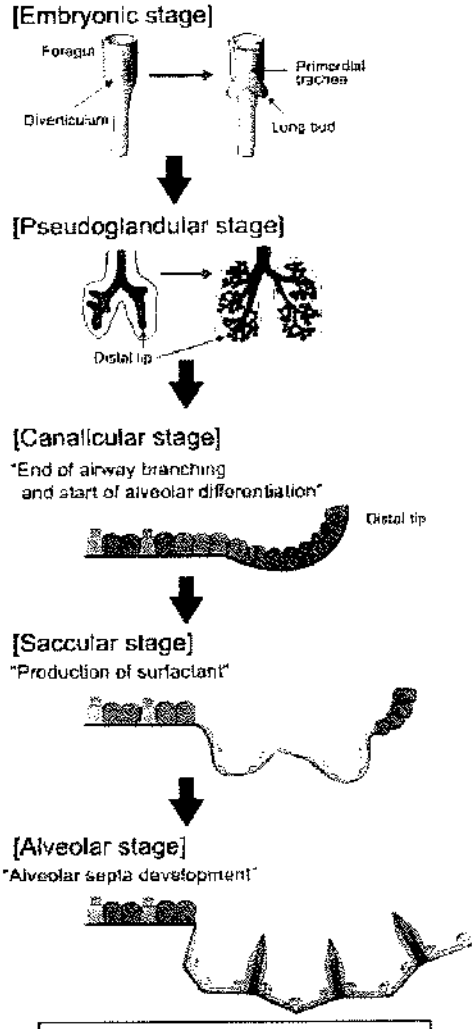


Fig 10.6: Maturation of lungs.

ABNORMALITIES OF RESPIRATORY SYSTEM:

For the sack of clear understanding abnormalities related with the genesis of respiratory system is classified as under;

- Abnormalities related with larynx
- Abnormalities related with trachea
- Abnormalities related with lungs.

ABNORMALITIES RELATED WITH LARYNX:

✓ LARYNGEAL ATRESIA: It is the obstruction of the laryngeal tube, rarely occurring birth defect. It occurs due to the failure of recanalization. If recanalization does not occur then there is obstruction in the upper air passage of the fetus, this condition is called as congenital airway obstruction syndrome. This obstruction in the airway may lead to ascites or hydrops.

✓ LARYNGEAL WEB: It is also a birth defect which is due to the incomplete recanalization of the laryngeal lumen. The incomplete recanalization leads to the covering of connective tissue between the vocal cards takes place by a mucous membrane. The diagnosis of this defect is neonate cry with the hoarse voice. Its management can be done by endoscopic dilation.

ABNORMALITIES RELATED WITH TRACHEA:

✓ TRACHEAL STENOSIS AND ATRESIA:

These disorders are of the minor occurrence however these are usually associated with the tracheoesophageal fistulas. These maybe due to unequal partioning of foregut into oesophagus and trachea or sometimes due to web tissue obstructing the airflow. Tracheal agenesis and atresia both are fetal.

✓ TRACHEOESOPHAGEAL FISTULA:

It is the abnormal passage between oesophagus and trachea mostly occurs in male infants. It is associated with the atresia that forms obstruction. In addition to the obstruction in the airflow commonly occurring disorder associated with tracheoesophageal fistula is polyhydramnios that is accumulation of amniotic fluid due to defective absorption.

ABNORMALITIES RELATED WITH LUNGS:

✓ OLIGOHYDRAMINOS INDUCED PULMONARY HYPOPLASIA.

The development of the lung tissues retarded when there is insufficient production of amniotic fluid or leakage of the amniotic fluid from the cavity. The mechanism behind the hypoplasia lungs is that whenever there is insufficient production of amniotic fluid

then there is the decrease hydraulic pressure which in turn causes low stretching of the receptor of lungs which later on affect the calcium regulation and growth of the lungs.

✓ RESPIRATORY DISTRESS SYNDROME:

Respiratory distress syndrome is the phenomena in which there is the laboured breathing. It is also known as hyaline membrane disease. The major cause of this disease is insufficient surfactant production which causes the lungs to underinflate and alveoli to contain protein rich fluid with hyaline appearance. Insufficient surfactant production comes out from the prolonged asphyxia in the intrauterine life that later on deteriorate the physiology of type tw alveolar cells.

✓ CONGENITAL LUNG CYSTS:

It is the abnormal fluid filled sac that is formed by the dilation of terminal sacs. Subsequently it results into the abnormal bronchial development.

✓ PULMONARY AGENSIS:

This occurs due to the failure of development of respiratory diverticulum. In unilateral pulmonary agenesis the lung is shifted to the opposite and the existing lung is hyperexpanded.

✓ ACCESSORY PULMOGENESIS:

An accessory pulmogenesis is the condition in which abnormal pulmonary sequestration takes place that is abnormal production of small accessory lung. It does not communicate with any lower respiratory structure. It has usually systemic blood flow.

KEY NOTES!
A- The development of respiratory system commences with the formation of respiratory diverticulum which soon elongates, modify and differentiate to give rise various structures of lower respiratory system. However, the muscles and cartilages of the most of the structures are formed by surrounding splanchnic mesenchyme while internal lining and glands are formed by endodermal cells.
B- Regarding abnormalities related the respiratory system; they have been classified according to the respective structures just for the sack of understanding. Laryngeal abnormalities include laryngeal atresia and laryngeal web while anomalies of trachea are tracheal stenosis, atresia and tracheoesophageal fistulas. In addition to this some defects related with the development of lungs have also been discussed that includes oligohydramnios induced pulmonary hypoplasia, RDS, pulmonary cysts, pulmonary agenesis and accessory lung development.

11

THE DEVELOPMENT OF DIGESTIVE SYSTEM

LEARNING OBJECTIVES

- GENERAL INTRODUCTION OF THE DEVELOPMENT OF DIGESTIVE SYSTEM
- THE FORMATION OF PRIMITIVE GUT
- THE FORMATION OF FOREGUT
- THE DEVELOPMENT OF OESOPHAGUS
- THE DEVELOPMENT OF STOMACH
- THE DEVELOPMENT OF DUODENUM
- DEVELOPMENT OF LIVER AND BILIARY APPRATUS
- DEVELOPMENT OF PANCREAS
- DEVELOPMENT OF SPLEEN
- THE FORMATION OF MIDGUT
- THE FORMATION OF HINDGUT
- ABNORMALITIES RELATED WITH THE DEVELOPMENT OF GASTROINTESTINAL SYSTEM
- KEY NOTES

The digestive system is the system of canalicular tract from the oral opening to the anus associated with digestive organs and glandular system. The formation of digestive system begins with the primordial gut during the fourth week of gastrulation as the consequence of cephalocaudal and lateral foldings. The primitive gut is formed as blind tube, since it has oropharyngeal membrane on its cranial end and cloacal membrane on caudal end. The endoderm serves to form most of digestive tract including its epithelium and glands. However, the epithelium of cranial and caudal ends forms as the result of the modification of stomodial and proctodial epithelium. Moreover, the accessory digestive system formed as the result of outpocketings from the primitive gut tube.

THE FORMATION OF PRIMITIVE GUT:

The formation of primitive gut takes place as the result of a little incorporation of yolk sac into the embryo which could be possible after cephalocaudal and lateral foldings, however yolk sac and allantois remain outside the embryo. As digestive canal begins as blind ended tube, its cephalic part is the presumptive foregut and caudal part is the presumptive hind gut. Additionally, middle portion serves as the midgut but it is connected with the yolk stalk.

For the sake of understanding; the formation of primitive gut has been divided into three sections;

1. The formation of fore gut and its derivatives
2. The formation of mid gut
3. The formation of hind gut

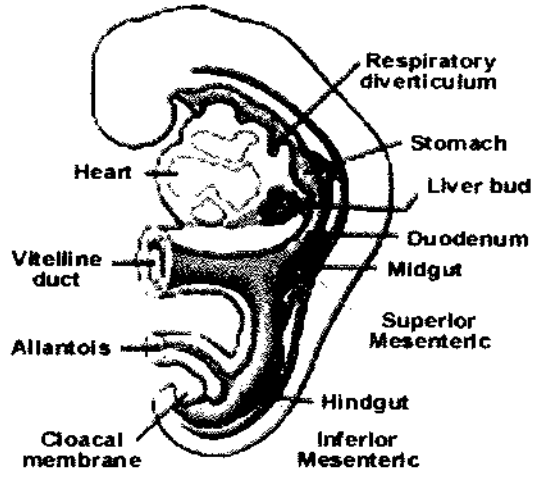


Fig 11.1 The formation of primitive gut

THE FORMATION OF FORE GUT:

The foregut consists of the following derivatives;

- The primordial pharynx along with its derivatives.
- Lower respiratory system
- Oesophagus
- Stomach
- Proximal part of duodenum
- Liver, pancreas and the biliary apparatus.

THE DEVELOPMENT OF OESOPHAGUS:

- ✓ The foregut is portioned ventrally into trachea and dorsally into oesophagus, initially by the tracheoesophagal folds which later on fuses to form tracheoesophagal septum.
- ✓ The formation of oesophagus is prompt elongation of short oesophagus and that is due to rapid growth and descent of the viscera like heart and lungs.
- ✓ Oesophagus first develops as the solid tube which is later on obliterated due to the molecular signalling.
- ✓ The formation of oesophageal epithelium and glands takes place from endoderm however striated muscles developed as the mesenchymal differentiation of the caudal pharyngeal arches. While the formation of smooth muscles takes place from the neighbouring splanchnic mesenchyme.
- ✓ The Trans differentiation of the myology of oesophagus is due to certain regulatory factors however all parts are supplied by cranial nerve i.e. vagus nerve.
- ✓ The formation completed physiologically and anatomically by the eighth week of gestation.

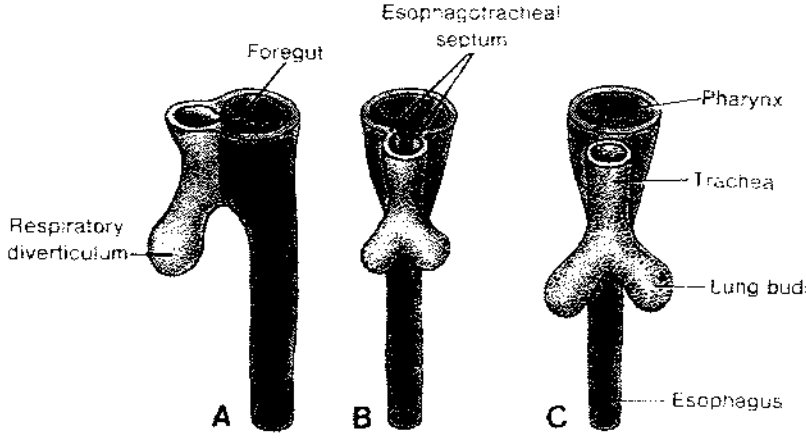


Fig 11.2 The development of oesophagus

THE DEVELOPMENT OF STOMACH:

- ✓ The distal portion of the oesophagus dilates to form a fusiform enlargement during the fourth week of gestation in a midline orientation, later on it enlarges and broadens in the ventrodorsal direction due to rapid positional changes in the surrounding visceras. During the later weeks, there is relative restriction in the growth of ventral border than the dorsal border and it depicts the dorsal greater curvature.
- ✓ Regarding the rotation of stomach, it takes place through 90 degree clockwise around its longitudinal axis along with its blood and nerve supply. Thus the left sides faces ventrally and the right side faces dorsally, innervated by the left and right vagus nerve respectively. After rotation, stomach assumes the final position, with its long axis approximately transverse to the body.

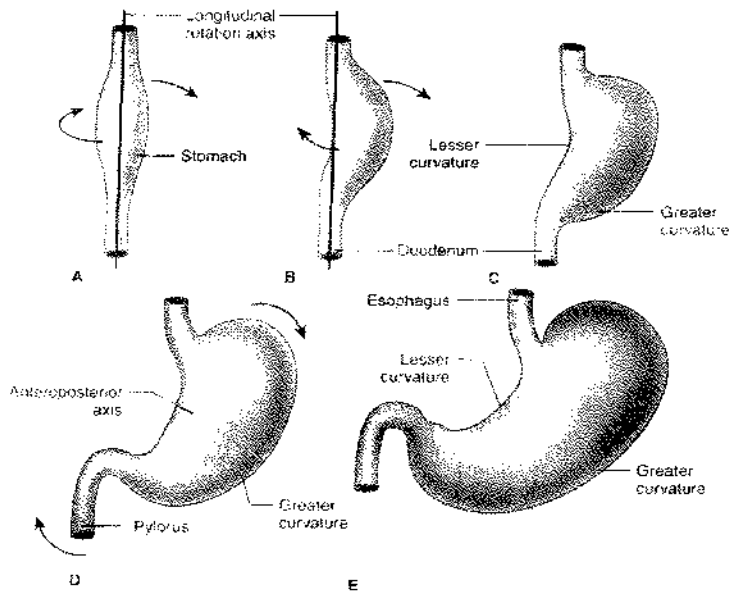


Fig 11.3 The development and rotation of stomach

- ✓ Stomach is suspended by the mesentery dorsally; .mesentery is the double membrane of peritoneum that enclose an organ and connect it to body wall. This mesentery is basically in the midline orientation, is pulled to the left during rotation of stomach and it marked the formation of omental bursa or the lesser sac. However, the primitive ventral mesogastrium attach to the stomach, duodenum, liver and the ventral body wall.
- ✓ The development of the mesenchymal clefts soon coalesce to form a single cavity known as lesser peritoneal sac. Then expansion both in cranial and transverse direction occurs that facilitate the movements of the stomach. With the enlargement of stomach there

is also a disproportionate expansion in omental bursa that acquires inferior recess of omental bursa between the layers of the elongated dorsal mesogastrium. The membrane overhangs in apron like fashion over the developing intestines. Both the omental bursa and peritoneal cavity communicates through the foramina known as EPIPLOIC FORAMINA.

✓ Subsequently, the definitive endoderm develops into the epithelial lining of the stomach and other digestive organs. Abutting this epithelium is a connective tissue called the lamina propria; smooth muscles develops beneath the lamina propria and a thin layer of serosa forms the outermost radial layer.

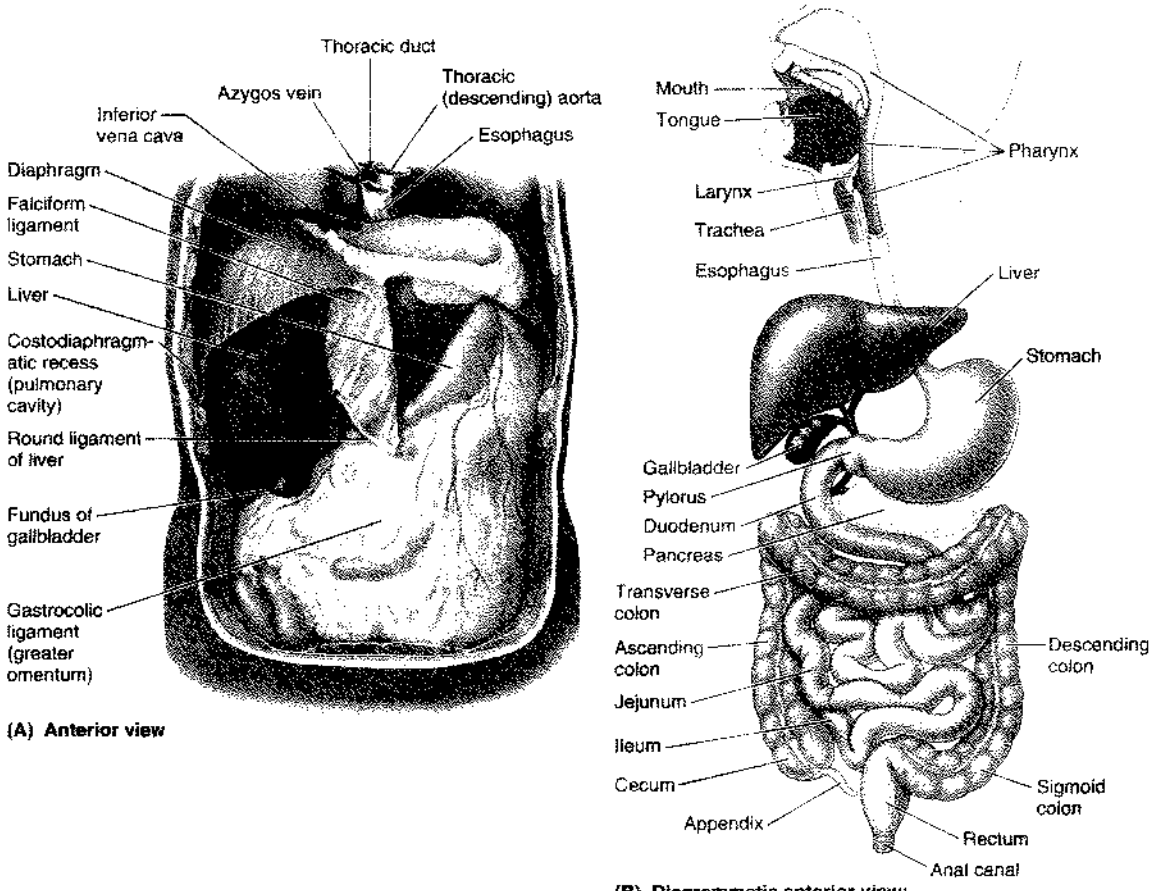


Fig 1.1.1: Stomach with mesentry

EMBRYOLOGICAL TID BITS!
A- Double layers of peritoneum that enclose an organ and connect it to body wall is known as **MESENTERY.**
B- Double layers of peritoneum that connect the one organ to another or an organ to body wall is known as **PERITONEAL LIGAMENT.**
C- The function of mesentery and ligament is t provide pathways for vessels, nerves and lymphatics to and from the abdominal visceras.

THE FORMATION OF DUODENUM:

- ✓ In the fourth week of gestation, the duodenum starts to develop from two sources; the caudal part of the foregut and the cranial part of the midgut. However, the junction lies just distal to the origin of bile duct. The developing duodenum forms a C- shaped curve that initially projects ventrally. Moreover, once the stomach rotates to the right and becomes pressed against the posterior abdominal wall, thus become retroperitoneal.
- ✓ During the second month of gestation, the lumen of the duodenum is obliterated by proliferation of cells in its wall while the recanalization occurs shortly thereafter. And by this time ventral mesentery of the duodenum disappeared.
- ✓ Due to its dual origin it has dual blood supply; proximal part is supplied by coeliac artery while distal part is supplied by superior mesenteric artery.

DEVELOPMENT OF LIVER AND BILIARY APPARATUS:

- ✓ Approximately at the 23rd day of gestation a ventral endodermal outgrowth embarks from the distal part of foregut, it is known as hepatic diverticulum.
- ✓ This hepatic diverticulum has extensive potential of proliferation and penetration due to certain growth factors, it extends into the septum transversum (It is the septa that has splanchnic mesodermal origin, separates pericardial and peritoneal cavities). Furthermore, hepatic diverticulum increase in size rapidly ad proliferates into two parts as it is growing between the two layers of the ventral mesogastrium.
- ✓ Subsequently, the two parts of hepatic diverticulum, cranial and caudal one differentiates into the primordium of the liver and primordium of the gall bladder respectively. Moreover the rapidly dividing endodermal cells interlaced to form the cord like structures that give rise the epithelium of intrahepatic biliary apparatus. With the help of certain factors hepatic cords morphed into hepatic sinusoids and mesenchyme of septum transversum give rise to kupffer cells, fibrous and hematopoietic tissues.
- ✓ During the 5th to 10th week of gestation, liver grows proficiently and occupies the larger part of upper abdominal cavity.

- ✓ However the caudal part which is small in size grows and forms the gall bladder. The stalk of hepatic diverticulum forms the cystic duct. At first, the extra hepatic biliary apparatus is solid which later on obliterates to canalize the duct.
- ✓ Regarding the rotation and entrance of bile duct, initially the duct attaches to the ventral aspect of duodenal loop; because of the growth and rotation it comes to dorsal aspect of the duodenum. The bile enters the duodenum during 13th week of gestation gives the intestinal discharges of the fetus a dark green colour, the discharge is known as meconium.
- ✓ However the thin double layered membrane that is ventral mesentery give rise to the lesser omentum passing from liver to the lesser curvature in the form of hepatogastric ligament and from liver to the duodenum in the form of hepatoduodenal ligament. In addition to this, it also form falciform ligament that extends from liver to ventral abdominal wall.
- ✓ Liver is covered by peritoneum except its bare area.

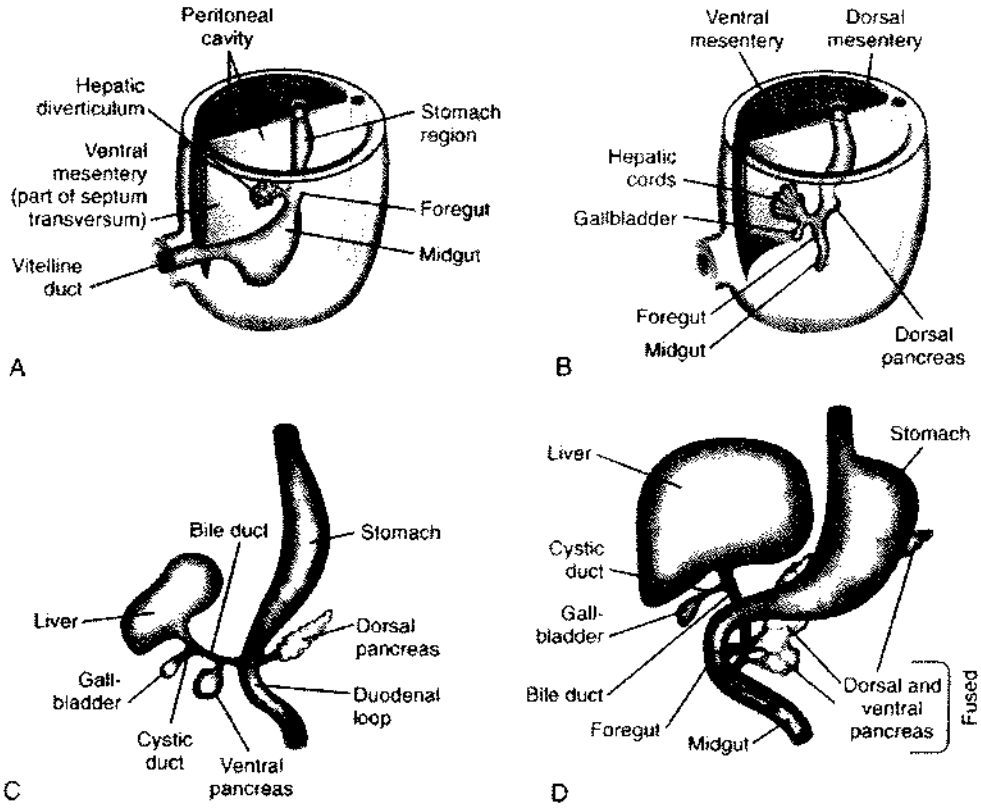


Fig 13.5. The development of liver and biliary apparatus.

EMBRYOLOGICAL TID BITS!
A- The quantity of oxygenated blood flowing from the umbilical vein into the liver determines the developmental and functional segmentation of liver.
B- Regarding the size of lobes of liver, initially they are of equal size but later on the right blood becomes the larger due to certain factors which enhances its blood supply.

DEVELOPMENT OF PANCREAS:

✓ The development of pancreas takes place from the endodermal cells of duodenum that give rise to the dorsal and ventral pancreatic bud. The dorsal bud is located within the dorsal mesentery while ventral bud lies close to the bile duct. Furthermore, the rotation of stomach and duodenum ends up into the fusion of the both. The derivatives of the ventral bud are uncinate process and inferior part of pancreas while dorsal bud forms the superior part of head, neck and tail of pancreas. However, the pancreatic duct is formed by the fusion of distal part of dorsal pancreatic duct and entire ventral pancreatic duct.

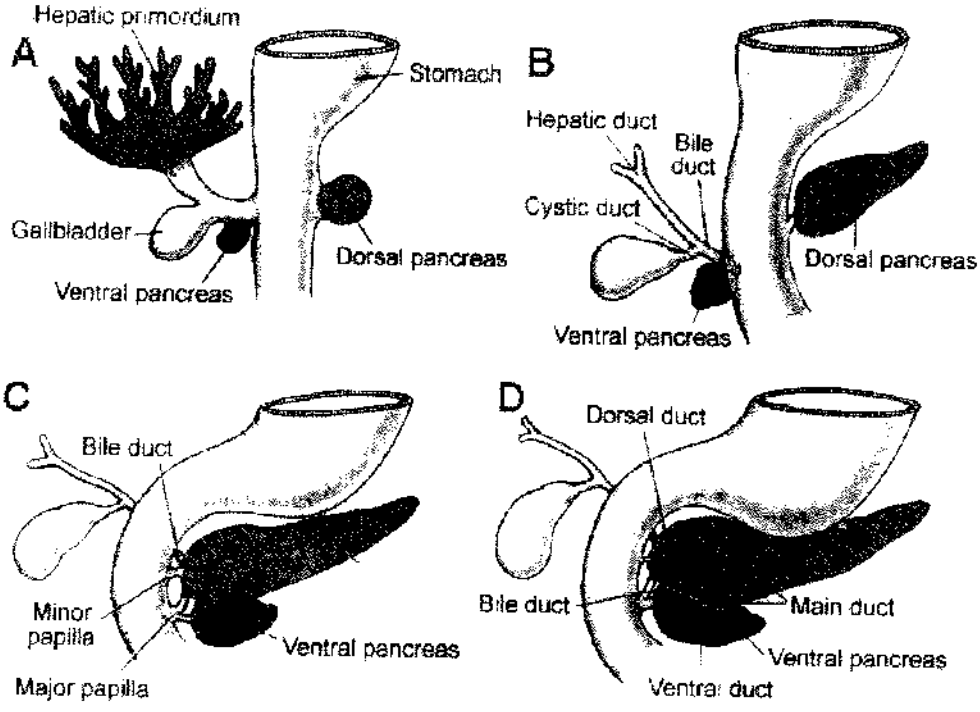


Fig 11.6: The development of pancreas

- ✓ The parenchyma of pancreas is derived from the endoderm of the pancreatic buds, which forms a network of tubules. The acinar cells of the pancreas begins to form in the ninth week of gestation from the cell clusters around the primordial pancreatic ducts.
- ✓ The connective tissue sheath and interlobular septa of pancreas develop from the surrounding splanchnic mesenchyme.
- ✓ The secretion of insulin and glucagon begins in fetal period of embryogenesis while differentiation of different secretory cells begin before the formation of insulin in the beta cells.

DEVELOPMENT OF SPLEEN:

- ✓ The spleen is a vascular organ that begins to develop during the fifth week of gestation however, it is not completely differentiated until fetal period.
- ✓ Spleen is mesenchymal in origin develops between the layers of dorsal mesogastrium.
- ✓ Initially spleen is a lobulated structure later on it fuses to form adult spleen before birth.
- ✓ The mesenchymal cells of primitive spleen differentiate to form the capsule, the framework of connective tissue and the parenchyma of the spleen.
- ✓ The rotation of stomach shifts the left surface of the mesogastrium that fuses with the peritoneum over the left kidney and therefore splenorenal ligament lies posteriorly.

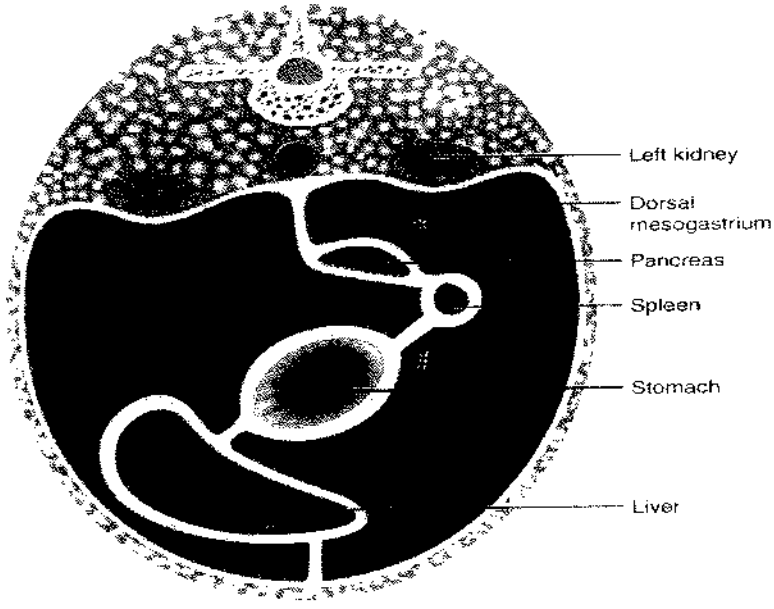


Fig 11.7: **The development of spleen.**

THE FORMATION OF MIDGUT:

- ✓ The midgut consists of the following parts;
  - The small intestine including distal part of duodenum.
  - Caecum, appendix, ascending colon and right two third of transverse colon. They all are supplied by superior mesenteric artery.
- ✓ Development of midgut is significantly characterize by the prompt elongation of gut and its associated structures like mesentery. Consequently, with the rapid elongation the formation of intestinal loop takes place. At its cranial end, the loop remain in connection with the yolk sac by a narrow vitelline duct.
- ✓ Afterwards at the start of 6th week of gestation the midgut undergoes a process of loop formation and that is U-shaped loop which herniates through the primitive umbilical ring into the extra embryonic body cavity this process is called as *"THE PHENOMENA OF PHYSIOLOGICAL HERNIATION"*. The midgut loop has two ends that is the cephalic and caudal end. The cephalic end forms the distal part of the duodenum, the jejunum and the upper portion of the ileum. However the caudal end forms the lower portion of the ileum, the ascending colon and proximal two third of the transverse colon. In addition to this, an outgrowth appears at caudal end of midgut loop that is known as cecal diverticulum which forms the cecum and vermiform appendix.
- ✓ Next to this, within the extra embryonic body cavity the midgut rotates by 90 degree around the axis formed by superior mesenteric artery and vitelline duct. This phenomena of rotation is significantly important in settling the loops of cranial end to the right and caudal end to the left.
- ✓ Moreover, by the 10th week of gestation the herniated loops return to the abdominal cavity by making the 180 degree counter clockwise movement and it set forth the total rotation b 270 degrees.
- ✓ Regarding the fixation of intestinal loops, with the rotation of foregut structures the duodenum and pancreas fall to the right. However, the enlarged colon presses the duodenum and pancreas against the posterior abdominal wall. Consequently, most of the duodenal mesentery is absorbed. At first, the dorsal mesentery is in the midline orientation, with the enlargement and lengthening of intestine the mesentery is pressed against the posterior abdominal wall. On the other hand, the jejunum and ileum retain their mesenteries.

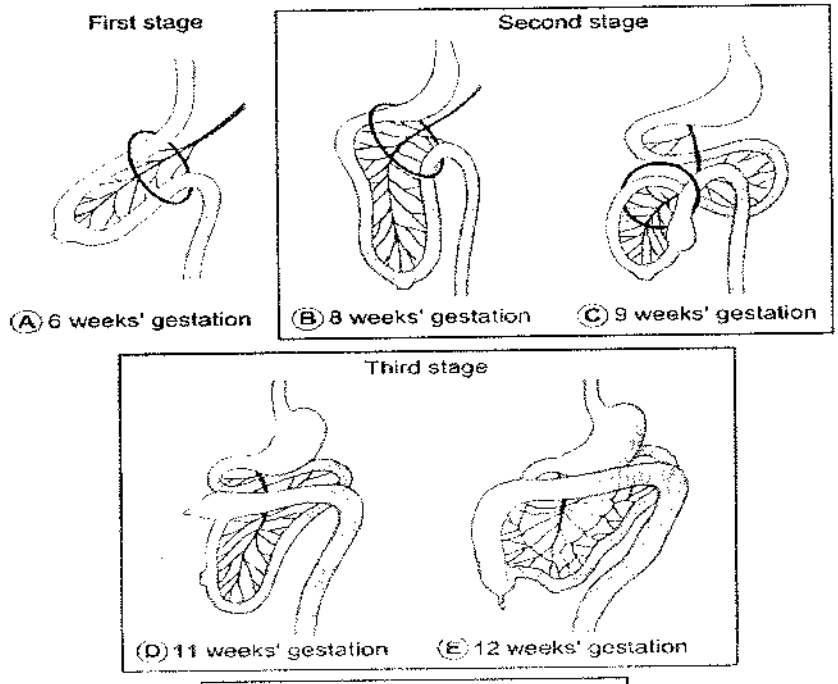


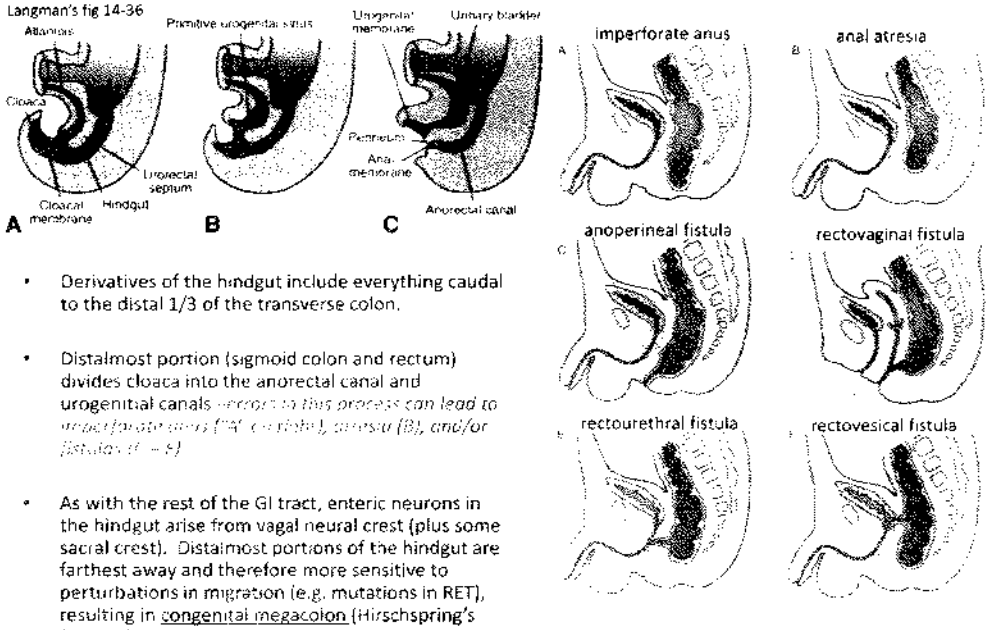
Fig 11.8: The rotation of midgut.

- ✓ The cecum and appendix develops from the outgrowth of the caudal limb of intestinal loop on the antimesentric border during sixth week of development and that outgrowth is known as cecal diverticulum.

THE FORMATION OF HINDGUT:

- ✓ It gives rise to;
  - Distal one third of transverse colon.
  - The descending colon.
  - Sigmoid colon.
  - The rectum and the upper part of anal canal.
- ✓ Cloaca is the terminal portion of the hindgut and it is lined by epithelium which is of endodermal origin. It is in direct contact with the ectoderm at the cloacal membrane. Cloaca membrane is composed of endoderm of cloaca and ectoderm of proctodeum. Cloaca receives allantois ventrally as well.
- ✓ Regarding the partioning, the cloaca is divided into dorsal and ventral part by a wedge shaped mesenchyme, the urorectal septum that develops in the angle between the allantois and hindgut. Urorectal septum grows towards the cloacal membrane and forms fordlike extensions that produce infoldings in the lateral wall of cloaca which later on

fuses to form a partition that divides cloaca into three parts; the rectum, the cranial portion of anal canal and urogenital sinus.



- Derivatives of the hindgut include everything caudal to the distal 1/3 of the transverse colon.
- Distalmost portion (sigmoid colon and rectum) divides cloaca into the anorectal canal and urogenital canals *errors in this process can lead to imperforate anus (A), cloacal persist (B), and/or fistulas (C – F)*
- As with the rest of the GI tract, enteric neurons in the hindgut arise from vagal neural crest (plus some sacral crest). Distalmost portions of the hindgut are farthest away and therefore more sensitive to perturbations in migration (e.g. mutations in RET), resulting in congenital megacolon (Hirschspring's Disease).

Fig 11.9: The development of hindgut.

- ✓ The superior two third of anal canal is formed from the anorectal canal of cloaca and inferior one third originates from ana. pit. The junction of both is marked as pectinate line.
- ✓ The hindgut is supplied by inferior mesenteric artery.

ABNORMALITIES RELATED WITH THE DEVELOPMENT OF GASTROINTESTINAL SYSTEM:

Abnormalities related with gastrointestinal system have been classified into two categories for the sack of clear understanding;

1. Abnormalities related with gastrointestinal tract.
2. Abnormalities related with associated structures.

1. ABNORMALITIES RELATED WITH GASTROINTETINAL TRACT:

Abnormalities related with gastrointestinal system includes:

A. Oesophageal abnormalities.
B. Stomach abnormalities.
C. Duodenal abnormalities.
D. Vitelline duct abnormalities.
E. Gut related abnormalities.

A- OESOPHAGEAL ABNORMALITIES:

- ✓ Oesophageal abnormalities include oesophageal atresia or tracheoesophageal fistula and oesophageal stenosis.
- ✓ Regarding oesophageal atresia, the blockage of oesophageal lumen occurs due to some predisposing factors like spontaneous posterior deviation of the tracheoesophageal septum or from mechanical factors that push dorsal wall of foregut anteriorly. A fetus with oesophageal atresia is unable to swallow the amniotic fluid and resultantly the fluid cannot pass to the intestine for the absorption and transfer through the placenta for the process of disposal. This results into the accumulation of excessive amniotic fluid known as polyhydramnios. Depending upon the occurrence there are four types of oesophageal atresia but atresia with tracheoesophageal fistula is of prominently more than 90% and isolated oesophageal atresia is also occurring with remarkable percentile. However, the communicative types of atresia is of minor occurrence.
- ✓ Regarding oesophageal stenosis, it is the narrowing of the lumen anywhere along the oesophagus, albeit it occurs majorly occurring at lower 2/3rd. Stenosis occurs due to incomplete recanalization of oesophagus or due to failure of oesophageal blood channels development.

B- STOMACH ABNORMALITIES:

- ✓ Abnormalities related with stomach is of minor occurrence but rarely pyloric stenosis occurs;

- ✓ It is the narrowing of the opening from the stomach. Symptoms include projectile vomiting without the presence of bile. This most often occurs after the baby is fed. The typical age that symptoms become obvious is two to twelve weeks old. The cause of pyloric stenosis is unclear. Risk factors in babies include birth by cesarean section, preterm birth, bottle feeding, and being first born. The diagnosis may be made by feeling an olive-shaped mass in the baby's abdomen. This is often confirmed with ultrasound.

C- DUODENAL ABNORMALITIES:

- ✓ Duodenal abnormalities include the duodenal stenosis and duodenal atresia.
- ✓ Duodenal stenosis is all about narrowing of duodenal lumen and it is due to defective recanalization of the duodenal lumen.
- ✓ Regarding duodenal atresia, it is complete occlusion of duodenal lumen by epithelial cells. This occurs due to complete failure of obliteration of the duodenal lumen. It significantly occurs at hepatopancreatic ampulla. Polyhydramnios also takes place due to duodenal atresia as it prevents the normal intestinal absorption of swallowed amniotic fluid.

D- VITELLINE DUCT ABNORMALITIES:

- ✓ It includes the Meckle's Diverticulum, vitelline cyst and vitelline fistula.
- ✓ Regarding Meckel's diverticulum is an outpouching or bulge in the lower part of the small intestine. The bulge is congenital (present at birth) and is a leftover of the umbilical cord. Meckel's diverticulum is the most common congenital defect of the gastrointestinal tract. It occurs in about 2% to 3% of the general population.
- ✓ Regarding vitelline cyst, it is developmental defects relating to the closure of the omphalomesenteric duct.
- ✓ Regarding vitelline fistula, generally, the duct fully obliterates (narrows and disappears) during the 5–6th week of fertilization age (9th week of gestational age), but a failure of the duct to close is termed a vitelline fistula. This results in discharge of meconium from the umbilicus.

E- ABNORMALITIES OF THE GUT:

- ✓ Abnormalities of gut include the rotational defects and hind gut related disorders.
- ✓ Regarding the rotational defects there may be some twists along the intestinal loops known as volvulus that can compromise the blood supply. In addition to this, there may also be the occurrence of reversed rotation and duplication of the intestinal loops.

- ✓ Moreover, atresia and stenosis of the gut also occurs that is due to vascular accidents or incomplete or failure or recanalization. APPLE PEEL ATRESIA accounts for 10% of atresias and this is the atresia of proximal jejunum.
- ✓ Anomalies of hind gut include rectourethral or rectovaginal fistula that is due to septal defect. In addition to this imperforate anus occurs in which anal membrane fails to rapture.
- ✓ Another abnormality that is Hirschsprung disease or congenital megacolon occurs that is due to absence of parasympathetic ganglia. These ganglia are derived from neural crest cells that migrate from the neural folds to the wall of bowel.

2. ABNORMALITIES RELATED WITH ASSOCIATED STRUCTURES:

- ✓ Abnormalities related with associated structures include; defects related to liver, extra hepatic biliary apparatus, pancreas, accessory spleens and mesenteries.
- ✓ Anomalies of liver are of minor occurrence, sometimes accessory hepatic ducts are present. The accessory ducts are narrow channels running from the right lobe of the liver into the anterior surface of the body of the gall bladder.
- ✓ Regarding extra hepatic biliary atresia, also known as extra hepatic ductopenia and progressive obliterative cholangiopathy, is a childhood disease of the liver in which one or more bile ducts are abnormally narrow, blocked, or absent. It can be congenital or acquired.
- ✓ Regarding the defects of pancreas, it includes ectopic pancreas and annular pancreas.
- ✓ An ectopic pancreas is an anatomical abnormality in which pancreatic tissue has grown outside its normal location and without vascular or other anatomical connections to the pancreas. It is a congenital disease and is also known as heterotopic, accessory, or aberrant pancreas.
- ✓ Annular pancreas is a rare condition in which the second part of the duodenum is surrounded by a ring of pancreatic tissue continuous with the head of the pancreas. This portion of the pancreas can constrict the duodenum and block or impair the flow of food to the rest of the intestines.
- ✓ An accessory spleen is a small nodule of splenic tissue found apart from the main body of the spleen. Accessory spleens are found in approximately 10 percent of the population and are typically around 1 centimeter in diameter. They may resemble a lymph node or a small spleen.
- ✓ The body wall defects include gastroschisis and omphalocele.
- ✓ Gastroschisis is a birth defect of the abdominal (belly) wall. The baby's intestines are found outside of the baby's body, exiting through a hole beside the belly button.

The hole can be small or large and sometimes other organs, such as the stomach and liver, can also be found outside of the baby's body.

- ✓ Omphalocele, also known as exomphalos, is a birth defect of the abdominal (belly) wall. The infant's intestines, liver, or other organs stick outside of the belly through the belly button. The organs are covered in a thin, nearly transparent sac that hardly ever is open or broken.

KEY NOTES!

a. The dorsal part of umbilical vesicle gives rise to primitive gut. The foregut gives rise to pharynx, lower respiratory system, oesophagus, stomach proximal part of duodenum, liver, pancreas and extra hepatic biliary apparatus
b. The midgut gives rise to the distal part of the duodenum, the jejunum, the ileum cecum, appendix, ascending colon, and right two third of transverse colon.
c. The hind gut gives rise to distal transverse colon, descending colon, sigmoid colon and superior part of anal canal.

12

THE DEVELOPMENT OF UROGENITAL SYSTEM

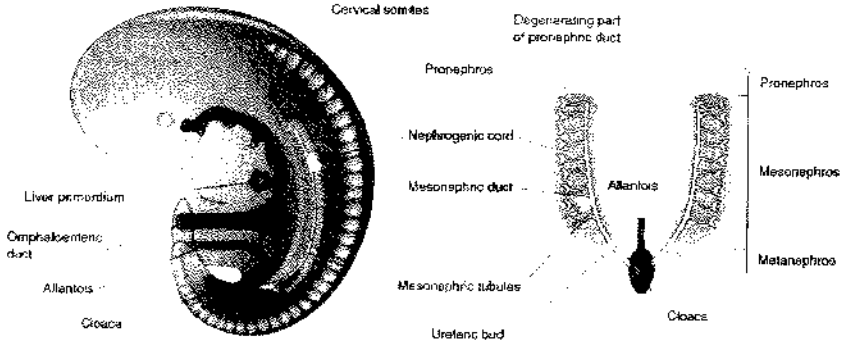
LEARNING OBJECTIVES

- GENERAL INTRODUCTION OF THE DEVELOPMENT OF UROGENITAL SYSTEM
- THE DEVELOPMENT OF URINARY SYSTEM
- DEVELOPMENT OF KIDNEYS
- DEVELOPMENT OF URETER
- DEVELOPMENT OF URINARY BLADDER
- DEVELOPMENT OF URETHRA
- THE DEVELOPMENT OF PROSTRATE GLAND
- THE DEVELOPMENT OF SUPRARENAL GLANDS
- THE DEVELOPMENT OF GENITAL SYSTEM
- DEVELOPMENT OF GONADS
  - I. DEVELOPMENT OF TESTIS
  - II. DEVELOPMENT OF OVARIES
- DEVELOPMENT OF GENITAL DUCTS
- DEVELOPMENT OF EXTERNAL GENITALIA
- THE DEVELOPMENT OF INGUINAL CANAL
- THE PROCESS OF DESECENT OF TESTIS AND OVARIES
- THE ABNORMALITIES OF UROGENITAL SYSTEM
- KEY NOTES

This chapter deals with the development of urinary system, suprarenal glands, genital system, external genitalia and inguinal canals. In addition to this relocation of testis and ovaries and the developmental abnormalities associated with the urogenital system have also been discussed.

The embryological manifestation of both the systems i.e. urinary system and genital system is same that they are derived from intermediate mesoderm along the posterior wall of body cavity, albeit they are distinguished functionally. In addition to this, both the system initially opens into a common opening known as cloacal opening which later o portioned into the respective ones.

During the fourth week of gestation, when embryo folds the horizontal plane of the mesenchyme is carried to the ventral direction and it loses connection with somites. A



Overview of development of urogenital system.

longitudinal mass of elevated cells appear on each side of primitive aorta called as urogenital ridge. The formation of urogenital system takes place from this ridge; the part of ridge that gives rise to urinary system is known as nephrogenic cord. However, the part of urogenital system that gives rise to the genital system is known as Gonadal ridge.

THE DEVELOPMENT OF URINARY SYSTEM:

- ✓ The development of urinary system is closely associated with the development of following structures and its development starts before the formation of urogenital system.
  - Development of kidneys
  - Development of ureters
  - Development of urinary bladder
  - Development of urethra.

DEVELOPMENT OF KIDNEYS:

There is the three tier successive development of the kidney systems that are closely interwoven to each other they are enlisted as under;

The pronephros kidney system: This system begins to develop early in the fourth week. Pronephros shows the tubular solid cell structures that arise bilaterally in the cervical region for the transient period. The cells are probably 7 to 10 in number. The pronephros runs in the cranio caudal direction and opens into the cloacal chamber. The pronephros kidney system is non-functional and transient. Therefore, the pronephros soon degenerate however most of the caudal part persist for the use of later developing system.

The mesonephros kidney system: This system arise from the intermediate mesoderm of the upper thoracic and upper lumber region late in the 4th week. The mesonephros kidney system act as interim kidney and it consist of glomeruli, mesonephric tubules and mesonephric ducts. All the mesonephric tubules disappear in the female however some tubules persists in the male for the formation of genital system.

The metanephros kidney system: This is the formation of definitive kidney system. It start to appear late in the 5th week. The metanephric kidney system has dual development. Its sources are;

1. The ureteric bud that is the metanephric diverticulum
2. The metanephrogenic cap the metanephric cap of intermediate mesoderm.

The metanephros kidney system is the permanent kidney system comprises of;

1. The collecting system: it develops from the outgrowth of the mesonephric duct close to the entrance in cloaca, this outgrowth is known as ureteric bud. As ureteric bud penetrates the metanephric mesoderm, it sets forth the formation of metanephric cap of mesoderm. Furthermore, ureteric bud undergoes repeated proliferation to

form first three to four generations of tubules which lengthen, dilate and become confluent to form major calyces while second four generations of tubules join together to form minor calyces. However, the formation of collecting tubules of the definitive kidney takes place from the remaining generation of tubules.

2. The excretory system: metanephric tissue cap at the distal end covers the collecting tubules. As these collecting tubules grows more inside the metanephric tissue cap it produces inductive influence which propense the formation of renal vesicles. Capillaries grows inside the pocket like structure formed by interaction of collecting tubules and tissue cap and differentiate into glomeruli. This whole structure constitute the BOWMAN'S CAPSULE. The metanephric blastema also form the proximal and distal convoluted tubules and the loop of henle. Kidney, initially is a lobulated structure but later on it disappears as the consequent growth of nephrons.

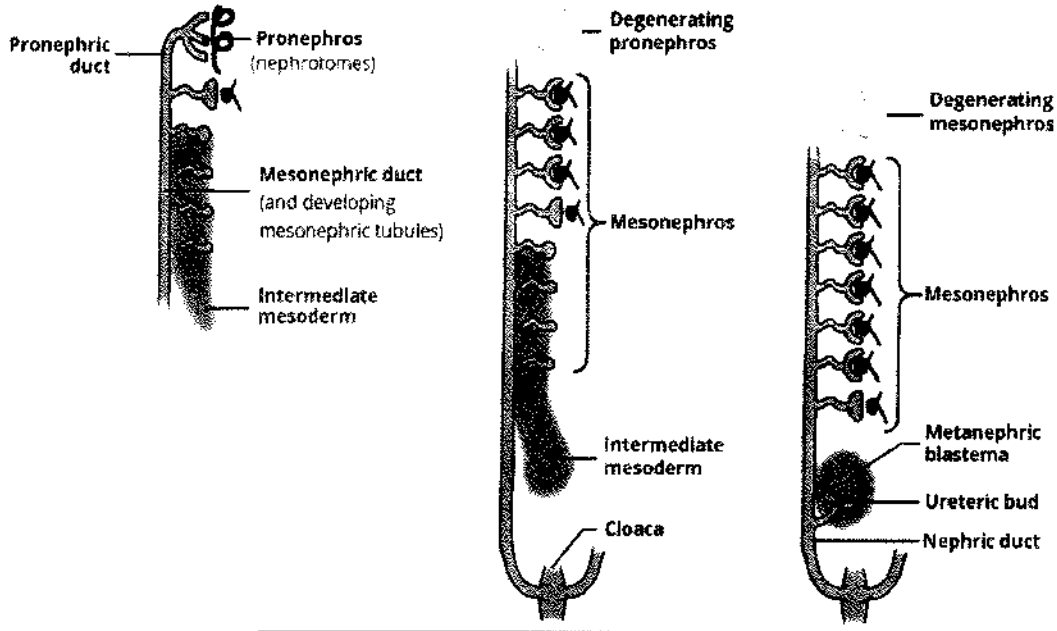


Fig 12.2: Different types of kidney system.

POSTIONAL CHANGES OF KIDNEY:

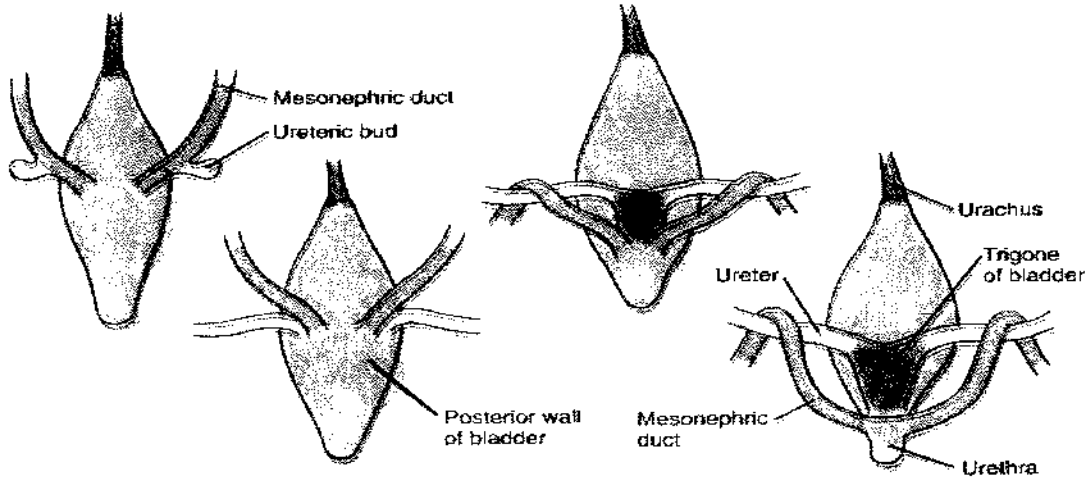
- ✓ At absolute first, the primordial definitive kidneys develop into the pelvic region. With the development of abdominal region they gradually relocate in the abdomen and attain its final position during fetal period. The main predisposing factors in the ascent of kidneys are the growth of embryo's body caudal to the kidneys and the diminution of the body curvature.

- ✓ Regarding the blood supply changes, as with the relocation of kidneys blood supply also changes. Initially the renal arteries are the branches of common iliac arteries but later on they receive blood supply from the distal branches of abdominal aorta. When kidneys approach to the higher level and attain the adult position after coming in contact with suprarenal glands, they receive blood supply from their respective renal arteries which are the branches of abdominal aorta.

EMBRYOLOGICAL TID BITS!
Right renal artery is longer than left renal artery and often in a more superior position than the left renal artery.

THE DEVELOPMENT OF URETERS:

At the fifth week of development, the ureteric bud arises as a diverticulum from the mesonephric (Wolfian) duct. The bud grows laterally and invades the center of the metanephrogenic blastema, the primordial renal tissue. The meeting of these two tissues cause changes in the bud and the metanephros. The metanephrogenic blastema forms glomeruli, proximal tubules and distal tubules. The ureteric bud divides and branches forming the renal pelvis, infundibulae, calyces, and collecting tubules which will provide a conduit for urine drainage in the mature kidney. This process is known as the induction of the kidney.



The mesonephros kidney system.

THE DEVELOPMENT OF URINARY BLADDER:

The development of urinary bladder commences when urorectal septum partitions the cloaca into anorectal septum and primordial urogenital sinus during the 4th to 7th week of gestation.

Moreover, for the sack of understanding the development of urinary bladder is divided into three part.

1. The vesicle part: It is the most cranial part of urogenital sinus and it forms the largest part of urinary bladder which is continuous with the allantois

2. The pelvic part: from this part the development of prosthetic and membranous part of the urethra takes place. It is the middle and narrow part of urinary bladder.

3. The phallic part: This part is the most caudal part of urogenital sinus grows toward the genital tubercle.

The development of urinary bladder takes place mostly from the vesicle pat of urogenital sinus. However the trigone region is formed by the caudal end of the mesonephric duct. The endodermal lining give rise the transitional epithelium of urinary bladder. As apex of the bladder is continuous with the allantois it becomes cord like structure known as urachus that forms the median umbilical ligament in the adult.

DEVELOPMENT OF URETHRA:

The development of the male prostatic urethra is of dual origin. The most proximal part of urethra is derived from the mesonephric duct and the distal part is formed by urogenital sinus while the penile urethra is formed by urogenital sinus and surface ectoderm. In the females urethra is derived from mesonephric duct and urogenital sinus.

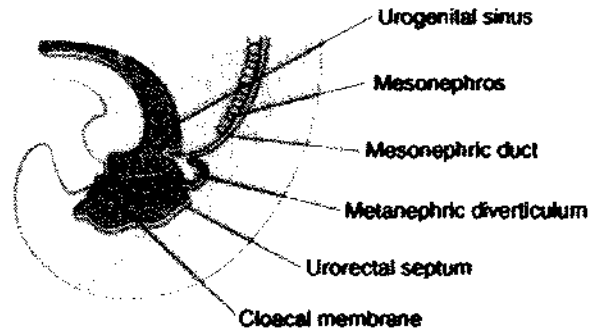


Fig 10.4: Different components of urinary system

The epithelium of most of the male urethra is formed from the endodermal lining f urogenital sinus albeit the epithelium of glans penis is of ectodermal origin.

The connective tissue and smooth muscles of the urethra in both sexes s derived from splanchnic mesenchyme.

THE DEVELOPMENT OF PROSTATE GLAND:

The epithelium from the prostatic part of urethra evaginates and coupled with the surrounding mesenchyme to form prostatic gland. Females have urethral and paraurethral glans in place of prostatic glands.

✓ THE DEVELOPMENT OF SUPRARENAL GLANDS:

Developmentally, the suprarenal glands have two distinct regions; one is the cortex which is of mesenchymal origin while other one is medulla which is of neural crest cell origin.

The development of cortical region commences during the sixth week of gestation. It begins to develop between the root of dorsal mesentery and the developing gonads as a mesenchymal aggregated structure.

However the formation of medulla takes place from adjacent sympathetic ganglion which in turn is derived from neural crest cells. At very first, a mass of neural crest cells appear on the medial side of neural crest cells which later on differentiate to form secretory cells of the suprarenal glands.

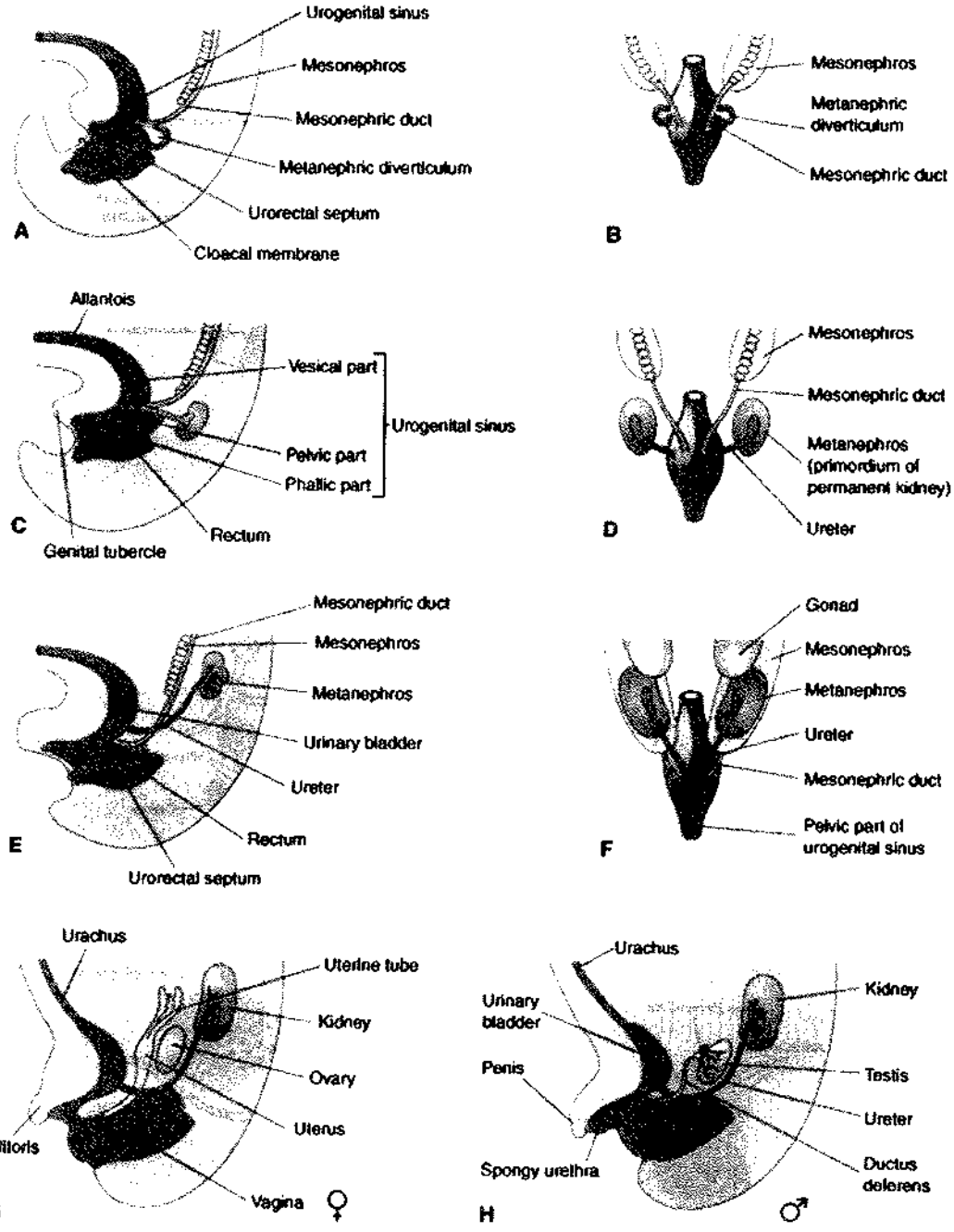


Fig 12.5: Overall development of urinary system.

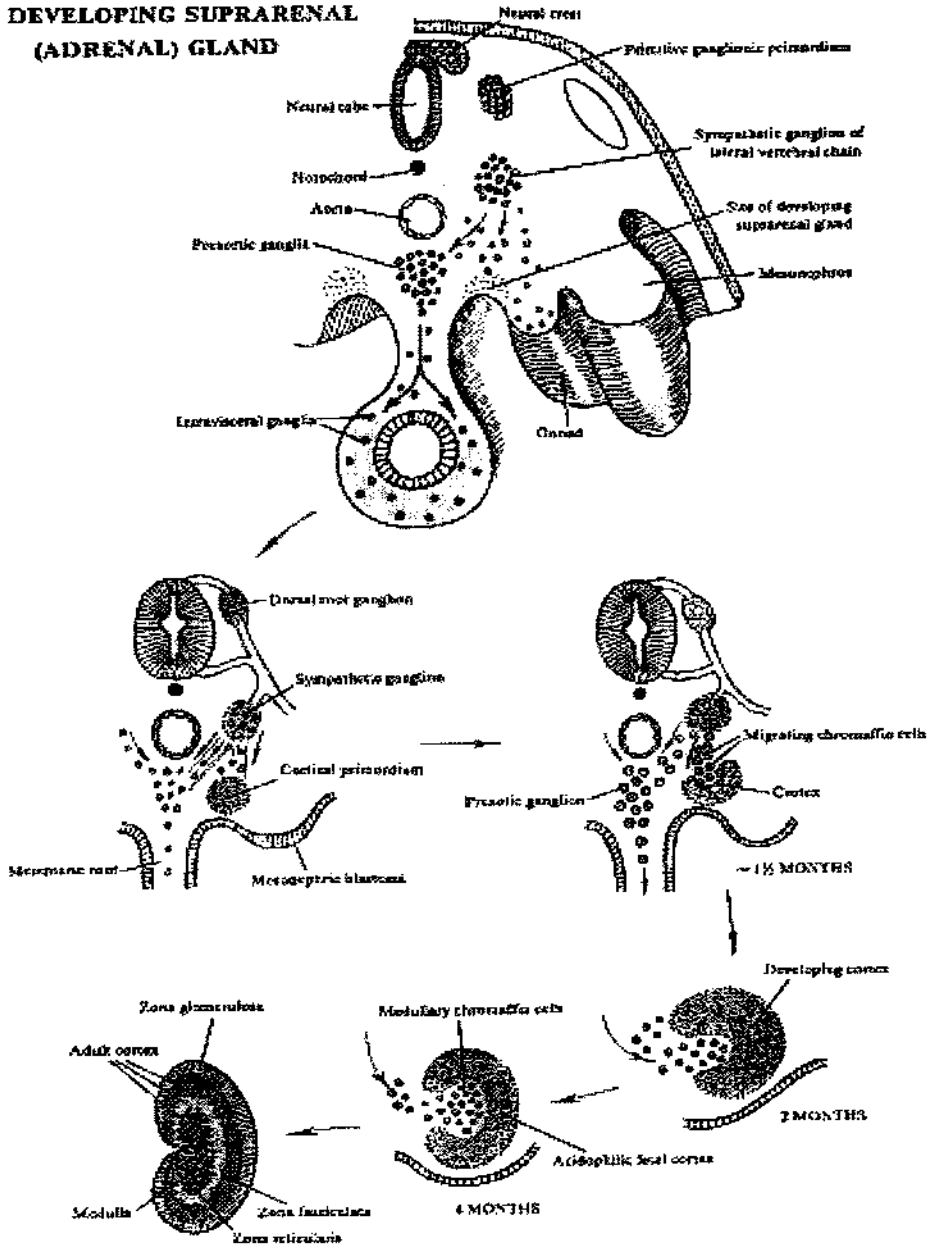


Fig 12.6: The development of suprarenal glands.

EMBRYOLOGICAL TID BITS!
The size of suprarenal gland of fetus is larger than size of adult because of extensive cortical circumference of the gland in fetus which produces plethora of steroid precursors that later on are manifested in the formation of estrogen by the placenta.

THE DEVELOPMENT OF GENITAL SYSTEM:

Genetic sex of an individual is determined by the process of fertilization albeit the morphological expression of individual characters is still a complex process until the 12th week of gestation. It is however complete in the 20th week of development.

THE DEVELOPMENT OF GONADS:

- Initially, gonads appear by the interaction of a pair of longitudinal ridges that are known as the gonadal ridges and underlying mesenchyme. After the sixth week of development sex cells start to appear.
- The primordial germ cells start to appear in the epiblast, migrate through primitive streak to the yolk sac and during the 4th week of gestation it migrates along the dorsal mesentery. At about 5th week it reaches to the primitive gonads. Primordial germ cells are large, spherical sex cells that are migrated along the whole aforementioned path by genetic signalling.

  The initial stages of the gonads development is known as indifferent gonads as the sex cannot be distinguished. It is because of the interaction of rapidly proliferating epithelium of gonadal ridges and underlying mesenchyme which in turn form a number of irregularly shaped cords known as primitive sex cords.

DEVELOPMENT OF TESTIS:

Development of the testis commences when the genital ridges start to secrete testosterone hormone. And it is usually the 7th week of gestation. Under the influence of testosterone hormone the sex cords tends to separate and rapidly proliferate. The proliferating mesenchyme condenses to form the tunica albugenia. The formation of seminiferous tubules takes from the U-shaped sex cords at about fourth month of gestation. Moreover the sertoli cells are derived from the surface epithelium of the testis while spermatogonia are derived from primordial germ cells.

DEVELOPMENT OF OVARIES:

The development of ovaries are associated with the proliferation of gonadal ridges which later on differentiates to form the primary sex cords. Later on, by the convergence of primary sex cords a structure is formed, which is known as rete ovarii. However the

surface epithelium give rise to the cortical cords. By the 16th week of gestation cortical cords break up into the cluster of follicles known an oogonium.

DEVELOPMENT OF GENITAL DUCTS:

- ✓ Both male and female embryos have two pairs of genital ducts at very first that are wolffian ducts and the mullerian ducts. The mullerian duct arise as the invagination of the epithelium on the anterolateral surface of the urogenital ridge. This duct on the upper end opens into the abdomen however on its path, it runs laterally to the Wolffian duct. The caudal tip of both the ducts projects in the posterior wall of the urogenital sinus, where it causes a little swelling known as sinus tubercle. This stage is known as the indifferent stage of genital ducts development. For the sack of clearing concept, wolffian and mullerian ducts are also known as mesonephric and paramesonephric ducts respectively.

- ✓ Formation of genital ducts in male: Under the influence of testosterone hormone which is secreted by the testis of the fetus, the formation of male genital ducts such as epididymis, ductus deferens, seminal vesicle and ejaculatory duct takes place from the mesonephric duct. However mullerian inhibiting hormone suppress the growth of paramesonephric duct.

- ✓ Formation of genital ducts in female: Under the influence of estrogen and in the absence of antimullerian substance most of the formation of female genital ducts takes place from paramesonephric ducts; its upper vertical portion forms the upper part of uterine tube while lower part of uterine tube is formed by the middle horizontal portion. However uterus and some part of vagina is formed form caudal vertical part.
  In females mesonephric duct is completely regress however, its remnant persists as appendix vesiculosa, epoophoron, paroophoron and Gartner's duct.
  - The uterus is formed from the fusion of caudal part of paramesonephric ducts of both sides. However, endometrial stroma and myometrium are derived from adjacent splanchnic mesenchyme.
  - The superior third of the vagina is formed from the uterovaginal primordium which is derived from the midline fusion of paramesonephric ducts. The uterovaginal primordium projects into the posterior wall of urogenital sinus to form sinus tubercle. It also induces the formation of sinovaginal bulbs from the endodermal outgrowths. These sinovaginal bulbs later on fuse to form vaginal plate and this vaginal plate after recanalization forms the lower two thirds of vagina. Endodermal lining of the urogenital sinus give rise to the epithelium of vagina while fibro muscular wall develops from surrounding mesenchyme.

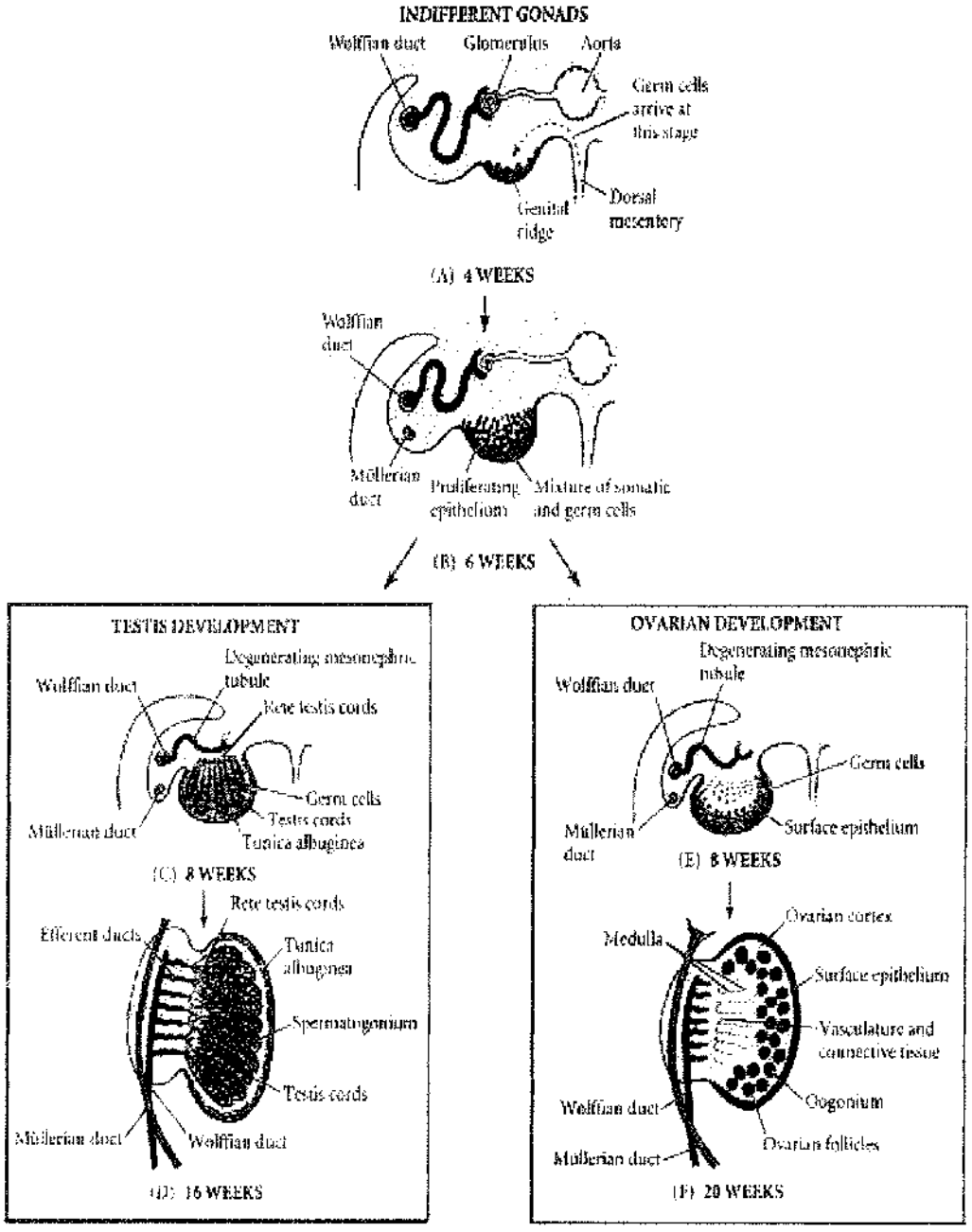


Fig 12.7: Development of genital ducts

DEVELOPMENT OF EXTERNAL GENITALIA:

The proliferating mesenchyme of the cranial end of cloacal membrane produces an elevated structure known as genital tubercle. Later on labioscrotal swellings and urogenital folds start to appear on each side of the cloacal membrane. The genital tubercle elongates to form the primordial phallus. The urogenital membrane lies in the floor of a median cleft which is bounded by urethral folds. In female foetuses the urethra and vagina opens into a single cavity known as the vestibule of vagina.

- DEVELOPMENT OF MALE EXTENAL GENITALIA:
  In male fetus, phallus elongates to form the penis however the ventral surface is formed by the fusion of urogenital folds while labioscrotal swellings grow in a median plane and subsequently fuses together to form the scrotum.
- DEVELOPMENT OF FEMALE EXTERNAL GENITALIA:
  In female fetuses as there is the production of estrogen so phallus elongates slightly and converted into the clitoris. However in female fetuses the urogenital folds do not fuse and they form labia minora while labioscrotal swellings becomes the labia majora.

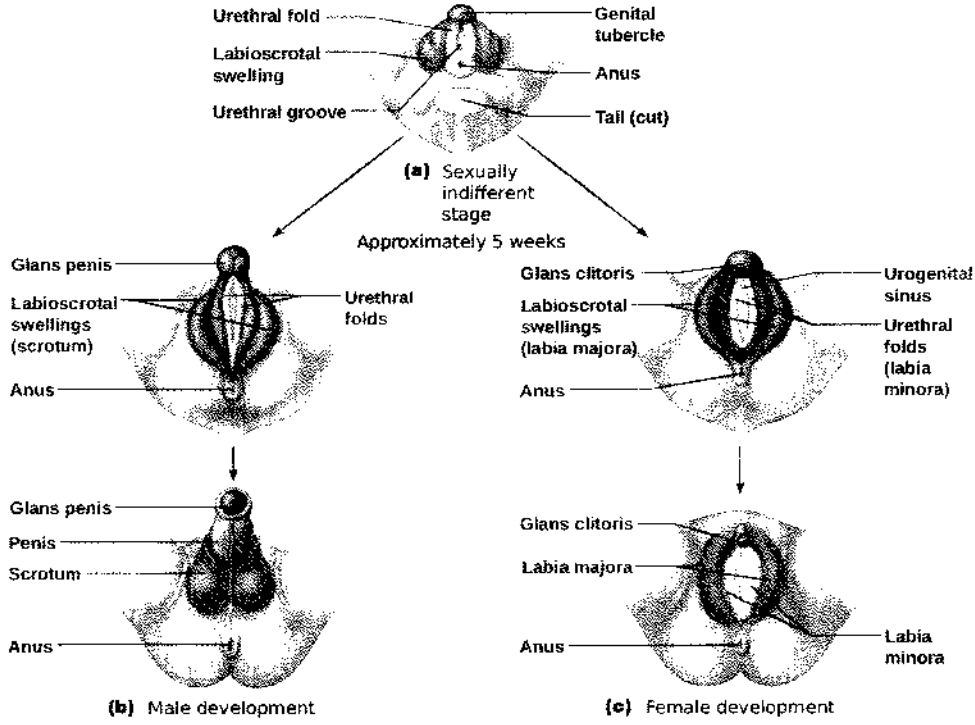


Fig 12.3: Development of External genitalia of Male and Female

THE DEVELOPMENT OF INGUINAL CANAL:

- The inguinal canal is the course for the descent of testis from the dorsal abdominal wall through the anterior abdominal wall into the scrotum. The development of inguinal canal is dual in origin.
- One is from the ligamentous structure which arises from the caudal pole of the gonad to the labioscrotal swellings. This ligamentous structure is known as "GABERNACULUM".
- Secondly, a peritoneal diverticulum appears which protrudes through the anterior abdominal wall ventral to the ligamentous gubernaculum. The walls of inguinal canal and covering of spermatic cord in males is also formed by this structure. This structure is known as "PROCESS VAGINALIS".
- The opening in the transversalis fascia produced by the process vaginalis is known as deep inguinal ring. However the opening created in external oblique aponeurosis is called as superficial inguinal ring.

THE PROCESS OF DESCENT OF TESTIS AND OVARIES:

- THE DESCENT OF TESTIS:

  There are some factors that induce the descent of testis;

  Firstly, the atrophy of mesonephric duct associated with the enlargement of testicles induce the caudal movement of testis along the posterior abdominal wall.

  Secondly, the atrophy of paramesonephric duct and antimullerian substance plays quintessential role in the trans abdominal relocation of testis.

  Finally, the enlargement of process vaginalis guide the testis through inguinal canal into the scrotum.

  By the 28th week of gestation, testis start to descend retroperitoneally from the posterior abdominal wall to the deep inguinal ring, however testis remain near the deep inguinal ring.

  At the 28th week of gestation, certain factors plays crucial role in the rapid transference of testis from deep inguinal ring through inguinal canal into the scrotum and usually it takes place before birth. Within the scrotum, testis projects into the distal end of the process vaginalis. Moreover, during the prenatal life connecting stalk obliterates to form the serous membrane around the testis that is known as Tunica vaginalis.

- THE DESCENT OF OVARIES:

  The descent of ovaries takes place from posterior abdominal wall into the pelvic region. The gubernaculum which is attached to the uterus near the uterine tube gives

its crania part for the formation of ovarian ligament while its caudal part forms the round ligament of the uterus. The vaginal process in females persists as canal of nuck.

✓ THE ABNORMALITIES OF UROGENITAL SYSTEM:

For the sack of description this section has been classified into two parts;

1. The anomalies of urinary system
2. The anomalies of genital system.

1. THE ANOMALIES OF URINARY SYSTEM:

The anomalies of urinary system include; the congenital anomalies of kidneys, ureters, urinary bladder and suprarenal glands.

CONGENITAL ABNORMALITIES OF KIDNEYS AND URETERS:

RENAL AGENESIS

Renal agenesis is a condition in which a newborn is missing one or both kidneys. Unilateral renal agenesis (URA) is the absence of one kidney. Bilateral renal agenesis (BRA) is the absence of both kidneys.

Both types of renal agenesis occur in less than 1 percent of births annually, according to the March of Dimes. Less than 1 in every 1,000 newborns has URA. BRA is much rarer, occurring in about 1 in every 3,000 births.

The kidneys perform functions that are necessary for life. In healthy people, the kidneys:

- produce urine, which removes urea, or liquid waste, from the blood
- keep a balance of sodium, potassium, and other electrolytes in the blood
- supply the hormone erythropoietin, helping red blood cell growth
- produce the hormone renin to regulate blood pressure
- produce calcitriol, also known as Vitamin D, which helps the body absorb calcium and phosphate from the GI tract

Everyone needs at least part of one kidney to survive. Without either kidney, the body cannot remove waste or water properly. This accumulation of waste and fluid can offset the balance of important chemicals in the blood, and leads to death without treatment.

MALROTATED KIDNEY:

A malrotated kidney, which is a variation of kidney malrotation, is a rare congenital kidney anomaly. Kidney malrotation is often accompanied by vascular variations such as the renal arteries and veins and common iliac arteries and veins, for surgical procedures.

ECTOPIC KIDNEYS:

An ectopic kidney is a birth defect in which a kidney is located in an abnormal position. In most cases, people with an ectopic kidney have no complaints. In other cases, the ectopic kidney may create urinary problems, such as urine blockage, infection, or urinary stones.

HORSESHOE KIDNEY:

The horseshoe kidney is the most common type of renal fusion anomaly. It consists of two distinct functioning kidneys on each side of the midline, connected at the lower poles (or rarely at the upper poles) by an isthmus of functioning renal parenchyma or fibrous tissue that crosses the midline of the body.

CYSTIC KIDNEY DISEASES:

Polycystic kidney disease (PKD) is an inherited disorder in which clusters of cysts develop primarily within your kidneys, causing your kidneys to enlarge and lose function over time. Cysts are noncancerous round sacs containing fluid. The cysts vary in size, and they can grow very large.

POTTER SEQUENCE:

Potter sequence is the atypical physical appearance of a baby due to oligohydramnios experienced when in the uterus. It includes clubbed feet, pulmonary hypoplasia and cranial anomalies related to the oligohydramnios.

DUPLICATION OF URINARY TRACT:

Duplicated ureters, also known as duplicated collecting system or duplex kidney, is the most common birth defect related to the urinary tract. Both males and females are affected but the condition is more common in females. Ureters are long, narrow tubes that drain urine from the kidneys to the urinary bladder.

ECTOPIC URETER:

It is a medical condition where the ureter, rather than terminating at the urinary bladder, terminates at a different site. In males this site is usually the urethra, in females this is usually the urethra or vagina.

URACHAL ANOMALY:

It develops from the failure of the urachal communication between the bladder and umbilicus to properly obliterate during fetal development. A major theory is that fetal bladder outlet obstruction may cause urine to escape via a patent urachus like a pop-off valve.

CONGENITAL MEGACYSTIS:

It is a rare distension of the bladder with thin walls and massive vesicoureteral reflux. The distension of the bladder starts prenatally. The surgical treatment (after 6 months) is directed against the vesicoureteral reflux.

BLADDER EXSTROPHY:

It is a congenital abnormality of the bladder. It happens when the skin over the lower abdominal wall (bottom part of the tummy) does not form properly, so the bladder is open and exposed on the outside of the abdomen.

CONGENITAL ADRENAL HYPERPLASIA:

It is an inherited condition caused by mutations in genes that code for enzymes involved in making steroid hormones in the adrenal glands. The most common enzyme defect, 21-hydroxylase deficiency, leads to excess amounts of male hormones being produced by the adrenal glands.

CLASSIC (CHILD AND ADULT) ADRENOGENITAL SYNDROME:

It is also known as congenital adrenal hyperplasia (CAH), is caused by an inherited enzyme deficiency in the adrenal cortex that leads to altered levels of adrenal cortical hormones.

2. ABNORMALITIES OF GENITAL SYSTEM:

Anomalies of genital system include; the defects of genital ducts, sex determination defects, defects the uterine tube, vagina and uterus. It also include the defects related to urethra, testis and inguinal canal.

MIXED GONADAL DYSGENESIS

It is a condition that affects how the body grows and develops before birth and at puberty. People with MGD have gonads (glands) that may not develop fully, and they may not make typical amounts of hormones.

HYPOSPADIAS:

It is a condition in which the opening of the urethra is on the underside of the penis instead of at the tip. The location of the opening can vary and can be anywhere from underneath the tip of the penis (more common) to the base of the penis (less common).

EPISPADIAS:

It is a rare birth defect located at the opening of the urethra. In this condition, the urethra does not develop into a full tube, and the urine exits the body from an abnormal location. The causes of epispadias are unknown. It may be related to improper development of the pubic bone.

AGENESIS OF EXTERNAL GENITALIA:

Females with vaginal agenesis typically have normal external genitalia and ovaries. As a result, they go through puberty and develop breasts and pubic hair, but they will not have periods. There may be a small pouch or dimple where a vaginal opening should be.

BIFID PENIS AND DIPHALLIA:

True diphallia refers to complete penile duplication, each with two corpora cavernous and a corpus spongiosum, whereas bifid phallus is characterized by only one corpus cavernosum present in each penis. It is most frequently associated with bladder exstrophy, due to a malformation of the anterior abdominal wall.

MICROPENIS:

It is a medical term for a condition usually discovered in infants through a newborn examination. As the term suggests, micropenis refers to an abnormally small but normally structured penis. The condition is caused by hormonal or genetic abnormalities.

ECTOPIC TESTIS:

It is where one of the testicles has not descended into the scrotum as normal, but instead has taken a different path and has descended through the abdominal cavity until it has settled in the pre-pubic area in the inguinal canal, instead of in the scrotum.

CRYPTORCHIDISM:

It is the failure of one or both testicles to move down into the scrotum. This is due to abnormal androgen production or gubernaculum shortening.

HYDROCELE:

It is the build-up of fluid around the testicles, causing swelling in the scrotum. Hydroceles can be present at birth or affect infants and children. They may also occur adolescents or adults as a result of infection, inflammation, or injury to the testicles.

CONGENITAL INGUINAL HERNIA

It occurs when a sac-like projection of the abdominal cavity extends down the groin on one or both sides toward the scrotum in males or labia in females.

KEY NOTES
A- The formation of urinary and genital system are so much interwoven embryologically that both arise from intermediate mesoderm however both are distinguished functionally.
B- The evolution of kidney system is three tier: pronephros, mesonephros and metanephros kidney system.
C- There are certain developmental abnormalities associated with the urogenital system associated with the kidneys, ureters, urethra, intersex defects, bladder defects etc.

13

THE DEVELOPMENT OF NERVOUS SYSTEM

LEARNING OBJECTIVES

- GENERAL INTRODUCTION OF THE DEVELOPMENT OF NERVOUS SYTEM
- THE DEVELOPMENT OF CENTRAL NERVOUS SYSTEM
- THE DEVELOPMENT OF SPINAL CORD
- THE DEVELOPMENT OF BRAIN
- THE DEVELOPMENT OF HIND BRAIN
- THE DEVELOPMENT OF MID BRAIN
- THE DEVELOPMENT OF FORE BRAIN
- THE FORMATION OF DIENCEPHALON
- THE DEVELOPMENT OF PITUTIARY GLAND
- THE DEVELOPMENT OF TELENCEPHALON
- THE DEVELOPMENT OF CEREBRAL COMMISURE
- THE DEVELOPMENT OF PERIPHERAL NERVOUS SYTEM
- THE DEVELOPMENT OF SPINAL NERVES
- THE DEVELOPMENT OF CRANIAL NERVES
- THE DEVELOPMENT OF AUTONOMIC NERVOUS SYSTEM
- SYMPATHETIC NERVOUS SYSTEM
- PARASYMPATHETIC NERVOUS SYSTEM
- DEVELOPMENTAL ABNORMALITIES OF THE NERVOUS SYSTEM
- KEY NOTES.

THE DEVELOPMENT OF NERVOUS SYSTEM:

This chapter deals with the formation of nervous system and its associated anomalies. The development of nervous system is three tier in origin:

1. The development of central nervous system which comprises of the development of spinal cord and brain along with their protective structures.
2. The development of the peripheral nervous system which is associated with the development of cranial and spinal nerves. However it also deals with the formation of the neurons outside the central nervous system that connects the peripheral structures to central nervous system.
3. The development of the autonomic nervous system which gives innervation to the combination of tissues, smooth muscles and glandular epithelium.

THE DEVELOPMENT OF CENTRAL NERVOUS SYSTEM:

- ✓ Initially, the development of central nervous system begins from the flattened ectodermal cellular plate on the posterior aspect of the trilaminar embryo. This flattened cellular plate is known as neural plate which develops the groove like structure called as neural groove. Afterwards the lateral appendages of the neural groove elevates to form the neural folds that later on approximate to each other and form the neural tube.
- ✓ The development of neural tube starts in the cranio- caudal direction, It continues to fuse until a small orifice remain at the caudal end albeit it has also the opening at cranial end which is known as rostral neuropore which closes at the 25th day of gestation. While

the caudal neuropore closes at 27th day of gestation. The tube has a hollow canal known as neural canal which communicates freely with the amniotic cavity.

- The neural tube demarcates from the surface ectoderm after the closure of neuropore and aggregation of the neural folds cell occur between the neural tube and the surface ectoderm. This separated cluster of cells is known as the neural crest cells. These neural crest cells later on differentiate into the autonomic ganglia, sensory ganglia, spinal ganglia, Schwann cells, the melanocytes and the cells of suprarenal medulla.

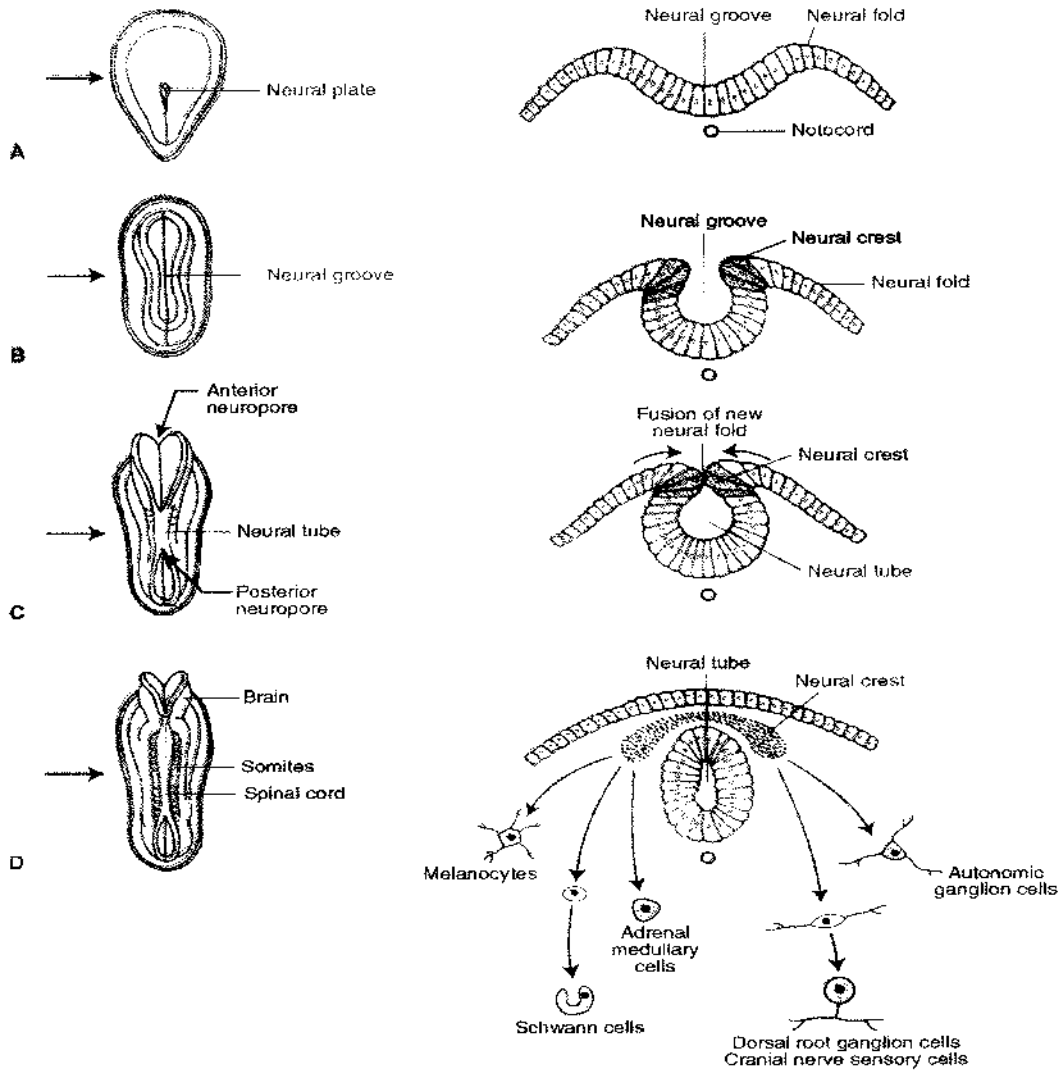


Fig 13.1: The process of Neurulation

THE DEVELOPMENT OF SPINAL CORD:

- ✓ The development of the spinal cord begins caudal to the 4th pair of somites from the caudal eminence of the neural plate. Initially the walls of the neural tube are thick and have pseudo stratified columnar epithelium. For the sack of description the development of spinal cord has been categorized in the following three phases;
  1. The ventricular Phase: This phase consists of the ependymal layer of the cells and it constitutes the innermost layer of the neural tube. It forms the neuroepithelial cells. This phase has two forms of precursor cells known as neuroblasts and glioblasts that form the neurons and neuroglia respectively.
  2. The intermediate Phase: This phase has the mantle layer of cells which surrounds the myoepithelial cells. It forms the gray matter of the spinal cord.
  3. The marginal phase: It is formed of marginal layer of cells. It forms the outermost layer of the neural tube. It contains nerve fibres which later on myelinated to give white appearance to the neural tract therefore it is also called as white matter.
- ✓ Regarding the development of the horns of gray matter the neural tube continues to be narrowed and form the dorsoventral groove, moreover the thickenings in the lateral

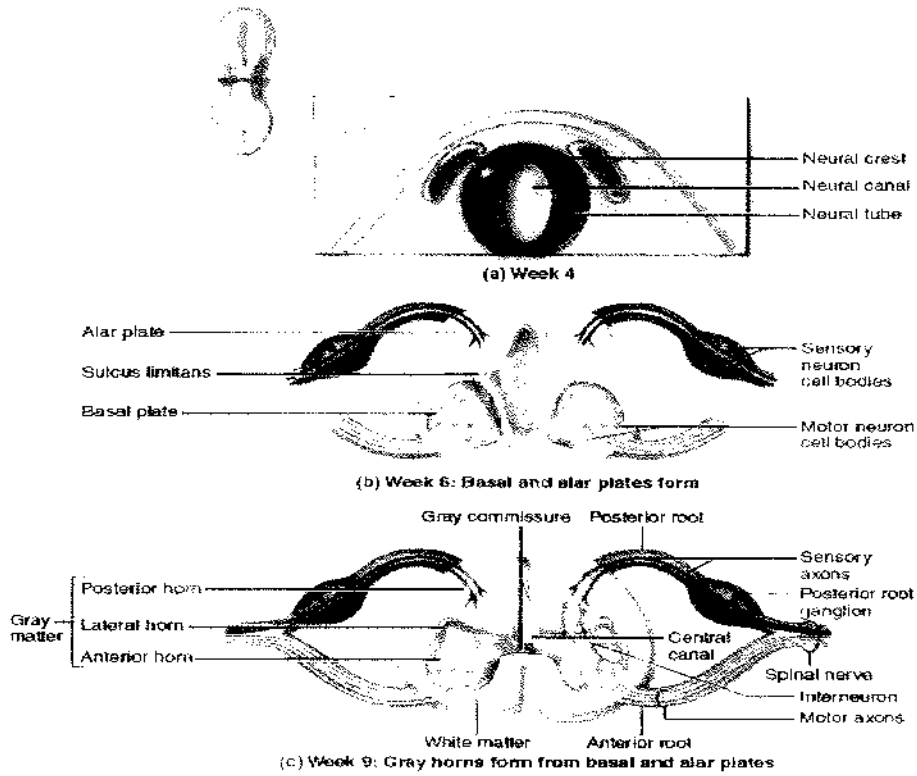


Fig 13.2: The development of Spinal cord

- ✓ wall also takes place but the roof, alar and basal plates remain thin. Basal plates form the anterior horn of spinal cord while alar plates form the posterior horn of the spinal cord. Roof plates is formed by the approximation of two alar plates however the approximation of basal plates form the floor of the central canal. There is the clear demarcation between the basal and alar plates which is formed by the longitudinal ridges known as sulcus limitans.

THE DEVELOPMENT OF SPINAL GANGLIA:

Neural crest cells gives rise to the unipolar neurons in the spinal ganglia. Initially the spinal ganglia has bipolar axons but later on these process join together in T shaped manner to give rise characteristic appearance of unipolar neurons. Its peripheral process conduct the signals towards the cell body. The dorsal roots of spinal nerves are formed by the central processes of spinal ganglion however its peripheral process give rise to sensory endings to various organs.

THE DEVELOPMENT OF SPINAL MENINGES:

Initially the condensation of mesenchyme around the neural tube develops presumptive meninges. This membrane soon divides into the outer thicker membrane called as the dura matter while the inner thin layer is known as the pia arachnoid. Both are jointly known as leptomeninges. The formation of vacuolation between the leptomeninges takes place which soon coalesce to form the fluid filled cavity. The formation of cerebrospinal fluid begins to secrete during 2nd month of development.

POSITIONAL CHANGES OF THE SPINAL CORD:

Spinal cord is present at entire the length of embryo however at birth the termination of the spinal cord occurs at the 3rd lumber vertebrae while in adult the termination takes place at the 2nd lumber or the 3rd lumber or somewhere between them. Below this termination end a fine hair like structure appears known as filum terminale.

THE PROCESS OF MYELINATION OF NEURONS:

Myelin is basically a protein that clothes the neuron and reduces the impedance in the transmission of impulses. The process of myelination begins in the fetal period and continues till the 1st year of post natal life.

The myelin sheath is formed by the oligodendroglial cells that originates from the neuroepithelial cells. The plasma membrane of these cells wrap around the axons in onion like manner to form its several layers. However myelin sheaths around the peripheral neuron are of Schwann cell origin.

THE DEVELOPMENT OF BRAIN:

The development of brain is associated with the formation of the neural tube. As neural tube forms during the 4th week of development, with that the portion of neural tube cranial to the 4th somite begins to develop into the brain. The first indication of the brain development appears when there is the formation of primary brain vesicles. The primary brain vesicles later on develops into the different parts of the brain named as prosencephalon, mesencephalon and rhombencephalon. However during the early 2nd month of development prosencephalon further divides into the secondary brain vesicles.

THE FLEXURES OF BRAIN:

Initially the presumptive brain has the same basic outline structure like the developing spinal cord however with the formation of flexures there are categorical variations in the basic structure of brain at different levels. With the development of flexures there is also alteration of gray and white along the different levels of brain.

The process of development of flexure begins during the early 2nd month of development, mid brain flexure appear as the consequence of head folding at mesencephalic region while cervical flexure appears at the junction of spinal cord and rhombencephalon. Later on due to unequal growth of brain between these flexures produces pontine flexures. Pontine flexure demarcates the hind brain into myelincephalon and metancephalon.

THE DEVELOPMENT OF HIND BRAIN:

The development of hind brain begins as the hind brain vesicle which is soon demarcated by the pontine flexure into caudally lying myelincephalon and rostrally lying metancephalon.

MYELENCEPHALON

It develops into the structure that is considered as a transition channel between the spinal cord and the brain, this developing part is named as medulla oblongata. Its alar and basal plates likewise the spinal cord also contain the motor nuclei. Theses nuclei are;

1. Somatic efferent group; It lies medially and form the cephalic continuation of the anterior horn cells. It includes the neurons of hypoglossal nerve, abducent nerve, accessory nerve and glossopharyngeal nerve. It is also known as the somatic efferent motor column
2. Special visceral efferent; It lies in intermediate position and supply to the striated muscles of the pharynx.

3. General visceral efferent; It lies laterally and supply to the involuntary musculature of respiratory, alimentary, and cardiac system. The alar plates in this region contains three plates of sensory relay nuclei ;
   a- Lateral sensory relay nuclei; It receives the general sensory fibres that perceives the sensations of pain temperature and touch from the pharyngeal region through glossopharyngeal nerve. These nuclei are also known as somatic afferent neurons.
   b- Intermediate sensory relay nuclei; It receives impulses from the taste buds of the tongue, palate, oropharynx and epiglottis by the vestibulochochlear nerve. These nuclei are also known as special afferent neurons.
   c- Medial sensory relay nuclei; it receives the interceptive perceptions from the heart and alimentary system. These nuclei are also known as general visceral afferents

METENCEPHALON:

The pons and cerebellum develop from the walls of metencephalon however the cavity of metencephalon forms the cranial part of the 4th ventricle.

The basal plates of the metencephalon have three groups of motor nuclei which are named as; the medially lying somatic efferent group which contains the nucleus of abducent nerve, the special visceral efferent group which contain the nuclei of trigeminal and facial nerve and the general visceral group having axons the supply to the submandibular and sublingual glands.

The alar plates contain the three groups of sensory nuclei which include; the laterally lying somatic afferent group having nuclei of trigeminal nerve, the special afferent group and the general visceral afferent group.

Moreover the marginal part of basal plates by expanding forms the bridge like connecting link between cerebral and cerebellar cortexes which is known as pons.

THE DEVELOPMENT OF CEREBELLUM:

The cerebellum develops from the thickened portion of the alar plates lying dorsolaterally, this thickened portion is known as the cerebellar swellings which later on approximate and overgrow in the rostral half of the 4th ventricle however it also overlaps with pons and medulla oblongata.

Neuroblasts of the alar plates differentiate into the various groups' neurons and nuclei.

The cerebellum is divided into three lobes according to its evolution.

1. The archicerebellum: It is the oldest part of cerebellum has connection with the vestibular apparatus. It is also known as floccunodular lobe.
2. The paleocerebellum: It is phylogenetically more recent in development, it constitute the vermis an anterior lobe of cerebellum. It is associated with the sensory signalling of the limbs.
3. The neocerebellum: It constitute the posterior lobe of the cerebellum. It is phylogenetically a nascent in development. It controls the selective limb movements.

THE DEVELOPMENT OF CHOROID PLEXUSES:

- ✓ The development of choroid plexuses take place from the roof plates of the rhombencephalon and diencephalon. Choroid plexuses is the modification of ependymal cells of the 4th ventricle which is clothed by the pia mater. The vascular membrane along with pia mater form the tela choroidea that is the sheet of pia mater covering the caudal portion of the 4th ventricle. Furthermore with the act of active proliferation pia mater grows inside the 4th ventricle where it is differentiated into the choroid plexuses. Initially the function of the choroid plexuses is to secrete the ventricular fluid which later on mixes with fluid of brain, spinal cord and fluid of leptomeninges to form the cerebrospinal fluid.

THE DEVELOPMENT OF MIDBRAIN:

- ✓ The development of the midbrain starts with the appearance of midbrain vesicle. The midbrain vesicle like other vesicles consist of the basal and alar plates which later on receive and give out various processes and have different sensory and motor nuclei.
- ✓ The neuroblasts of the basal plates n differentiation forms the red nuclei, substantia nigra, reticular formation of tegmentum and the nuclei of occlumotor and trochlear nerves. The marginal layer of the basal plates develop into the descending tracts such as the corticopontine tract, corticobulbar tract and corticospinal tract.
- ✓ The alar plates form the superior and inferior nuclei however alar plates along with the roof plates form the tectum.
- ✓ The neural canal of the midbrain narrows and forms the cerebral aqueduct which connects the 3rd and the 4th ventricles.

THE DEVELOPMENT OF FOREBRAIN:

- ✓ The development of forebrain begins early in the 2nd month of gestation with the closure of rostral neuropore, with this two pairs of diverticula appears laterally. One is converted into the optic vesicle and forms the presumptive retina and optic nerves and the second pair of diverticula known as telencephalic vesicles one on each side forms the primordia for cerebral hemisphere however their cavities forms the lateral ventricles. The

primordial cerebral hemisphere soon demarcates into the anterior part known as telencephalon and posterior part known as diencephalon. The cavities of telencephalon and diencephalon forms the 3rd ventricle.

THE FORMATION OF DIENCEPHALON:

- ✓ The development of diencephalon takes place from the caudal part of primitive cerebral hemisphere. The diencephalon comprises of the two alar plates and a roof plate however it does not have basal plates and floor.

- ✓ The roof plate is formed by the aggregation of ependymal cells having vascular mesenchyme. The pineal body which is initially mere an epithelial outgrowth later on becomes the solid organ by evagination and serves as the channel through which light affect the endocrine and behavioural system develops from the caudal part of roof plate.
- ✓ The alar plates develop into the lateral walls of the diencephalon; the hypothalamic sulcus divide the alar plates into dorsal and ventral regions which are known as thalamus and hypothalamus respectively. The portion of thalamus after active proliferation opens into the lumen of diencephalon and both sides of thalamic region fuse to form the Massa intermedia. However the hypothalamic area furthermore differentiate into the different areas which control the visceral activity. Mammillary body develops on the ventral surface of the hypothalamus in midline orientation.

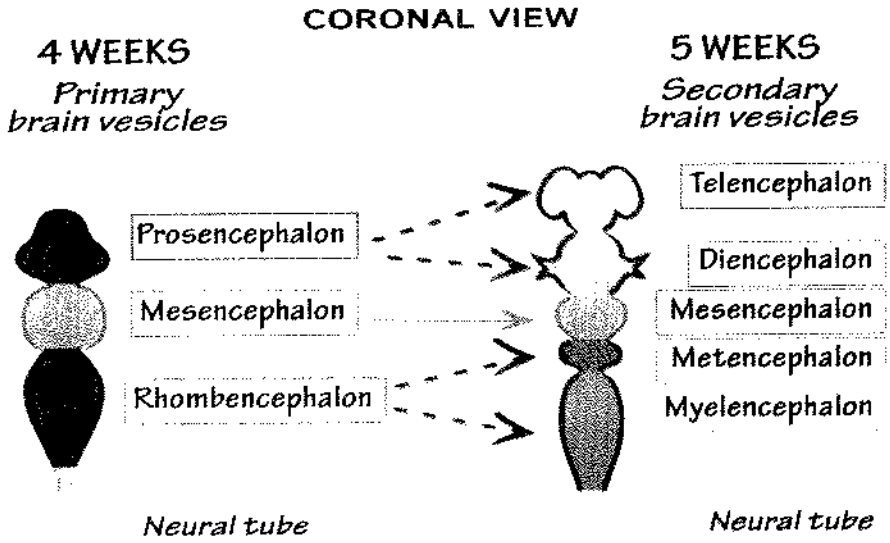


Fig 13.3: Differentiation of neural tube.

THE DEVELOPMENT OF PITUTIARY GLAND:

The pituitary gland develops from dual source however both are ectodermal in origin.

1. From Hypophyseal diverticulum which is also known as Rathke's pouch, it develops as an outgrowth from the ectoderm of the roof of stomodaeum.
2. From neurohypophyseal diverticulum which is the downgrowth of neuroectoderm. Due to the dual origin of pituitary gland it has two types of tissues one that has glandular manifestation and the other which has nervous manifestation. Both are known as adenohypophysis and neurohypophysis respectively.
   - ✓ During the late 2nd month of gestation the rathke's pouch elongates and constrict at its attachment to oral epithelium. At this stage it forms the connection with the infundibulum. By the 6th week connection between oral cavity and the diverticulum degenerates. Moreover after proliferation the anterior wall of hyophyseal pouch forms the adenohypophysis albeit it extends further to form pars tuberalis around the infundibulum. Cells of the posterior wall of the Hypophyseal pouch do not proliferate and converted into pars intermedia. The part of neuroectoderm that develop from the neuroectoderm is known as neurohypophysis. The infundibular portion gives rise to the median eminence, infundibular stem and pars nervosa.

THE DEVELOPMENT OF TELENCEPHALON:

Telencephalon develops from two anterolateral outpocketings of the presumptive cerebral hemisphere. The median portion forms the lamina terminalis however cavities form the lateral ventricles that have the communication with the interventricular foramina of monro.

- ✓ The development of cerebral hemisphere starts early in the 2nd month of development. The developing cerebral hemisphere slowly expands and covers the diencephalon, mid brain and hind brain. Afterwards both cerebral hemispheres approximate towards each other in the midline orientation to form a fissure known as falx cerebri. Later on from the floor of each cerebral hemisphere the development of corpus striatum takes place. Corpus striatum expands posteriorly and divide into the caudate and lentiform nucleus. By the continuous expansion of cerebral hemisphere in dorsal, ventral and inferior directions to form the frontal, temporal and occipital lobes respectively, with further organization of the surface of cerebral hemispheres the formation of sulci and gyri takes place.

- ✓ The formation of cerebral cortex takes place from the pallium which is divided into two regions;
  1. The paleopallium which is located in the corpus striatum.
  2. The neopallium which is located between the hippocampus and paleopallium.

THE DEVELOPMENT OF CEREBRAL COMMISSURE:

With the development of different parts of brain there is also the concomitant development of nerve fibres which connect one part of brain to another, it is known as the commissure. There are certain number of commissure which include the lamina terminalis, anterior commissure, corpus collasum and hippocampal commissure etc.

EMBRYOLOGICAL TIDBITS!
A- The first commissure to appear is anterior commissure.
B- The 2nd commissure to appear is hippocampal commissure.
C- The largest commissure of the brain which connects the both cerebral hemisphere is corpus collasum.

THE DEVELOPMENT OF PERIPHERAL NERVOUS SYSTEM:

The peripheral nervous system comprises of the ganglia and nerves. The ganglia are of spinal, cranial and autonomic origin while the nerves are of spinal and cranial origin. The peripheral nervous system develops from the following constituents;

1. The neural crest cells which give rise the schawnn cells, dorsal root ganglia and the peripheral ganglia.
2. Mesoderm forms the dura mater and connective tissue of nerve fiber.
3. Neural tube give rise to the preganglionic fibers of autonomic nerves.

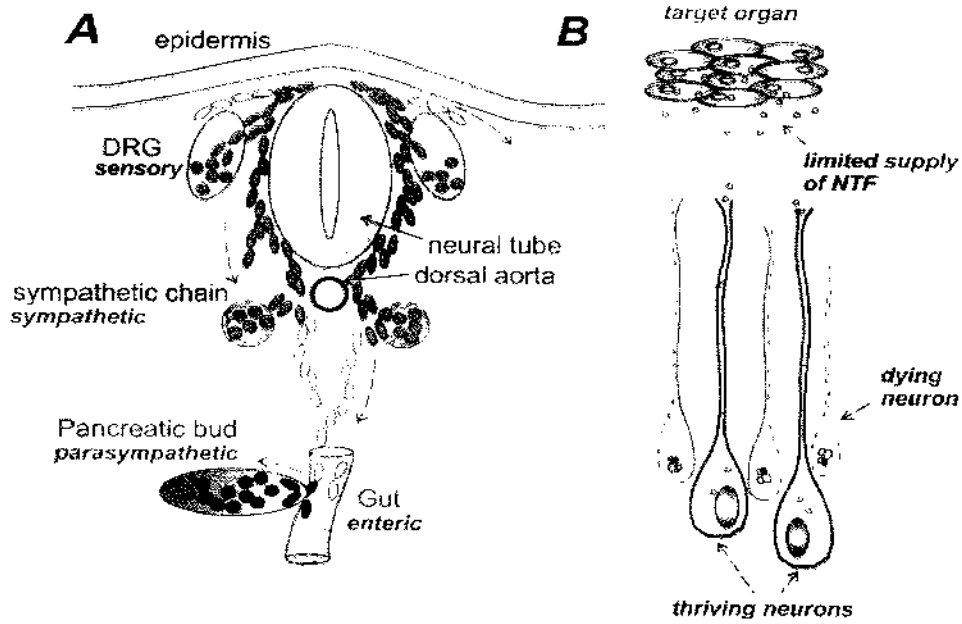


Fig 13.4: The development of peripheral nervous system.

THE DEVELOPMENT OF SPINAL NERVES:

Spinal nerves start to appear late in the 1st month of gestation from the nerve cells of the ventral horn of spinal cord. It consist of the two roots ventral and the dorsal one. The collection of dorsal nerve roots form the dorsal root ganglia and it has two processes the central process and the dorsal process. The spinal nerve divides immediately into two rami the ventral rami and the dorsal rami.

THE DEVELOPMENT OF CRANIAL NERVES:

Twelve pairs of cranial nerves start to develop during the 5th week of development.

1. Olfactory nerve. It forms from the olfactory placodes.

2. Optic nerve: It forms from the ganglion cells of the retina.
3. Occlumotor nerve: It forms from the basal plate of rostral mesencephalon.
4. Trochlear nerve: It forms from the basal plate of caudal mesencephalon.
5. Trigeminal nerve: It has two divisions the motor division which is derived from the basal plate of rostral pons while the sensory division which is derived from the neural crest cells.
6. Abducent nerve: It forms from the basal plate of caudal pons.
7. Facial nerve: It forms from the basal plate of pons.
8. Vestibulochochlear nerve: It is formed by the otic placodes.
9. Glossopharyngeal nerve: the sensory division of this plate is formed by the neural crest cells. While the motor division is formed by basal plate of medulla.
10. Vagal nerve: Sensory division is of neural crest cell origin while motor division forms from the basal plate of medulla.
11. Accessory nerve. It is derived from the basal plates of C_1 TO C_6 spinal segment.
12. Hypoglossal nerve: It forms from the basal plate of medulla.

THE DEVELOPMENT OF AUTONOMIC NERVOUS SYSTEM:

- ✓ THE AUTONOMIC NERVOUS SYSTEM is composed of 2 major portions which are anatomically and physiologically distinct: the sympathetic (thoracolumbar) and parasympathetic (craniosacral) systems. These systems are essentially motor systems since the sensory afferent nerves, with but a few exceptions, follow the ordinary sensory pathways. They are also essentially a 2-chain system of pre-and postganglionic fibers

THE SYMPATHETIC NERVOUS SYSTEM:

- ✓ Cells from the neural crest and ventral portion of the neural tube of the thoracic region migrate on either side of the spinal cord, toward the region just behind the dorsal aorta, at about 5th week of development. these are to become the sympathetic neuroblasts.
- ✓ Some detach themselves from the tube and arrange themselves along the motor root. The migrating cells form two chains of sympathetic ganglia on either side of the vertebral column
- ✓ The ganglia are segmental or metameric, but in contrast to the spinal ganglia, they are interconnected to each other by longitudinal nerve fibers or axons of some of the cells. The resulting interconnected ganglia form the lateral vertebral sympathetic chains

From their thoracic portion, the neuroblasts migrate and extend the sympathetic system into both the cervical (neck) and lumbosacral region

- An upward extension into the neck forms the superior, middle, and inferior cervical ganglia, which exist to supply structures of the head and neck
- Some of the sympathetic neuroblasts migrate even farther ventrally to form preaortic ganglia such as seen in the solar (celiac) and mesenteric plexuses, the
- visceral or gastrointestinal ganglia of the myenteric plexus of Auerbach, and in the submucous plexus of Meissner.
- Still other sympathetic cells migrate to the heart and lungs where they give rise to the sympathetic organ plexuses.

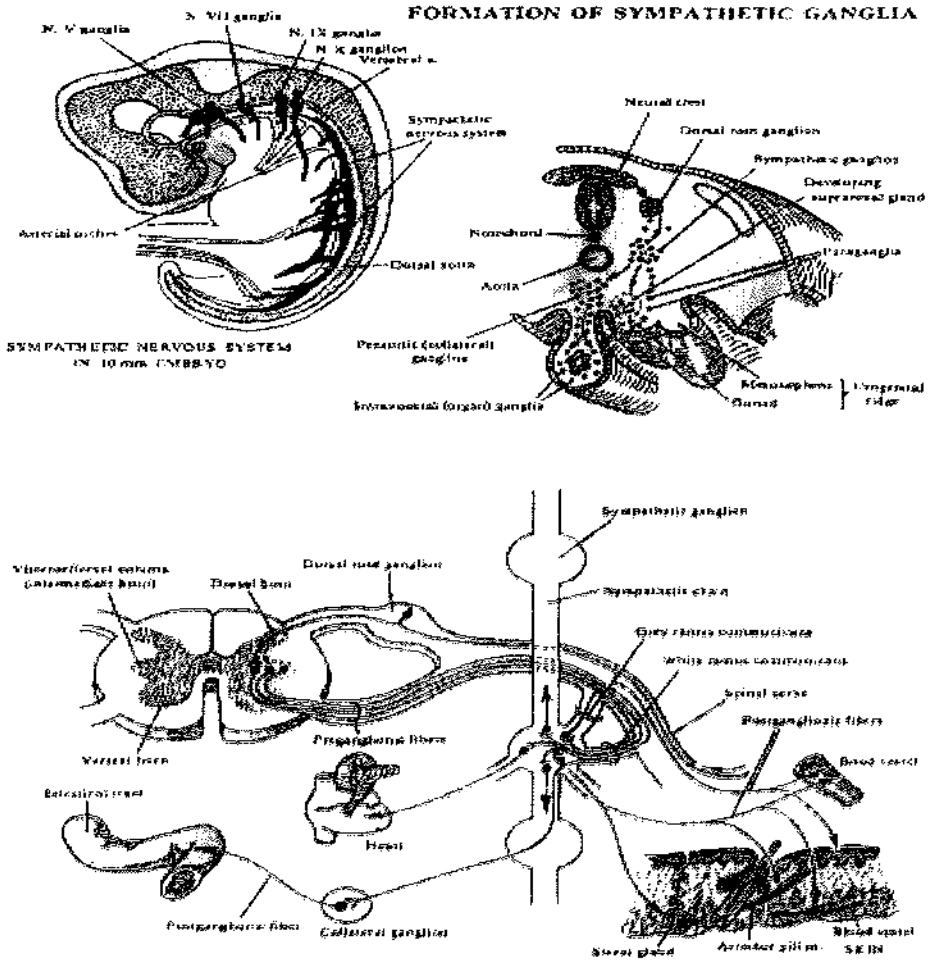


Fig 13.5 The development of sympathetic nervous

While the ganglia are forming, fibers coming from the visceral motor areas of the medulla and spinal cord make synapses with the sympathetic neuroblasts of 1 of the 3 ganglionic levels to form the preganglionic fibers.

- ✓ The preganglionic fibers are myelinated, and their paths from the spinal nerve to the sympathetic ganglia are thus called the white rami communicants.
- ✓ The axons of sympathetic neuroblasts, found in the ganglia, constitute the unmyelinated postganglionic fibers
  - These fibers leave the lateral chain ganglion system at 1 of its 3 levels to join the spinal nerves and are called the gray rami communicants.
  - The postganglionic fibers innervate diffuse structures such as smooth muscle, cardiac (heart) muscle and glands
  - The fibers innervating the eye, heart, and lungs, as well as the digestive system, originate in the three ganglion levels (cervical, thoracic, and preaortic, respectively).

THE PARASYMPATHETIC NERVOUS SYSTEM:

- The presynaptic parasympathetic fibers arise from neurons in nuclei of the brainstem and in the sacral region of the spinal cord. The fibers from the brainstem leave through the third cranial nerve that is occlumotor, facial nerve, glossopharyngeal and vagus nerves. The postsynaptic neurons are located in the plexuses near or within the structure being innervated.

DEVELOPMENTAL ABNORMALITIES OF THE NERVOUS SYSTEM:

1. NEURAL TUBE DEFECTS:

   Neural tube defects are birth defects of the brain, spine, or spinal cord. They happen in the first month of pregnancy, often before a woman even knows that she is pregnant. The two most common neural tube defects are spina bifida and anencephaly. In spina bifida, the fetal spinal column doesn't close completely. There is usually nerve damage that causes at least some paralysis of the legs. In anencephaly, most of the brain and skull do not develop. Babies with anencephaly are usually either stillborn or die shortly after birth.

2. SPINA BIFIDA OCCULTA:

   It is when a baby's backbone (spine) does not fully form during pregnancy. The baby is born with a small gap in the bones of the spine. Spina bifida occulta is common and happens in about 1 out of 10 people. Usually, it causes no health problems.

3. SPINA BIFIDA CYSTICA:

   A bony defect in the vertebral column that causes a cleft in that column. The meningeal membranes that cover the spinal cord and part of the spinal cord

protrude through this cleft, and are clearly visible. The opening can be surgically repaired, usually shortly after birth.

4. MENINGOMYELOCELE:

   It is a type of spina bifida. Spina bifida is a birth defect in which the spinal canal and the backbone don't close before the baby is born. This type of birth defect is also called a neural tube defect.

5. MYELOSCHISIS:

   It is the severest form of the spina bifida aperta. The nerve tissue is here fully bare and a dermal or meningeal covering is absent. With this abnormality, the closure of the neural folds fails to occur.

EMBRYOLOGICAL TID BITS!

The neural tube defects are due to the nutritional and environmental factors. Gene –gene or gene- environment interactions are probably occurs in the most cases. Folic acid supplements can reduce the incidence of neural tube defects.

1. CRANIOPHARYNGIOMA:

   It is a rare type of brain tumor derived from pituitary gland embryonic tissue that occurs most commonly in children, but also affects adults. It may present at any age, even in the prenatal and neonatal periods, but peak incidence rates are childhood-onset at 5–14 years and adult-onset at 50–74 years.

2. ENCEPHALOCELE:

   It is a neural tube defect characterized by sac-like protrusions of the brain and the membranes that cover it through openings in the skull. These defects are caused by failure of the neural tube to close completely during fetal development.

3. MEROENCEPHALY:

   It is a rare form of anencephaly characterized by malformed cranial bones and a median cranial defect, through which protrudes abnormal tissue, called the area cerebrovasculosa.

4. MICROENCEPHALY:

   It is a condition where a baby's head is much smaller than expected. During pregnancy, a baby's head grows because the baby's brain grows. Microcephaly can occur because a baby's brain has not developed properly during pregnancy or has stopped growing after birth, which results in a smaller head size.

5. HYDROCEPHALUS:

Hydrocephalus is a condition in which an accumulation of cerebrospinal fluid (CSF) occurs within the brain. This typically causes increased pressure inside the skull. Older people may have headaches, double vision, poor balance, urinary incontinence, personality changes, or mental impairment.

6. HOLOPROSENCEPHALY:

It is a cephalic disorder in which the prosencephalon (the forebrain of the embryo) fails to develop into two hemispheres. Normally, the forebrain is formed and the face begins to develop in the fifth and sixth weeks of human pregnancy. The condition also occurs in other species.

7. HYDRANENCEPHALY:

Hydranencephaly is a condition in which the brain's cerebral hemispheres are absent to a great degree and the remaining cranial cavity is filled with cerebrospinal fluid.

8. CHIARI MALFORMATION:

It is a condition in which brain tissue extends into your spinal canal. It occurs when part of your skull is abnormally small or misshapen, pressing on your brain and forcing it downward.

KEY NOTES!

a- This chapter deals with the formation of central nervous system, peripheral nervous system and the autonomic nervous system and their associated abnormalities. Formation of CNS commences by the formation of dorsal thickening of ectoderm in the mid line orientation. This thickening is known as neural plates which is induced by the underlying notochord and the mesenchyme.

b- Neural plate bends to form the neural folds which later on fuses to form the neural tube. The openings of tube on each side is communicated with overlying amniotic cavity which later on close on 25th and 27th day.

c- The cranial end of the neural tube cranial to the 4th somite stage forms the brain and the remainder part forms the spinal cord.

d- The pituitary gland develops from the neurohypophyseal diverticulum and the hypophyseal diverticulum.

e- Birth defects associated with the development of nervous system include; neural tube defects, meroencephaly, hydrocephalus etc.

14

THE DEVELOPMENT OF SKELETAL SYSTEM

LEARNING OBJECTIVES

- GENERAL INTRODUCTION OF THE DEVELOPMENT OF SKELETAL SYSTEM
- THE DEVELOPMENT OF CARTILAGE
- THE DEVELOPMENT OF BONE
- THE DEVELOPMENT OF JOINTS
- THE DEVELOPMENT OF AXIAL SKELETON
- THE DEVELOPMENT OF APPENDICULAR SKELETON
- DEVELOPMNTAL ABNORMALITIES ASSOCIATED WITH THE SKELETAL SYSTEM
- KEY NOTES

THE DEVELOPMENT OF SKELETAL SYSTEM:

This chapter deals with the formation of bones, cartilages and joints. It also deals with the structural arrangement of these bones, cartilages ad joints into the axial and appendicular orientations in order to facilitate the various types of movements in the body. In addition to this developmental abnormalities associated with the skeletal system have also been discussed in the last section of the chapter.

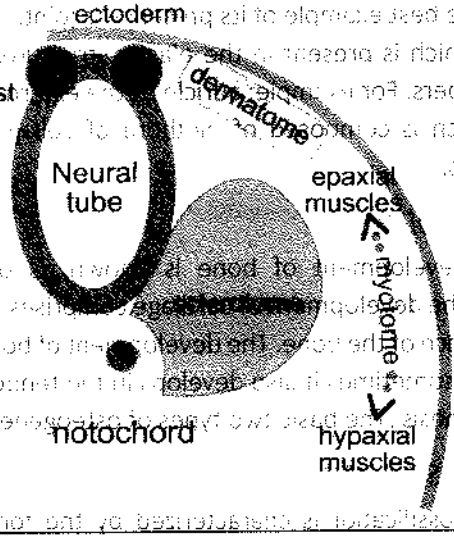


Fig 14.1 Initial stages of skeletal system development

Generally speaking, the development of skeletal system takes place from the mesoderm and the neural crest cells. What happens that mesodermal cells provide mesenchyme and during the early development of embryonic mesoderm it differentiates to form the three

different mesodermal regions that are known as paraxial mesoderm, intermediate mesoderm and lateral plate mesoderm. During the fourth week of gestation paraxial mesoderm comes to lie in the midline orientation and forms the clearly segmented blocks known as somites. Each somite later on distinguished into a sclerotome and a dermomyotome. Afterwards sclerotome differentiate to form the bones, cartilages and ligaments while dermomyotome derives the subcutaneous tissues and skeletal muscles. However the neural crest cells play role in the formation of the bones of craniofacial region after migration into the pharyngeal arches, discussed in detail in head and neck section.

THE DEVELOPMENT OF CARTILAGE:

During the early 2nd month of development the mesenchymal tissues differentiate to form the sclerotome which is enough capable to form the cartilage. Initially the condensation of mesenchymal cells form the basic framework of cartilage. Later on these mesenchymal congregations of cells undergoes the process of proliferation and enlargement to form the prechondrocytes. These prechondrocytes after some modification convert into the chondroblasts which secretes the ground substance called as chondrocytic matrix that is later on deposited by the collagenous or elastic fibers to form cartilage.

There are three basic types of cartilage;

2. Hyaline cartilage which is widely present in the body composed of fine bundles of collagen fibers. The best example of its presence is joint.
3. Elastic cartilage which is present in the elastic structures of the body. It is composed mainly of elastic fibers. For example; auricle of the external ears.
4. Fibrocartilage which is composed of plethora of collagen fibers. It is present in the intervertebral discs.

THE DEVELOPMENT OF BONE:

The process of development of bone is known as osteogenesis. The process of osteogenesis likewise the development of cartilage comprises of the genesis of the bone cells and the ground substance of the bone. The development of bone takes place in mesenchyme and cartilage however sometimes it also develops in the tendon. Patella is the best example of this type of osteogenesis. The basic two types of osteogenesis is given as under;

INTRAMEMBRANOUS OSSIFICATION:

Intramembranous ossification is characterized by the formation of bone tissue directly from mesenchyme. Flat bones, such as the parietal and occipital bones, are formed using this process.

Intramembranous ossification forms flat and irregular bones. In this process, mesenchymal cells differentiate directly into osteoblasts; specialized cells that secrete bone matrix. As the osteoblasts are housed within the matrix they become progressively distanced from each other

but remain connected through thin cytoplasmic processes. The osteoblasts differentiate into osteocytes and their processes are enclosed within canaliculi as the matrix becomes calcified. As the bone tissue develops, osteoblasts create a network of trabeculae and spicules. Concurrently, more surrounding mesenchymal cells differentiate into osteoprogenitor cells and come into contact with newly formed bone spicules. These cells will become osteoblasts, secrete more matrix, and continue to generate bone. This process is referred to as appositional growth.

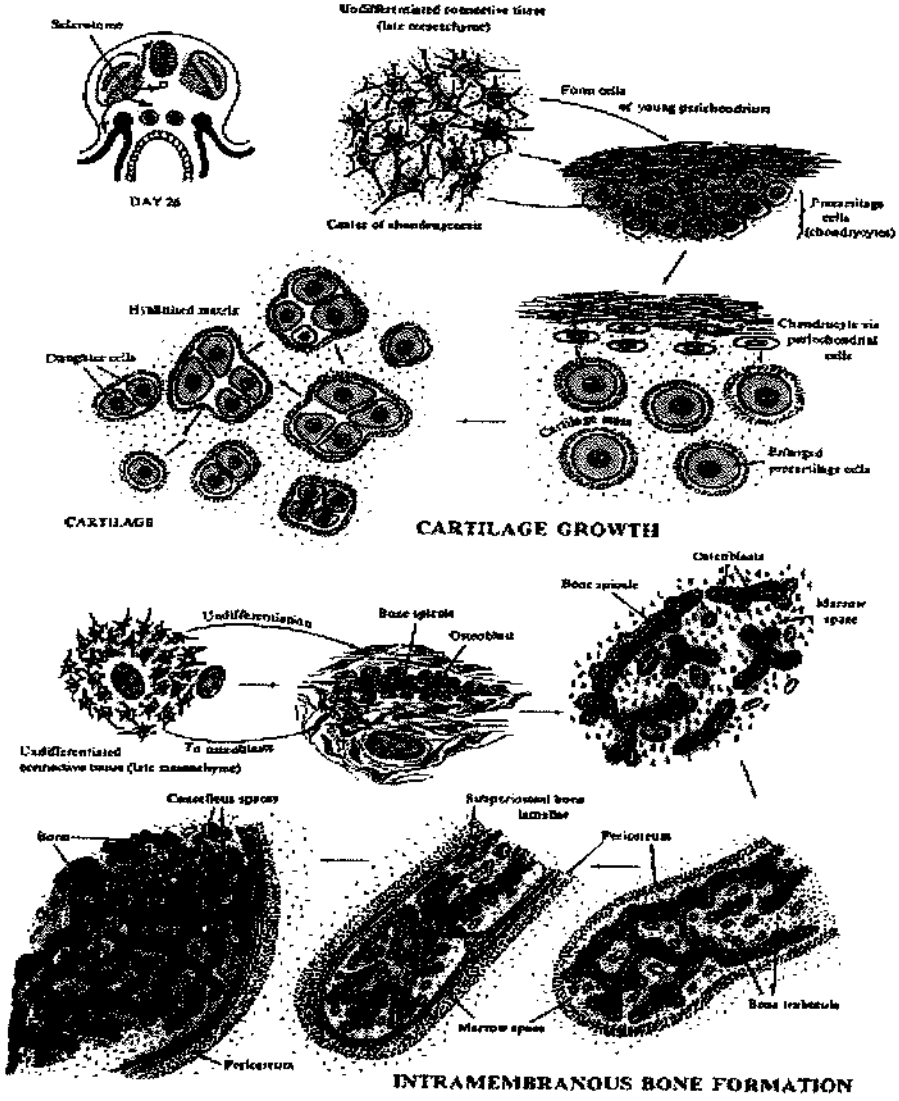


Fig 14.2: the process of intramembranous ossification.

ENDOCHONDRAL OSSIFICATION:

This type of ossification deals with the replacement of cartilaginous structure by the bony tissues. Example of this type of ossification is the long bones.

The process of endochondral ossification is given as under;

First, a cartilage model of the bone is formed; mesenchymal cells condense and differentiate into chondrocytes, forming the hyaline cartilage model. The chondrocytes hypertrophy and the extracellular matrix surrounding them becomes calcified. Blood vessels invade the center of the cartilage model and cause the perichondrium to differentiate into periosteum. As this occurs, chondrogenic cells convert to osteoprogenitor cells. Osteoprogenitor cells then convert to osteoblasts. Bone matrix secreted by the osteoblasts forms a bone collar. The bone collar prevents nutrients from reaching the hypertrophied chondrocytes, causing them to degenerate.

Osteoclasts, cells that break down bone, arrive and form holes in the bone collar allowing the passage of periosteal buds. Periosteal buds consist of blood vessels, osteoprogenitor cells, and hemopoietic cells.

Osteoprogenitor cells brought to the developing bone through the periosteal buds divide, forming more osteoprogenitor cells. Some of these cells will differentiate into osteoblasts that will continue to form bone matrix on the surface of the calcified cartilage.

As the bone matrix calcifies, it forms the calcified cartilage-calcified bone complex

The bone collar continues to grow in either direction towards the epiphyses and osteoclasts resorb the calcified cartilage-calcified bone complex to widen the marrow cavity.

Secondary ossification centers are found at the epiphyses of long bones. This process is similar to that of the primary center of ossification, but occurs without a bone collar. Instead, osteoprogenitor cells enter the epiphyseal cartilage, differentiate into osteoblasts, and secrete matrix on the cartilage framework. Long bones increase in length at the secondary ossification centers.

THE DEVELOPMENT OF JOINTS:

During the 6th week of development in the interzonal region of joints the mesenchymal condensation occurs which is marked by the beginning of joint development. However by the gradual modifications these primitive joints acquire the adult shape by the eighth week of development. There are three basic types of joints discussed here.

1. FIBROUS JOINTS:
   The development of these joints take place by the differentiation of mesenchyme into the fibrous tissue. The best example of this type of joint is the sutures which are present in the cranium.

2. CARTILAGINOUS JOINTS:

The development of these joints is associated with the interzonal mesenchymal differentiation which lead to the formation of hyaline cartilage or fibrocartilage. For example pubic symphysis and costochondral joints.

3. SYNOVIAL JOINTS:

The development of synovial joints is associated with the cartilaginous joints as the mesenchyme between the ends of cartilaginous bars undergoes the process of differentiation which consequently develops into the capsular and articular ligaments from the peripheral portion of mesenchyme. However central region of mesenchyme forms the joint cavity and the articular surfaces. For example; knee, hip and elbow joints.

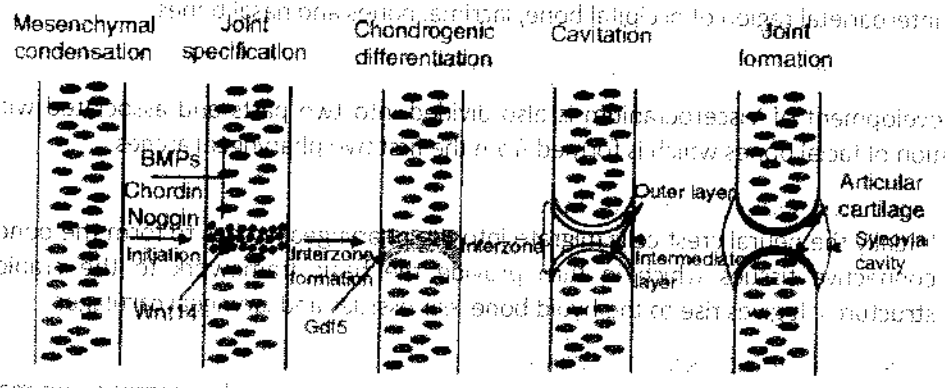


Fig 4: the development of joints

THE DEVELOPMENT OF AXIAL SKELETAL:

The development of axial skeleton includes the formation of cranium, vertebral column, ribs and sternum.

FORMATION OF THE CRANIUM:

The development of cranium is divided into two parts on the basis of structural development. These two parts are;

1. Neurocranium which is a bony part that covers the brain.
2. Viscerocranium which is the facial skeleton develops from the pharyngeal arches.

Generally speaking, the cranium is mesenchymal in origin. Initially the bony part of cranium develops by the ossification of primordial structure which is known as desmocranium mesenchyme.

THE DEVELOPMENT OF NEUROCARNIUM:

The development of Neurocranium has been classified into two parts;

a- CARTILIGINEOUS NEUROCRANIUM:
Initially it consists the various cartilages which lie in the front of rostral limit of notochord. These cartilages form the prechordal chondrocranium. The cartilages which is present posterior to this region arise from the occipital sclerotomes and form the chordal chondrocranium. The base of the skull is formed by the fusion and ossification of these cartilages. In short, cartilaginous neurocranium forms the base of skull which consists of sphenoid bone, ethmoid bone, base of occipital bone and petrous part of temporal bone.

b- MEMBRANOUS NEUROCRANIUM:
Intramembranous ossification of the head region gives rise the calvaria which consists of the flat bones such as frontal bone, parietal bone, squamous temporal bones, interparietal region of occipital bone, lacrimal bones and nasal bones.

THE DEVELOPMENT OF VISCEROCRANIUM:

The development of Viscerocranium is also divided into two parts and associated with the formation of facial bones which is formed from the first two pharyngeal arches.

a- CARTILAGINOUS VISCEROCRANIUM:
Initially the neural crest cells migrate into the pharyngeal arches to form the bones and connective tissues which in turn provide the basic framework to the craniofacial structures. It gives rise to the hyoid bone, ear ossicles and laryngeal cartilages.

b- INTRAMEMBRANOUS VISCEROCRANIUM:
This type of Viscerocranium gives rise to squamous, temporal, zygomatic and maxillary bones by the process of intramembranous ossification of maxillary prominence however the mandibular prominence after forming meckle's cartilage undergoes the further intramembranous ossification and gives rise to the mandible.

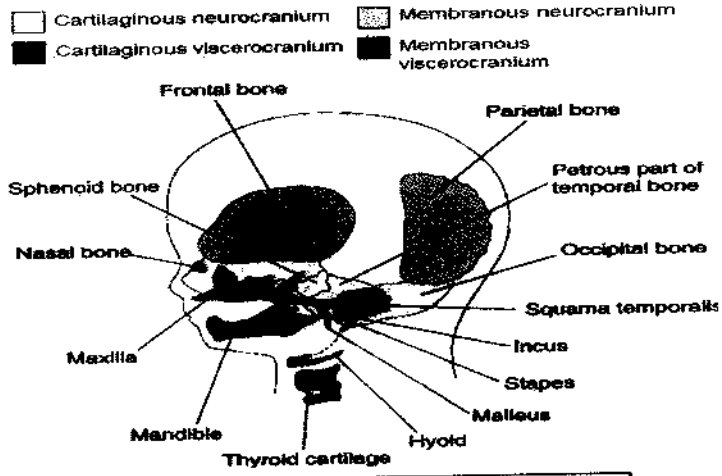
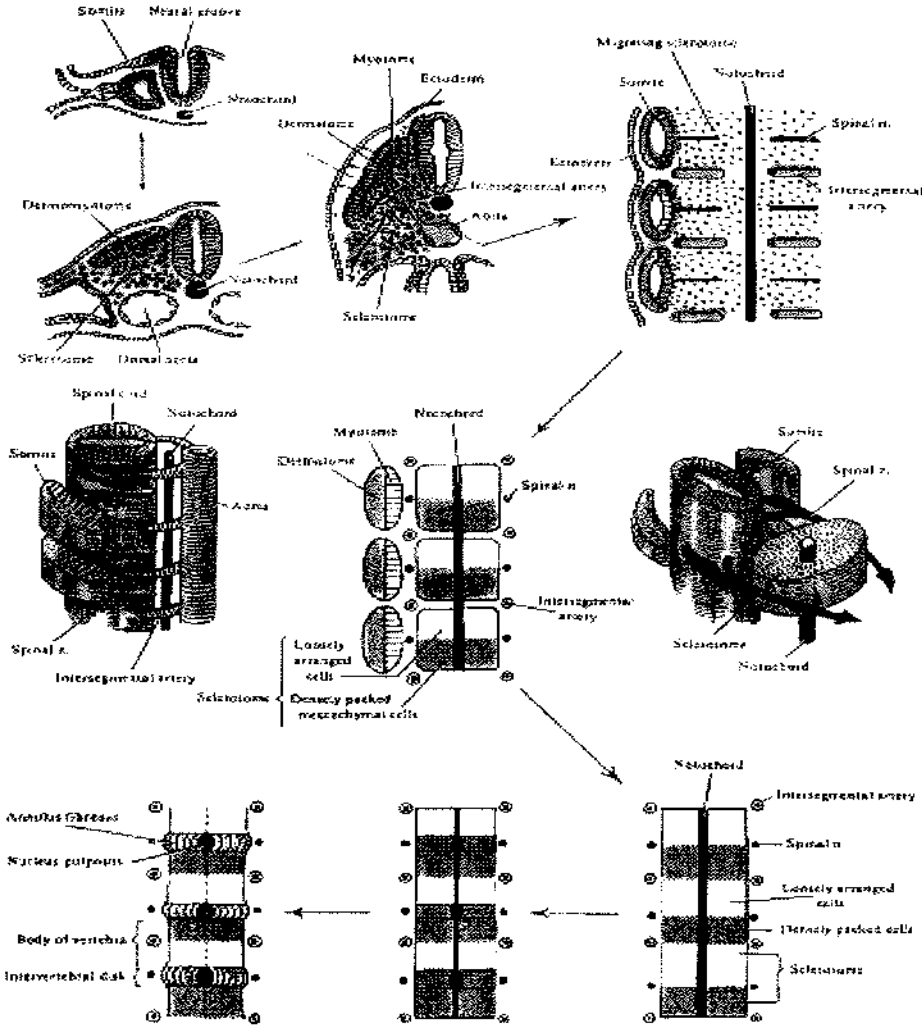


Fig 14.4: The development of neurocranium

FORMATION OF THE VERTEBRAL COLUMN:

The development of the vertebral column occurs when the mesenchymal cells differentiate to form the vertebrae by the fusion of caudal half of one sclerotome with the cranial half of the other. The notochord persists throughout the mesenchymal and cartilaginous stage of the vertebral column development. However it disappears as ossification of the vertebrae occurs. The remnant of notochord forms the central part of the intervertebral disc known as nucleus pulposus which is surrounded by the fibrous structure of sclerotomal origin known as annulus fibrosus. With the passage of development various processes are developed from the



STAGES IN DEVELOPMENT OF VERTEBRAE AND DISKS

Fig 14.5 Stages in development of vertebral column.

developing vertebrae, these processes are spinous process, transverse processes and vertebral arch.

FORMATION OF RIBS:

The development of ribs takes place from the mesenchyme of the costal process of thoracic vertebrae. With the passage of development these ribs undergo the process of ossification and grows into the adult ones. There are seven pair of true ribs, five pairs of false ribs and two pairs of floating ribs.

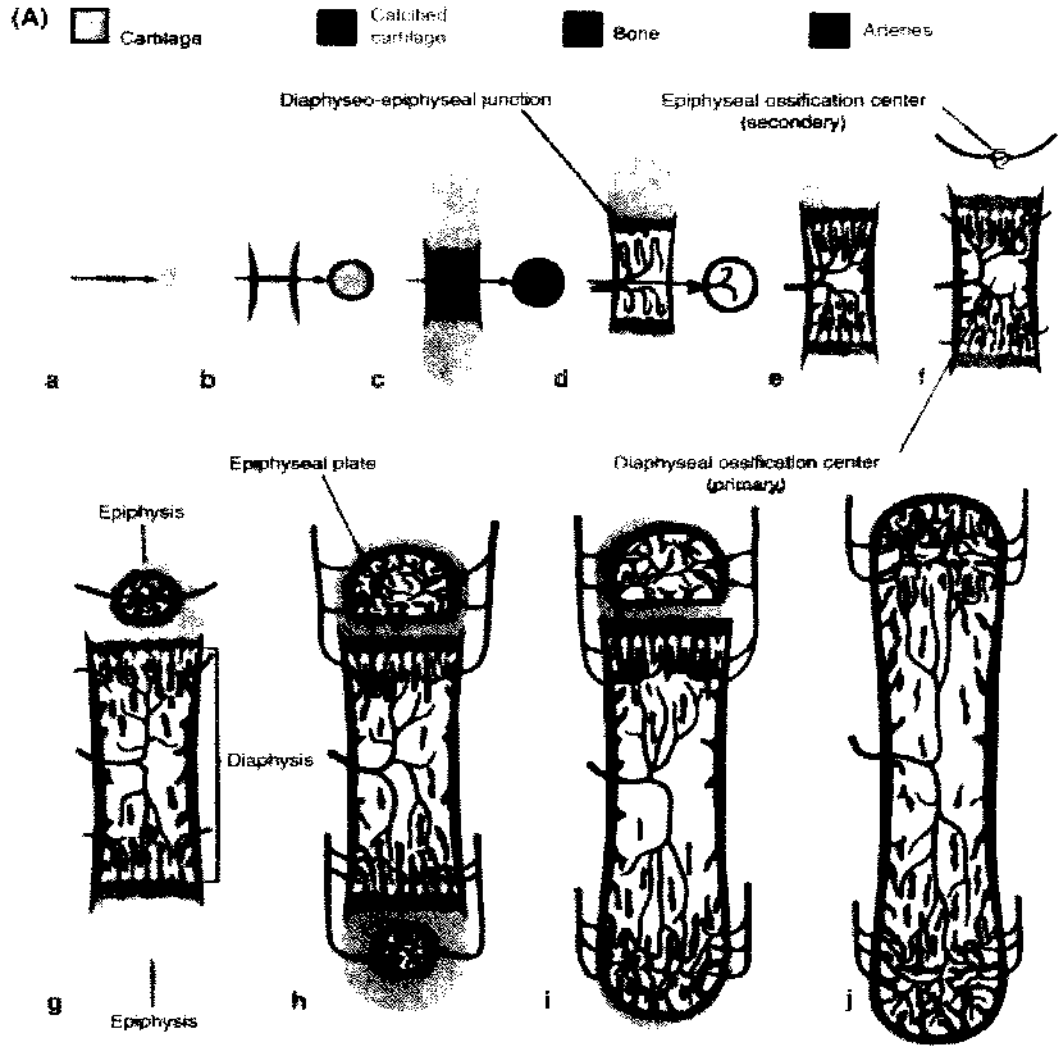


Fig 14.6. Formation of ribs.

FORMATION OF STERNUM:

Sternum develops from the sternal bars which are mesenchymal tissue bands appear on the ventrolateral aspect of the body wall. After chondrification they fuse craniocaudally in the midline orientation to form the framework of manubrium, sternbrae and xiphoid process.

THE DEVELOPMENT OF APPENDICULAR SKELETON:

The appendicular skeleton comprises of the limb bones and the pelvic and pectoral girdles. This skeleton begins to develop by endochondral ossification. Initially limb bones appear as the mesenchymal condensation early in the 2nd month of development which later on undergoes the process of chondrification. By the 12th week of development primary ossification centres begins to appear at diaphysis nearly in each bone. However after the birth secondary ossification centres appear at epiphysis.

DEVELOPMENTAL ABNORMALITIES ASSOCIATED WITH THE SKELETAL SYSTEM:

1. RICKETS:

   It is a condition that results in weak or soft bones in children. Symptoms include bowed legs, stunted growth, bone pain, large forehead, and trouble sleeping. Complications may include bone fractures, muscle spasms, an abnormally curved spine, or intellectual disability.

2. CHORDOMA:

   It is a rare type of cancerous tumor that can occur anywhere along the spine, from the base of the skull to the tailbone. It grows slowly, gradually extending into the bone and soft tissue around them.

3. KLIPPLE FEIL SYNDROME:

   It is a condition affecting the development of the bones in the spine. People with KFS are born with abnormal fusion of at least two spinal bones (vertebrae) in the neck. Common features may include a short neck, low hairline at the back of the head, and restricted movement of the upper spine.

4. SPINA BIFIDA:

   It is a birth defect that occurs when the spine and spinal cord don't form properly. It's a type of neural tube defect. The neural tube is the structure in a developing embryo that eventually becomes the baby's brain, spinal cord and the tissues that enclose them.

5. HEMIVERTEBRA:

   It is a condition where half of a vertebra in the spine does not form. This can cause scoliosis, which is an abnormal curve of the spine. Hemivertebrae occur in less than one in 1000 births.

6. RACHISCHISIS:

   It is a developmental birth defect involving the neural tube. This anomaly occurs in utero, when the posterior neuropore of the neural tube fails to close by the 27th intrauterine day.

7. ACRANIA:

   It is a rare congenital disorder that occurs in the human fetus in which the flat bones in the cranial vault are either completely or partially absent. The cerebral

hemispheres develop completely but abnormally. The condition is frequently, though not always, associated with anencephaly.

8. CRANIOSYNOSTOSIS:

It is a birth defect in which the bones in a baby's skull join together too early. This happens before the baby's brain is fully formed. As the baby's brain grows, the skull can become more misshapen. The spaces between a typical baby's skull bones are filled with flexible material and called sutures.

9. MICROCEPHALY:

It is a condition where a baby's head is much smaller than expected. During pregnancy, a baby's head grows because the baby's brain grows. Microcephaly can occur because a baby's brain has not developed properly during pregnancy or has stopped growing after birth, which results in a smaller head size.

10. ACHONDROPLASIA:

It is a disorder of bone growth that prevents the changing of cartilage (particularly in the long bones of the arms and legs) to bone. It is characterized by dwarfism, limited range of motion at the elbows, large head size (macrocephaly), small fingers, and normal intelligence.

11. OSTEOPETROSIS:

It is literally known as "stone bone", also known as marble bone disease or Albers-Schonberg disease, is an extremely rare **inherited disorder** whereby the **bones** harden, becoming **denser**, in contrast to more prevalent conditions like **osteoporosis**, in which the bones become less dense and more brittle, or **osteomalacia**, in which the bones soften. Osteopetrosis can cause bones to dissolve and break.

12. DYOSTOSIS:

It is a condition characterized by ribs that are fused together at the parts nearest the spine, along with misshapen or fused vertebrae. Babies born with this condition have small chests and severe breathing problems.

13. PLAGIOCEPHALY:

It is also known as flat head syndrome, is a condition characterized by an asymmetrical distortion (flattening of one side) of the skull. A mild and widespread form is characterized by a flat spot on the back or one side of the head caused by remaining in a supine position for prolonged periods.

14. ENCEPHALOCELE:

It is a neural tube defect characterized by sac-like protrusions of the brain and the membranes that cover it through openings in the skull. These defects are caused by failure of the neural tube to close completely during fetal development.

15. SCOLIOSIS:

Scoliosis is a sideways curvature of the spine. It is a sideways curvature of the spine that occurs most often during the growth spurt just before puberty. While scoliosis can be caused by conditions such as cerebral palsy and muscular dystrophy, the cause of most scoliosis is unknown.

16. SPNDYLOLISTHESIS:

It is a spinal condition that affects the lower vertebrae (spinal bones). This disease causes one of the lower vertebrae to slip forward onto the bone directly beneath it. It's a painful condition but treatable in most cases.

17. FUNEL CHEST:

It is also known as "Pectus excavatum" this occurs when child's breastbone is pressed inwards and they have a dip between their ribs. The deformity may be symmetrical (the same on both sides) or may be more prominent on one side of the chest. Some children with funnel chest will live a normal life.

KEY NOTES!

a- This chapter deals with the formation of bones, cartilages, joints and their orientation into the axial and appendicular skeletal in order to give the proper symmetry and facilitate the movements in the body.

b- The skeletal system is derived from the mesodermal cells which later on form the mesenchyme and the neural crest cells. The maturation of primitive bones into the adult structure is done by the process of ossification. Some bones like flat bones of skull undergo the process of intramembranous ossification while large bones undergo the process of endochondral ossification.

c- The cranium is comprised of the neurocranium and Viscerocranium. Both undergoes the process of intramembranous and endochondral ossification.

d- Regarding the formation of vertebral column and ribs, they take place from the sclerotomes, however sternum is derived by the mesoderm in the ventral body wall.

e- During the course of development of skeletal many anomalies may appear such as spina bifida, crainiosynostosis, plagiocephaly, microcephaly etc.

15

THE DEVELOPMENT OF MUSCULAR SYSTEM

LEARNING OBJECTIVES

- GENERAL INTRODUCTION OF THE DEVELOPMENT OF MUSCULAR SYSTEM
- THE DEVELOPMENT OF SKELETAL MUSCLES
- THE DEVELOPMENT OF SMOOTH MUSCLES
- THE DEVELOPMENT OF CARDIAC MUSCLES
- DEVELOPMENTAL ABNORMALITES ASSOCIATED WITH THE MUSCULAR SYSTEM
- KEY NOTES

THE DEVELOPMENT OF MUSCULAR SYSTEM:

This chapter deals with the process of myogenesis. Most of the muscular system, if not all, is formed by the modification of mesoderm. However, some exceptions are there; the muscles of the iris is derived from the neuroectoderm and the muscles of the oesophagus is formed by the transdifferentiation of the smooth muscles. The process of myogenesis is controlled by the genetic factors. The dermomyotome of each somite differentiates to form the myotome and dermatome. Myoblasts are mesenchymal in origin. In the later part of this chapter the development of three types of muscles have been discussed.

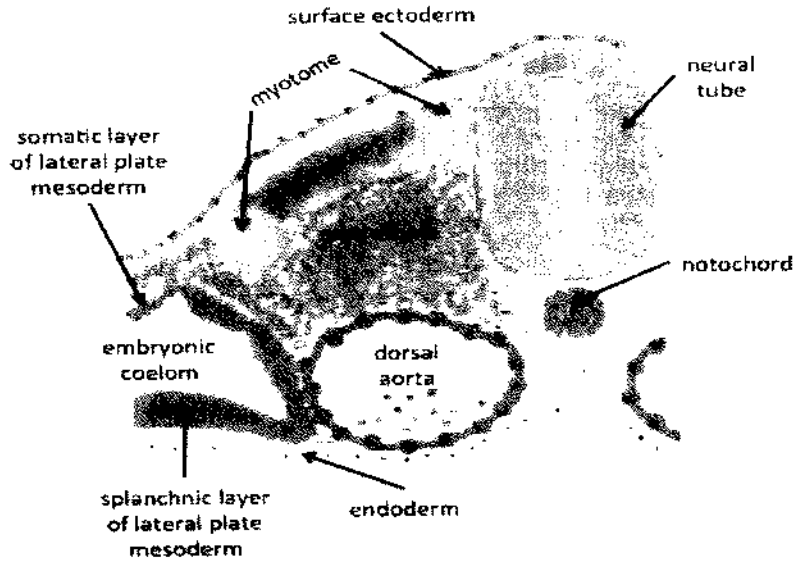


Fig 15.1. Initial stages in the development of muscular system.

1. THE DEVELOPMENT OF SKELETAL MUSCLES:

The formation of the skeletal muscles takes place from the mesoderm in the myotome part of the somite. The formation of myoblasts take place after the differentiation of thickened myotomes. Later on the approximation of the myoblasts form the multinucleated fibers. The myotome finally divides into the dorsal and ventral portion known as epimere and hypomere respectively. Epimere gives rise the extensor muscles of the neck and vertebral column while hypomere forms the flexor muscles of the sex organs, pelvic diaphragm, anus and the vertebral column. Epimere and hypomere are innervated dorsal primary ramus and ventral primary ramus respectively.

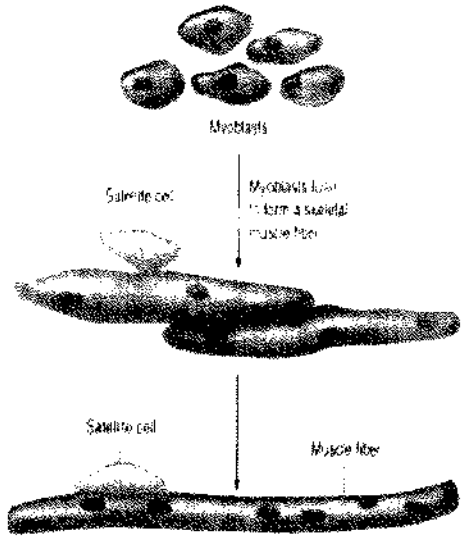


Fig 15.2: The development of skeletal system.

FORMATION OF THE HEAD MUSCLES:

The mesenchyme of pharyngeal arches give rise to the muscles of the head. Three pairs of the preotic myotomes form the muscles of eye while three pairs of the postotic myotomes form the muscles of the tongue.

FORMATION OF THE NECK AND TRUNK MUSCLES:

The muscles of the neck are formed from the hypomere. The fusion of hypomeres form the genohyoid, infrahyoid, prevertebral and scalene muscles. The muscles of the thorax are formed by the somatopleuric mesenchyme. However in the abdominal region muscles are derived from the mesenchyme.

FORMATION OF THE LIMB MUSCLES:

The limb musculature is formed by the myoblasts of the developing bones. These myoblasts form the tissue mass along ventral and dorsal aspect of the body which later on gives rise to the flexor and extensor muscles respectively.

2. THE DEVELOPMENT OF SMOOTH MUSCLES:

The splanchnic mesoderm forms the smooth muscle. The first indication of smooth muscle development is the formation of the elongated nuclei in spindle shaped myoblasts. Initially a plethora of myoblasts differentiate but they unlike skeletal muscles remain mononucleated. Later on the division of existing myoblasts slowly replace the new ones to form the smooth muscles. With further development filamentous but nonsacromeric contractile units are formed. The muscles of the lymphatics and blood vessels are formed by the somatic mesoderm. However, the formation of muscle of iris, myoepithelial cells of mammary glands and sweat glands are formed by the ectoderm.

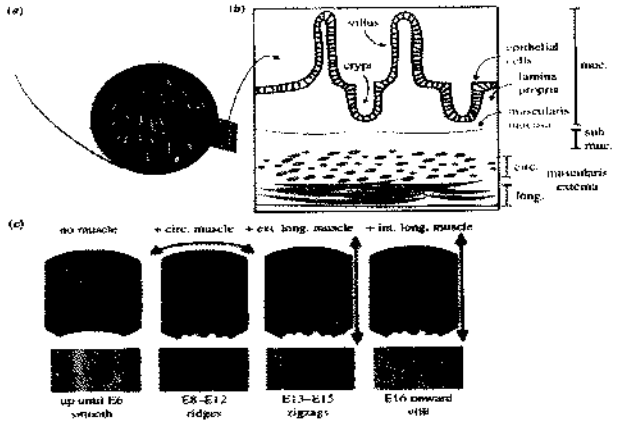


Fig 15.3: The development of smooth muscles.

3. THE DEVELOPMENT OF CARDIAC MUSCLES:

The splanchnic mesoderm forms the cardiac muscles. In the formation of cardiac muscle cells the myoblast adhere to form the intercalated discs. The development of myofibrils in the cardiac muscles are like the skeletal muscles except that myoblasts do not fuse. Afterwards, the development of purkinge fibers takes place from the myofibrils.

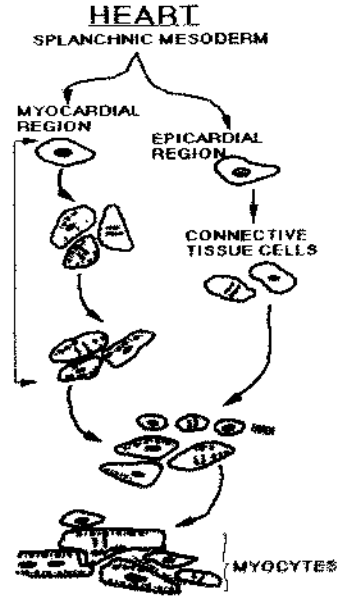


Fig 15.4: The development of cardiac muscles.

DEVELOPMENTAL ABNORMALITIES ASSOCIATED WITH THE MUSCULAR SYSTEM:

1. POLAND SYNDROME:
   It is a disorder in which affected individuals are born with missing or underdeveloped muscles on one side of the body, resulting in abnormalities that can affect the chest, shoulder, arm, and hand.

2. ARTHROGRYPOSIS:
   It is a term describing a number of conditions that affect the joints. Often times both the arms and legs are affected. The cause of arthrogryposis is unknown, but it almost always results from another condition. Arthrogryposis is typically discovered in utero or at birth.

3. CONGENITAL TORTICOLLIS:
   It is also called twisted neck or wry neck, is a condition in which an infant holds his or her head tilted to one side and has difficulty turning the head to the opposite side.

4. PRUNE BELLY SYNDROME:
   It is also known as Eagle-Barrett syndrome, is a rare disorder characterized by partial or complete absence of the stomach (abdominal) muscles, failure of both testes to descend into the scrotum (bilateral cryptorchidism), and/or urinary tract malformations.

5. MUSCULAR DYSTROPHIES:
   These are group of inherited diseases that damage and weaken your muscles over time. This damage and weakness is due to the lack of a protein called dystrophin, which is necessary for normal muscle function. The absence of this protein can cause problems with walking, swallowing, and muscle coordination.

6. THOMSEN'S DISEASE:
   It is an inherited myopathy, a disease that causes problems with the tone and contraction of skeletal muscles. It doesn't cause muscle atrophy (shrinkage); instead, it sometimes can cause muscle enlargement and increased muscle strength.

KEY NOTES!
a- This chapter deals with the formation of muscular system which occurs through the formation of myoblasts, which undergo proliferation to form myocytes.
b- The development of skeletal system takes place from the somites however muscles of head and neck are derived from the mesenchyme of pharyngeal arches.
c- Most of the smooth muscles and cardiac muscles are derived from the splanchnic mesoderm.
d- Regarding developmental anomalies, absence or variation of some muscles is prominent.

16

THE DEVELOPMENT OF LIMBS

LEARNING OBJECTIVES

- GENERAL INTRODUCTION OF THE DEVELOPMENT OF LIMBS
- FORMATION OF THE LIMB BUDS
- FORMATION OF THE DIGITS
- THE PROCESS OF OSTEOGENESIS
- THE PROCESS OF MYOGENESIS
- VASCULOGENESIS OF THE LIMBS
- ROTATION OF THE LIMBS
- DEVELOPMENTAL ABNORMALITIES ASSOCIATED WITH THE LIMBS

THE DEVELOPMENT OF LIMBS:

The upper and lower limbs (including the shoulder girdle and pelvic girdle) begin development in the 4th week of gestation. Usually the upper limb begins development first, with the lower limb often lagging 2-3 days behind. The limbs are well differentiated by the eighth week.

Formation of Limb Buds:

The limb buds are the precursor structures of the limbs. Their formation begins in the 4th week, with the activation of mesenchymal cells in the somatic layer of lateral plate mesoderm.

The limb buds first appear on the ventrolateral body wall initially and extend ventrally. They consist of a central core of undifferentiated mesenchyme tipped with a layer of ectoderm, the apical ectodermal ridge (AER).

Elongation occurs through proliferation of the underlying mesenchyme core, in which the AER plays a crucial role in ensuring that the mesenchyme immediately underneath it remains undifferentiated. As growth proceeds, the proximal mesenchyme loses signals from the AER and begins to differentiate into the constituent tissues of the limbs.

The AER itself is maintained by the Zone of Polarizing Activity (ZPA) which is found in the posterior base of the limb bud. The ZPA's secondary responsibility is to ensure asymmetry in the limbs.

The position of the AER is important as it marks the boundary between the dorsal and ventral limb ectoderm – the ectoderm is able to exert 'dorsalising and ventralising' influences over the mesenchyme core. For example, it removes hair follicles from the palms and soles of the feet.

Formation of the Digits:

As elongation continues, the mesenchyme condenses into plates forming the cartilaginous models of the future digital bones. The AER then breaks up and is maintained only over the tips of the future digits. The interdigital spaces are then progressively sculpted by cellular apoptosis.

THE PROCESS OF OSTEOGENESIS:

The process of ossification of long bones starts during the 7th week of development. The primary ossification centres located in the middle of long bones however ossification of small bones like carpel takes place in the post natal life probably a year after the birth.

THE PROCESS OF MYOGENESIS:

The muscle of limb is formed by the active proliferation of the mesenchymal cells known as the myogenic precursor cells originating from the somites. Moreover the myoblast assist in the formation of dorsal and ventral muscle masses which later on perform the function of extension and flexion respectively.

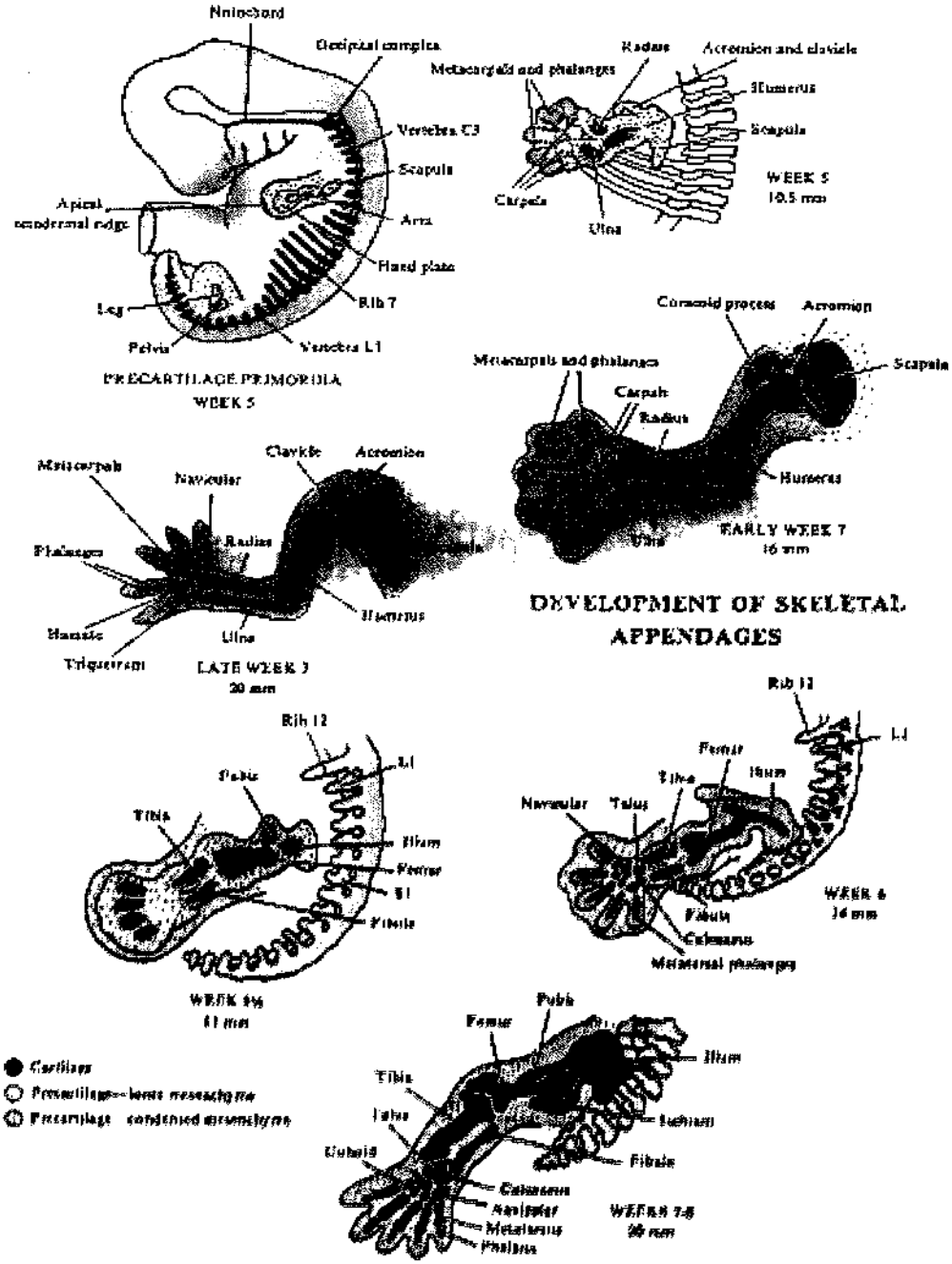
VASCULOGENESIS OF THE LIMBS:

The mesenchyme after active proliferation differentiates into the blood vessels. Most of the blood vessels, if not all, arise from the intersegmental arteries and drains into the cardinal veins.

ROTATION OF THE LIMBS:

The rotation of the limbs begins in the reverse direction probably in the 7th week of development.

- The upper limb rotates in the lateral direction by 90 degree and the presumptive elbows starts to appear dorsally and extensor muscles lie on the posterior aspect of the limb.
- The lower limb begins to rotate by 90 degree medially therefore the presumptive knees come to forward and extensor muscles lies on the ventral aspect of the lower limbs.


Notochord
Occipital somites
Vertebra C3
Scapula
Arm
Apical ectodermal ridge
Hand plate
Rib 7
Leg
Pelvis
Vertebra L1
PRECARTILAGE PRIMORDIA
WEEK 5
Radius
Acromion and clavicle
Metacarpals and phalanges
Humerus
Scapula
Carpals
Ulna
WEEK 5
10.5 mm
Coracoid process
Acromion
Metacarpals and phalanges
Scapula
Carpals
Radius
Humerus
Ulna
EARLY WEEK 7
16 mm
Clavicle
Acromion
Metacarpals
Navicular
Radius
Phalanges
Humerus
Hamate
Ulna
Triquetrum
LATE WEEK 7
20 mm
DEVELOPMENT OF SKELETAL APPENDAGES
Rib 12
L1
Pubis
Tibia
Ilium
Femur
S1
Fibula
WEEK 8½
31 mm
Rib 12
L1
Femur
Tibia
Ilium
Navicular
Talus
Fibula
Calcaneus
Metatarsal phalanges
WEEK 8
34 mm
Cartilage
Precartilage—loose mesenchyme
Precartilage—condensed mesenchyme
Pubis
Femur
Ilium
Tibia
Talus
Ischium
Fibula
Calcaneus
Navicular
Metatarsals
Phalanx
WEEK 7-8
26 mm

DEVELOPMENTAL ABNORMALITIES ASSOCIATED WITH THE LIMBS:

1. AMELIA:

It is the developmental defect of the limbs marked by the lack of one or more limbs.

2. SIRENOMELIA:

Sirenomelia, also called mermaid syndrome, is a rare congenital deformity in which the legs are fused together, giving the appearance of a mermaid's tail.

3. PHYCOMELIA:

It is a rare congenital deformity in which the hands or feet are attached close to the trunk, the limbs being grossly underdeveloped or absent. This condition was a side effect of the drug thalidomide taken during early pregnancy.

4. POLYDACTALY:

Polydactyly is a condition in which a person is born with extra fingers or toes. There are several types of polydactyly. Most often the extra digit grows next to the fifth finger or toe.

5. SYNDACTYLY:

The condition of having some or all of the fingers or toes wholly or partly united, either naturally (as in web-footed animals) or as a malformation.

6. BRACHYDACTYLY:

It is a shortening of the fingers and toes due to unusually short bones. This is an inherited condition, and in most cases does not present any problems for the person who has it.

7. GENU VALGUM:

Genu valgum, commonly called knock-knee, is a condition in which the knees angle in and touch each other when the legs are straightened. Individuals with severe valgus deformities are typically unable to touch their feet together while simultaneously straightening the legs.

8. GENU VARUM:

It is also called bow-leggedness, bandiness, bandy-leg, and tibia vara, is a varus deformity marked by (outward) bowing at the knee, which means that the lower leg is angled inward (medially) in relation to the thigh's axis, giving the limb overall the appearance of an archer's bow.

9. CLEFT FOOT:

Cleft foot is a rare congenital (meaning your baby was born with it) anomaly in which the foot didn't develop properly during fetal development. This causes the affected foot to have missing toes, a V-shaped cleft, and other anatomical differences. Cleft foot is very rare, affecting fewer than 1 in 1,000,000 babies.

10. CLUB FOOT:

Clubfoot refers to a condition in which a newborn's foot or feet appear to be rotated internally at the ankle. The foot points down and inwards, and the soles of the feet face each other. It is known as talipes equinovarus or congenital talipes equinovarus

11. PES PLANUS:

It also known as flat foot is the loss of the medial longitudinal arch of the foot, heel valgus deformity, and medial talar prominence. In lay terms, it is a fallen arch of the foot that caused the whole foot to make contact with the surface the individual is standing on.

12. PES CAVUS:

It is also known as high arch, is a human foot type in which the sole of the foot is distinctly hollow when bearing weight. That is, there is a fixed plantar flexion of the foot. A high arch is the opposite of a flat foot and is somewhat less common.

KEY NOTES!

a- The development of limbs start with the formation of limb buds late in the 4th week of development. The tissues of the limb bus are derived from two sources they are mesoderm and ectoderm.

b- Limb muscle are of mesenchymal origin. Initially the developing buds grow caudally then they project ventrally and lastly they rotate on the longitudinal axes.

c- The main defects of limb development are due to multifactorial inheritance.

17

THE DEVELOPMENT OF CARDIOVASULAR SYSTEM

LEARNING OBJECTIVES

- GENERAL INTRODUCTION OF THE DEVELOPMENT OF CARDIOVASCULAR SYSTEM
- THE DEVELOPMENT OF HEART
- THE DEVELOPMENT OF ARTERIAL SYSTEM
- THE DEVELOPMENT OF VENOUS SYSTEM
- THE DEVELOPMENT OF BLOOD
- FETAL CIRCULATION
- DEVELOPMENTAL ABNORMALITIES RELATED WITH CARDIOVASCULAR SYSTEM
- KEY NOTES.

THE DEVELOPMENT OF CARDIOVASCULAR SYSTEM:

The development of cardiovascular system occurs because the promptly multiplying embryonic cells can no longer satisfy the nutritional and oxygen needs by diffusion alone.
This chapter deals with the formation of following structures which satisfy the nutritional and oxygen needs of the body;

1. The development of Pumping system (HEART)
2. The development of Arterial system
3. The development of venous system
4. The development of blood vascular system.

1. THE DEVELOPMENT OF HEART:

- The development of the heart begins in the third week of gestation when the epiblastic cells differentiate to form the progenitor heart cells which are multipotent cardiac cells. Initially, they are present at the cranial end of primitive streak. Later on these cells transfer to the splanchnic layer of lateral plate mesoderm near the apex of neural folds where they clustered to form the primary heart field. Most of the parts of heart, if not all, develops from the primary heart field; Atria, left ventricle and some part of right ventricle develop from it. Concomitantly, the remaining parts of heart which includes the remaining right ventricle and the outflowing tract are formed by the secondary heart field cells which already reside in the splanchnic mesoderm anterior to the pharyngeal region.

- With the act of migration these cells try to arrange themselves in the maximum approximation and patterning so that later on spiralling of aorta and pulmonary artery maintained. This maintenance also ensure the exit of aorta and pulmonary artery from the right and left ventricles respectively. After the establishment of primary heart field, the pharyngeal endoderm undergoes the process of vasculogenesis then this region is called as cardiogenic area and the overlying embryonic cavity is known as pericardial cavity.

- The early development of the heart includes the formation of solid cord like structure in the cardiogenic area, these cords are known as the angioblastic cords which later on fuse to form the single heart tube. This heart tube undergoes the process of canalization. The heart tube continues to elongate as long as the cells are added from the secondary heart field. Tubular heart elongates and dilates to form the five dilations known as the truncus arteriosus, the bulbous cordis, the ventricle, the atrium and the sinus venosus. The truncus arteriosus is continuous to the aortic sac cranially which give rise to the aortic arch. The sinus venosus receives the umbilical, vitelline and the common cardinal veins from the chorion, yolk sac and embryo respectively. With further bending, the atrium and sinus venosus come to lie posterior to the truncus arteriosus, bulbous cordis and ventricle. The lengthening process is important for the formation of outflowing tract and the portion of right ventricle. This lengthening result into the formation of cardiac loop by the 4^{th} week of gestation. Regarding the formation of atrial portion, this is initially a paired structure outside the pericardial cavity, forms the common atrium and is incorporated into pericardial portion. The atrioventricular junction remains narrow and forms the atrioventricular canal which connect the early common atrium with the early embryonic ventricle.

- The proximal portion of the bulbous, bulbous cordis give rise to the trabeculated part of the right ventricle. The middle portion, the conus cordis give rise to the outflowing tracts of both ventricles however the distal part of bulbous, the truncus arteriosus will form the roots and proximal part of the aorta and pulmonary artery. The junction between the bulbous cordis and ventricle is known as bulbovetricular sulcus which remain narrow by primary interventricular foramen.

- External layer of the embryonic heart is formed by the splanchnic mesoderm and it is surrounded by cardiac jelly. Endocardium is formed by the endothelial lining of the heart tube. However visceral pericardium is derived from the cardiac jelly.

PARTIONING OF VARIOUS PARTS OF HEART:

Most of the times partioning occurs by the formation of two actively growing tissue masses from the opposite sides which later on approach each other and fuse. Thus, divide the lumen into two separate canals. Sometimes partioning may also occur by the single tissue mass which grows from one side and approach the opposite side to partition the lumen. This tissue mass is known as endocardial cushion.

- PARTIONING OF ATRIOVENTRICULAR CANAL:
  - ✓ Atrioventricular canal is portioned by the formation of endocardial cushions. These endocardial cushion fuse to separate the atrioventricular canal into right and left.

- PARTIONING OF PRIMITIVE ATRIUM:
  - ✓ Initially the atrium is one however later on it is separated into the left and right atrium by the development of septum primum and septum secundum.
  - ✓ Regarding septum primum, it is very fine membranous structure takes origin from the roof of primitive atrium and lengthens in the curtain like fashion leaving a large orifice while fusing with the endocardial cushions. Moreover the both sides cushions completely fuses with each other and obliterating the foramen primum. Just before this obliteration the central portion of the septum primum orifices to form the foramen secundum.
  - ✓ Regarding septum secundum, it is the thick membranous structure takes origin from the roof of primitive atrium and gradually overlaps the foramen secundum to partition the atrium incompletely leaving behind another foramen that is known as foramen ovale.
  - ✓ Cranial part of the septum primum disappears, however the caudal part forms the valve of foramen ovale. The foramen ovale closes after birth due to the approximation of septum primum and secundum albeit before birth it permits the blood to enter from right to left atrium.

- PARTIONING OF SINUS VENOSUS:
  - ✓ The development of sinus venosus begins as the separate tube but later on it dilated to form two horns, the left one is utilize in the formation of coronary sinus while the right one fuses with the right atrium to give rise its smooth part. The smooth part of the right atrium is known as sinus venarum. The smooth and rough part is demarcated internally as well as externally by crista terminalis and sulcus terminalis respectively.

- PARTIONING OF PRIMITIVE VENTRICLE:
  - ✓ The development of partioning in the ventricle begins as the septal partioning which arises from the floor of ventricle, this interventricular septum later on fuses with the

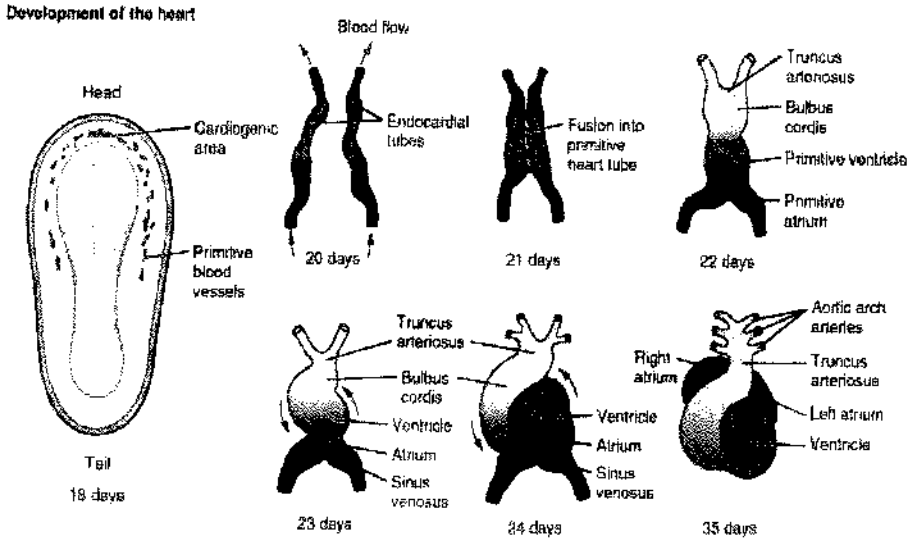


Fig 17.1: The development of heart.

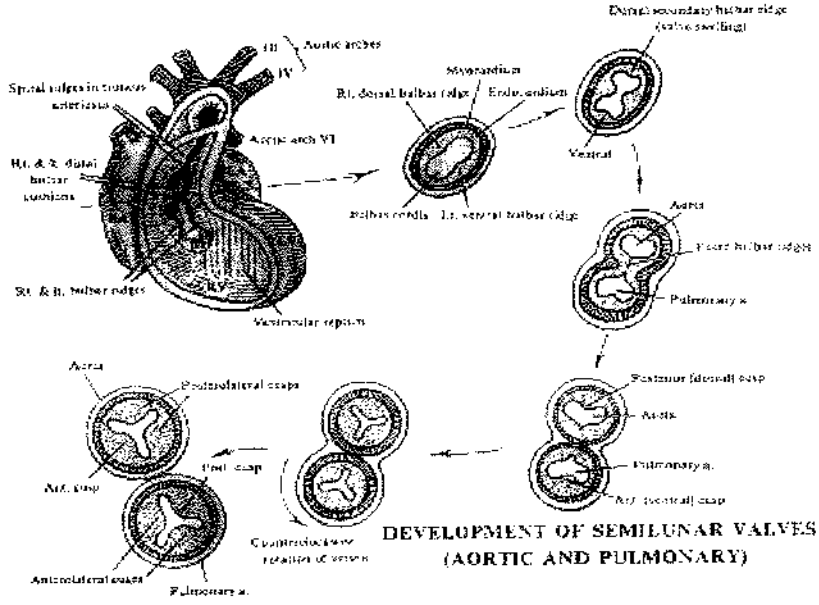
right bulbar ridge, left bulbar ridge and endocardial cushion to complete the septum. The cavitation of ventricle give rise the sponge like muscular bundles. These later on differentiate to form the pupillary muscles, chordae tendinea and trabeculae carneae.

- PARTIONING OF BULBUS CORDIS AND TRUNCUS ARTERIOSUS:
  - ✓ The partioning of bulbus cordis and truncus arteriosus develop by the proliferation of mesenchymal cells which give rise the bulbar ridges and truncal ridges

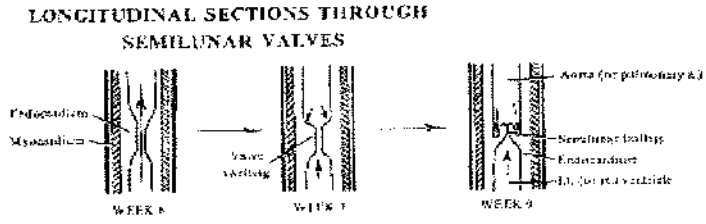
respectively. However both ridges are continuous, by the fusion and spiralling of both ridges at 180 degree forms the spiral aorticopulmonary septum which later on channelized the aorta and pulmonary trunk.

THE DEVELOPMENT OF HEART VALVE:

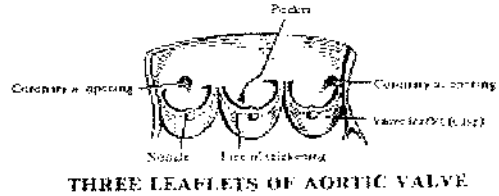
- ✓ Regarding the development of semilunar valves, it develops from the three outgrowth of subendocardial tissue around the opening of aorticopulmonary trunk and later on it modifies to form the cusps.



DEVELOPMENT OF SEMILUNAR VALVES (AORTIC AND PULMONARY)



LONGITUDINAL SECTIONS THROUGH SEMILUNAR VALVES



THREE LEAFLETS OF AORTIC VALVE

VALVE CUT OPEN AND SPREAD FLAT

Fig 1 / 2: The development of heart valves.

- ✓ Regarding the development of atrioventricular valves, it develops from the localized proliferation of cells around the atrioventricular canal.

THE DEVELOPMENT OF CONDUCTING SYSTEM:

- ✓ Conducting system comprises of sinoatrial node, atrioventricular node and bundle of his. At very first the pace maker of heart is present in caudal part of left cardiac lobe. Afterwards the sinus venosus assumes this function and sinus is shifted into the right atrium. Pace making tissue which is known as sinoatrial node lies near the opening of superior vena cava.

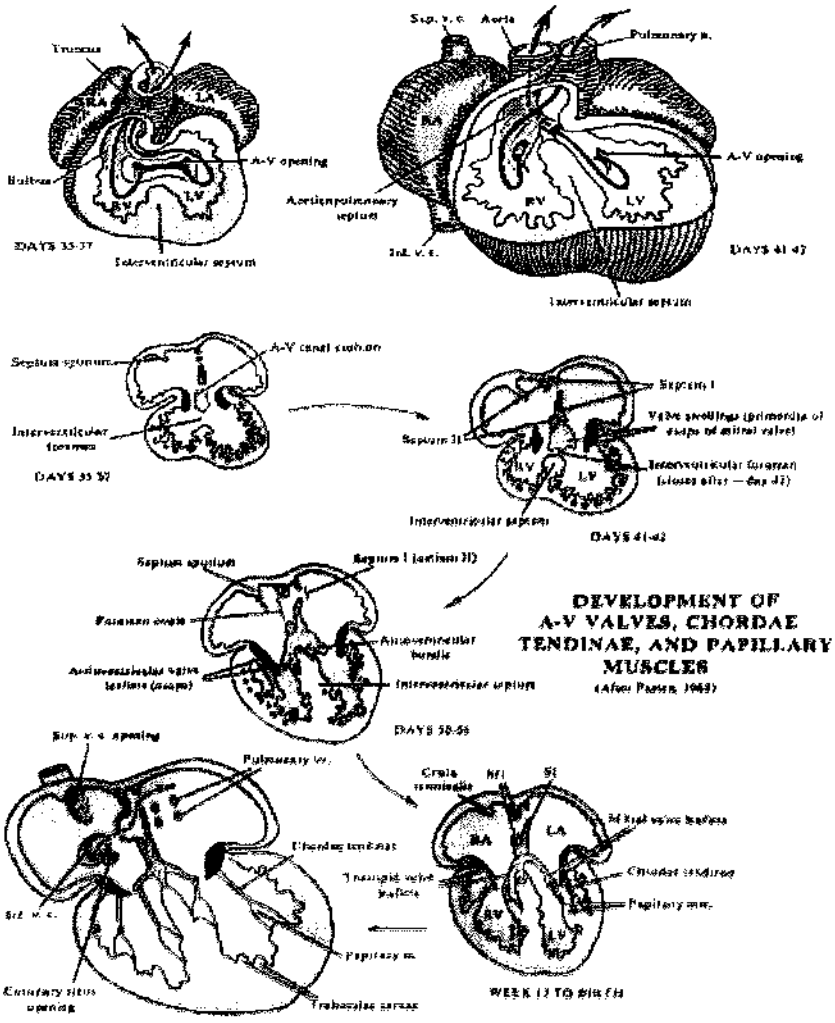


Fig. 17.3. The development of conducting system.

- ✓ Regarding the development of atrioventricular node and bundle of his, these are dual in origin derived from the myocardial cells in the left wall of sinus venosus and myocardial cells of atrioventricular canal.

2. THE DEVELOPMENT OF ARTERIAL SYSTEM:

The human arterial system originates from the aortic arches and from the dorsal aortae starting from the 4th week of embryonic life.

The development of the circulatory system initially occurs by the process of vasculogenesis, the formation of new blood vessels when there are no preexisting ones. Vasculogenesis occurs when endothelial precursor cells migrate and differentiate in response to local cues (such as growth factors and extracellular matrix) to form new blood vessels.

AORTIC ARCHES:

The aortic arches—or pharyngeal arch arteries—are a series of six, paired, embryological vascular structures that give rise to several major arteries. They are ventral to the dorsal aorta and arise from the aortic sac.

AORTIC ARCHES 1 AND 2:

The first and second arches disappear early, but the dorsal end of the second gives origin to the stapedial artery, a vessel that atrophies in humans, but persists in some mammals. It passes through the ring of the stapes and divides into supraorbital, infraorbital, and mandibular branches that follow the three divisions of the trigeminal nerve.

The infraorbital and mandibular branches arise from a common stem, the terminal part of which anastomoses with the external carotid. On the obliteration of the stapedial artery, this anastomosis enlarges and forms the internal maxillary artery; the branches of the stapedial artery are now branches of this vessel.

The common stem of the infraorbital and mandibular branches passes between the two roots of the auriculotemporal nerve and becomes the middle meningeal artery. The original supraorbital branch of the stapedial artery is represented by the orbital branches of the middle meningeal artery.

AORTIC ARCHES 3 AND 4:

The third aortic arch constitutes the commencement of the internal carotid artery, and is named the carotid arch. The fourth right arch forms the right subclavian artery as far as the origin of its internal mammary branch. The fourth left arch constitutes the arch of the aorta between the origin of the left carotid artery and the termination of the ductus arteriosus.

AORTIC ARCHES 5 AND 6:

The fifth arch disappears on both sides. The proximal part of the sixth right arch persists as the proximal part of the right pulmonary artery, while the distal section degenerates. The sixth left arch gives off the left pulmonary artery and forms the ductus arteriosus.

This duct remains during fetal life, but closes within the first few days after birth due to increased O2 concentration. This causes the production of bradykinin which causes the ductus to constrict, occluding all flow. Within one to three months, the ductus is obliterated and becomes the ligamentum arteriosum.

AORTIC BRANCHES:

The dorsal aortae are initially bilateral and then fuse to form the definitive dorsal aorta. Approximately 30 posterolateral branches arise off the aorta and will form the intercostal arteries, upper and lower extremity arteries, lumbar arteries, and the lateral sacral arteries.

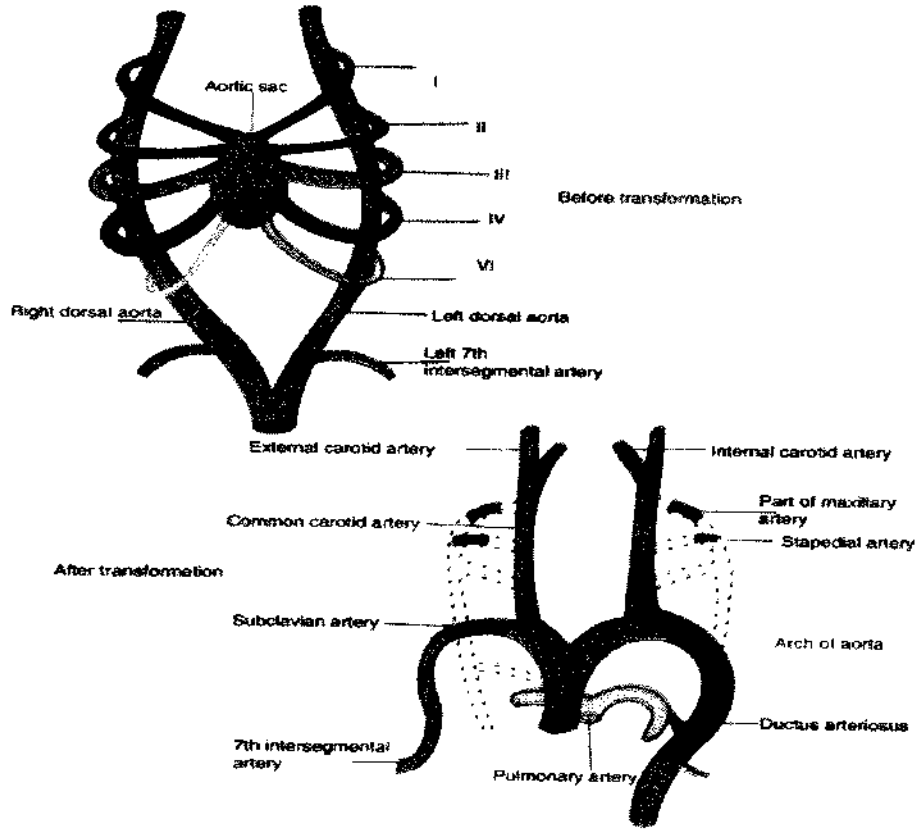


Fig 17.4: Aortic arches

The lateral branches of the aorta form the definitive renal, suprarenal, and gonadal arteries. Finally, the ventral branches of the aorta consist of the vitelline arteries and umbilical arteries.

The vitelline arteries form the celiac, and superior and inferior mesenteric arteries of the gastrointestinal tract. After birth, the umbilical arteries will form the internal iliac arteries.

3. THE DEVELOPMENT OF VENOUS SYSTEM:

The formation of the venous system is marked by the formation of three paired veins, which ultimately drains into the heart the heart tube. These are giving as follows;

a- The vitelline vein: It carries poorly oxygenated blood from the yolk sac into the sinus venosus. The fates of this vein are to form the hepatic vein and the segment of inferior vena cava, hepatic portal vein, superior and inferior mesenteric veins and splenic vein. The hepatic veins are formed by the remains of vitelline duct in the developing area of liver. However the formation of other aforementioned veins are taken place by the enlargement of right vitelline vein.

b- The umbilical vein: It carries oxygenated blood from the chorionic villi to the embryonic placenta. The fates of this vein are; right umbilical vein and the part of left of umbilical vein between liver and sinus venosus degenerated. However the persistent part of left umbilical vein carries all the blood from the placenta to fetus. The ductus venosus which performs the function of shunt with in the liver develops from the umbilical veins. It connects the umbilical vein to inferior vena cava. Moreover in the postnatal life left umbilical vein and ductus venosus become the ligamentum teres and ligamentum venosums respectively.

c- The common cardinal vein: It carries the poorly oxygenated blood from the body of embryo. It forms the major venous drainage of the embryo. The ventral and dorsal cardinal veins drain the cranial and caudal part of embryo respectively. Both these veins confluent to form the common cardinal vein.

i. During late in the 2nd month of development a shunt is formed between right and left ventral cardinal veins by a oblique channel known as oblique anastomosis which later on gives the brachiocephalic vein while the caudal part of ventral cardinal vein soon degenerate.

ii. Right ventral cardinal vein along with common cardinal vein forms the superior vena cava.

iii. Dorsal cardinal veins act as channel to mesonephric kidney. Root of azygos vein and common iliac vein are also derivatives of dorsal cardinal vein.

IV. Subcardinal veins develops into the root of renal vein, suprarenal vein, gonadal vein and segment of the inferior vena cava.

V. Supracardinal veins develop into the azygos and hemizygos veins. It also give rise the inferior part of vena cava.

THE DEVELOPMENT OF INFERIOR VENA CAVA:

The development of inferior vena cava is associated with the development of hepatic vein, Subcardinal vein, supracardinal vein and sub supracardinal vein. For the sack of description the development of inferior vena cava has been classified into four phases;

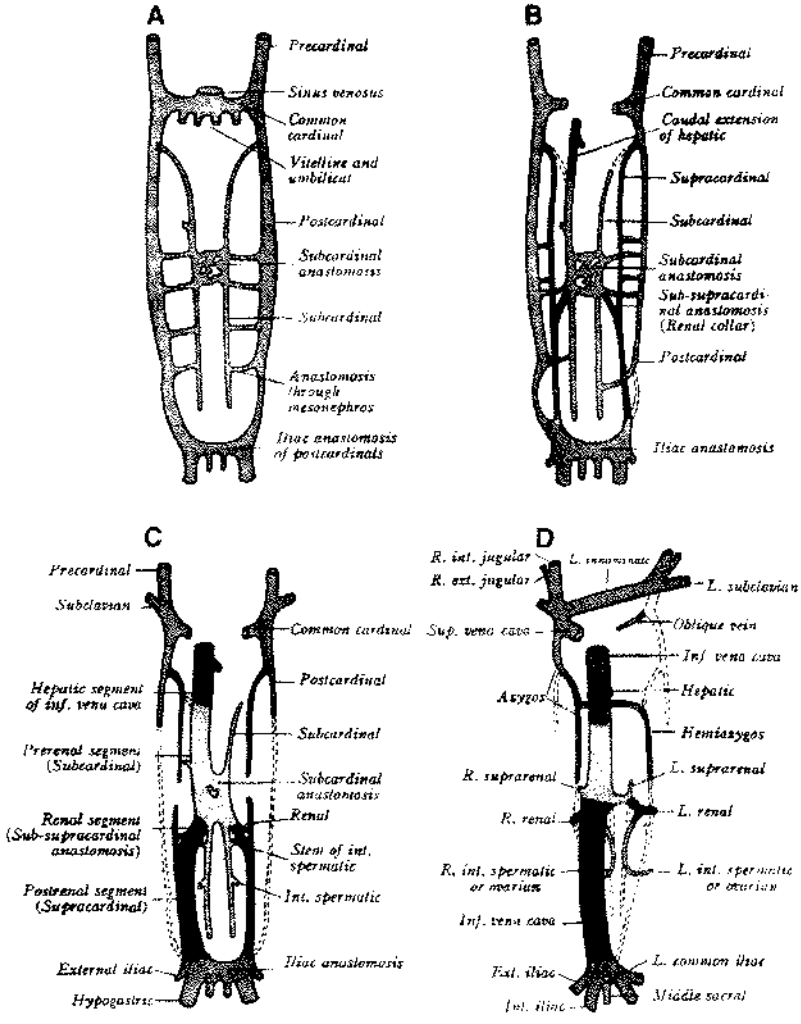


Fig 17.5: The development of inferior vena cava.

1. Hepatic phase which is derived from hepatic sinusoids and veins.
2. The prerenal phase which is derived from right Subcardinal vein.
3. Renal segment, it is derived from the sub supracardinal anastomosis.
4. Post renal phase which is formed by right supracardinal vein.

4. THE DEVELOPMENT OF BLOOD:

- ✓ Blood is a liquid connective tissue, its development begins in mesoderm inside the embryo as well as in extra embryonic mesoderm associated with the yolk sac and chorion. Mesoderm "blood islands" form both the vessel wall (endothelium) and the inner part forms blood stem cells. The blood stem cells initially form mainly fetal red blood cells that have their own specific hemoglobin.
- ✓ During development these blood stem cells transiently relocate to different tissues (liver, spleen, and thymus) until the cartilaginous skeleton has begun to form bone when they then relocate into the developing bone marrow. Recently, placental cord blood has become an important clinical source of stem cells and cord blood banking a significant resource.
- ✓ The development of blood vascular system occurs over the different period of natal life. During the 4th week of development the first blood cell and vessel develop in the extra embryonic mesoderm, allantois diverticulum and wall of yolk sac which later on clustered to form the angioblasts that give rise the blood islands which in turn form the blood cells.
- ✓ During the 2nd month of gestation production of blood cells occur mainly in liver, spleen thymus and lymph nodes
- ✓ Later on in the 4th month hematopoiesis commence in the red bone marrow and in the following months it becomes the main source of blood development. This sort of blood development continues till the formation of yellow bone marrow. Afterwards at puberty liver is the main source of blood development.

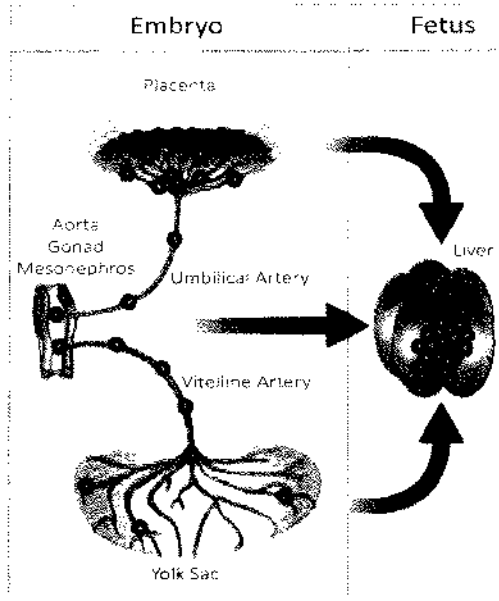


Fig 17.6: Sites of embryonic blood development.

FETAL CIRCULATION:

During pregnancy, the fetus depends on its mother for nourishment and oxygen. Since the fetus doesn't breathe air, however blood circulates differently than it does after birth:

- The placenta is the organ that develops and implants in the mother's womb (uterus) during pregnancy. The fetus is connected to the placenta by the umbilical cord.
- All the necessary nutrition, oxygen, and life support from the mother's blood goes through the placenta and to the fetus through blood vessels in the umbilical cord.
- Waste products and carbon dioxide from the fetus are sent back through the umbilical cord blood vessels and placenta to the mother's circulation to be eliminated.

While the fetus is still in the uterus, the lungs are not being used. The fetus' liver is not fully developed. Circulating blood bypasses the lungs and liver by flowing in different pathways and through special openings called shunts.

Blood flow in the fetus follows this pathway:

- Oxygen and nutrients from the mother's blood are transferred across the placenta to the fetus through the umbilical cord.
- This enriched blood flows through the umbilical vein toward the fetus' liver. There it moves through a shunt called the ductus venosus.
- This allows some of the blood to go to the liver. But most of this highly oxygenated blood flows to a large vessel called the inferior vena cava and then into the right atrium of the heart.
  - ✓ When oxygenated blood from the mother enters the right side of the heart it flows into the right atrium. Most of the blood flows across to the left atrium through a shunt called the foramen ovale.
  - ✓ From the left atrium, blood moves down into the left ventricle. It's then pumped into the first part of the large artery coming from the heart (the ascending aorta).
  - ✓ From the aorta, the oxygen-rich blood is sent to the brain and to the heart muscle itself. Blood is also sent to the lower body.
  - ✓ Blood returning to the heart from the fetal body contains carbon dioxide and waste products as it enters the right atrium. It flows down into the right ventricle, where it normally would be sent to the lungs to be oxygenated. Instead, it bypasses the lungs and flows through the ductus arteriosus into the descending aorta, which connects to the umbilical arteries. From there, blood flows back into the placenta. There the carbon dioxide and waste products are released into the mother's circulatory system. Oxygen and nutrients from the mother's blood are transferred across the placenta. Then the cycle starts again.

✓ At birth, major changes take place. The umbilical cord is clamped and the baby no longer receives oxygen and nutrients from the mother. With the first breaths of air, the lungs start to expand, and the ductus arteriosus and the foramen ovale both become close. The circulation and blood flow of baby takes place through the heart. At this time it functions like an adult's heart.

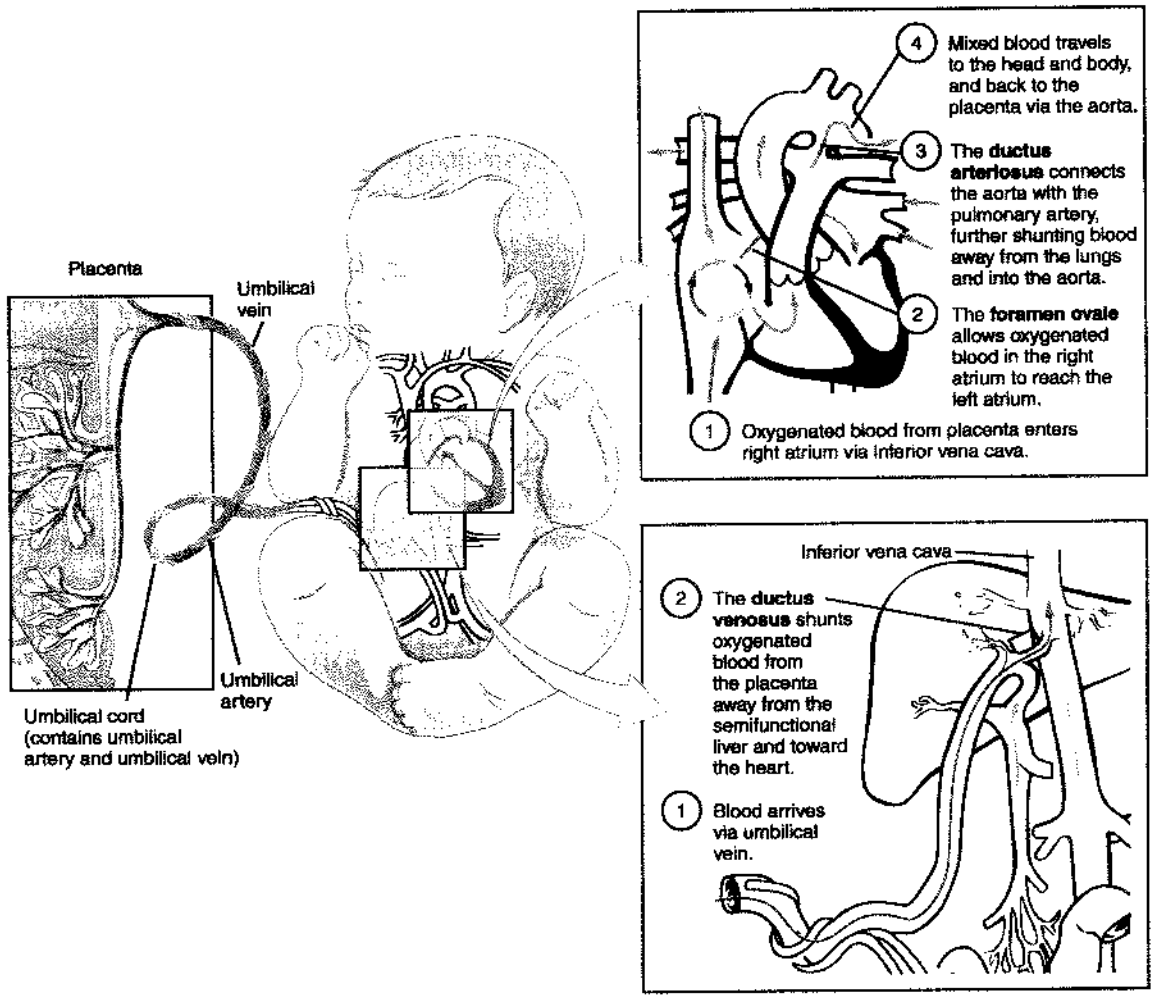


Fig 17.7: Fetal circulation.

DEVELOPMENTAL ABNORMALITIES RELATED WITH CARDIOVASCULAR:

1. DEXTROCARDIA:

It is a rare heart condition in which your heart points toward the right side of your chest instead of the left side. Dextrocardia is congenital, which means people are born with this abnormality. Less than 1 percent of the general population is born with dextrocardia.

2. ECTOPIA CORDIS:

Ectopic heart is a congenital malformation in which the heart is abnormally located either partially or totally outside of the thorax. The ectopic heart can be found along a spectrum of anatomical locations, including the neck, chest, or abdomen.

3. ATRIAL SEPTAL DEFECT:

- ✓ An atrial septal defect (ASD) is a hole in the wall (septum) between the two upper chambers of your heart (atria). The condition is present at birth (congenital).
- ✓ Small defects might be found by chance and never cause a problem. Some small atrial septal defects close during infancy or early childhood.
- ✓ The hole increases the amount of blood that flows through the lungs. A large, long-standing atrial septal defect can damage your heart and lungs. Surgery or device closure might be necessary to repair atrial septal defects to prevent complications.

4. VENTRICULAR SEPTAL DEFECT:

- ✓ A ventricular septal defect (VSD), a hole in the heart, is a common heart defect that's present at birth (congenital). The hole (defect) occurs in the wall (septum) that separates the heart's lower chambers (ventricles) and allows blood to pass from the left to the right side of the heart. The oxygen-rich blood then gets pumped back to the lungs instead of out to the body, causing the heart to work harder.
- ✓ A small ventricular septal defect may cause no problems, and many small VSDs close on their own. Medium or larger VSDs may need surgical repair early in life to prevent complications.

5. PERSISTENT TRUNCUS ARTERIOSUS:

Persistent truncus arteriosus (PTA) is a rare form of congenital heart disease that presents at birth. In this condition, the embryological structure known as the truncus arteriosus fails to properly divide into the pulmonary trunk and aorta.

6. AORTICOPULMONARY SEPTAL DEFECT:

It is a congenital anomaly where there is an abnormal communication between the proximal aorta and the pulmonary trunk in the presence of separate aortic and pulmonary valves.

7. TRANSPOSITION OF THE GREAT ARTERIES:

Dextro-Transposition of the Great Arteries or d-TGA is a birth defect of the heart in which the two main arteries carrying blood out of the heart – the main pulmonary artery and the aorta – are switched in position, or "transposed." Because a baby with this defect may need surgery or other procedures soon after birth, d-TGA is considered a critical congenital heart defect (CCHD).

8. TERATOLOGY OF FALLOT:

Tetralogy of Fallot is a combination of four congenital abnormalities. The four defects include a ventricular septal defect (VSD), pulmonary valve stenosis, a misplaced aorta and a thickened right ventricular wall (right ventricular hypertrophy).

9. AORTIC STENOSIS:

Aortic stenosis is one of the most common and serious valve disease problems. Aortic stenosis is a narrowing of the aortic valve opening. Aortic stenosis restricts the blood flow from the left ventricle to the aorta and may also affect the pressure in the left atrium.

10. AORTIC ATRESIA:

Congenital absence of the normal valvular opening from the left ventricle of the heart into the aorta.

11. HYPOPLASTIC LEFT HEART SYNDROME:

It is a birth defect that affects normal blood flow through the heart. As the baby develops during pregnancy, the left side of the heart does not form correctly. Hypoplastic left heart syndrome is one type of congenital heart defect.

12. COARCTATION OF AORTA:

Coarctation of the aorta is a birth defect in which a part of the aorta is narrower than usual. If the narrowing is severe enough and if it is not diagnosed, the baby may have serious problems and may need surgery or other procedures soon after birth.

13. PATENT DUCTUS ARTERIOSUS:

It is a medical condition in which the ductus arteriosus fails to close after birth: this allows a portion of oxygenated blood from the left heart to flow back to the lungs by flowing from the aorta, which has a higher pressure, to the pulmonary artery.

KEY NOTES!

a- The development of cardiovascular system is associated with the development of the heart, arteries, veins and blood. The cardiovascular system begins to develop during the 3rd week of development and primordial heart start beating during the 4th week of development. The heart primordium consists of 4 chambers named as bulbous cordis, atrium, ventricle and sinus venosus.

b- The development of arteries are associated with the pharyngeal arches. As these arches develops during the 4th and 5th week of development they penetrate the pharyngeal arteries and these pharyngeal arch arteries later on transformed into the adult arterial arrangement of subclavian, pulmonary and carotid arteries.

c- Regarding the development of veins, three paired veins drain into the primordial heart; vitelline veins, cardinal veins and umbilical veins

d- Regarding congenital anomalies of heart, various anomalies occurs as dextrocardia, Ectopia cordis, patent ductus arteriosus, ASDs and VSDs etc.

18

THE DEVELOPMENT OF LYMPHATIC SYSTEM

LEARNING OBJECTIVES

- GENERAL INTRODUCTION OF THE DEVELOPMENT OF LYMPHATIC SYSTEM
- DEVELOPMENT OF LYMPHOCYTES
- DEVELOPMENT OF LYMPH NODES
- DEVELOPMENT OF LYMPH SACS AND LYMPH BUDS
- DEVELOPMENT OF THORACIC DUCTS
- DEVELOPMENT OF SPLEEN AND TONSILS
- DEVELOPMENTAL ABNORMALITIES OF THE LYMPHATIC SYSTEM
- KEY NOTES

THE DEVELOPMENT OF LYMPHATIC SYSTEM:

This chapter deals with the formation of lymph vascular system which starts to develop approximately in the middle of 2nd month of gestation.

DEVELOPMENT OF LYMPHOCYTES:

Initially the formation of lymphocytes take place from the primordial stem cells in the mesenchyme of umbilical vesicle and then into the spleen and the liver. The very first lymphocytes enter into the bone marrow where they proliferate to form the lymphoblast. However the lymphocytes which are found at lymph nodes are of thymic origin.

DEVELOPMENT OF THE LYMPH NODES:

Lymph nodes are derived by the transformation of lymph sacs; the invasion of mesenchymal cells into the sacs break the cavity into fine channels known as the primordia for the lymph sinuses. The capsule and connective tissue architecture is also formed by mesenchymal cells.

DEVELOPMENT OF LYMPH SACS AND LYMPH DUCTS:

Primary lymphatic sacs are six in number two of them are jugular lymph sacs, two are iliac lymph sacs, one is retroperitoneal lymph sac and one is cisterna chyle. Lymphatic sacs are formed by the confluence of lymphatic vessels along the main veins to head, neck and upper limbs from the jugular lymph sacs; the primordial alimentary system from the retroperitoneal sac and cisterna chyle; to the lower trunk and lower limbs from the iliac sacs.

DEVELOPMENT OF THORACIC DUCT:

The development of thoracic duct takes place as the caudal part development and cranial part development. The caudal part is developed by the right thoracic duct while the cranial part is developed by left thoracic duct. The thoracic and right lymphatic duct connect with the venous system at the venous angle between internal jugular vein and subclavian vein.

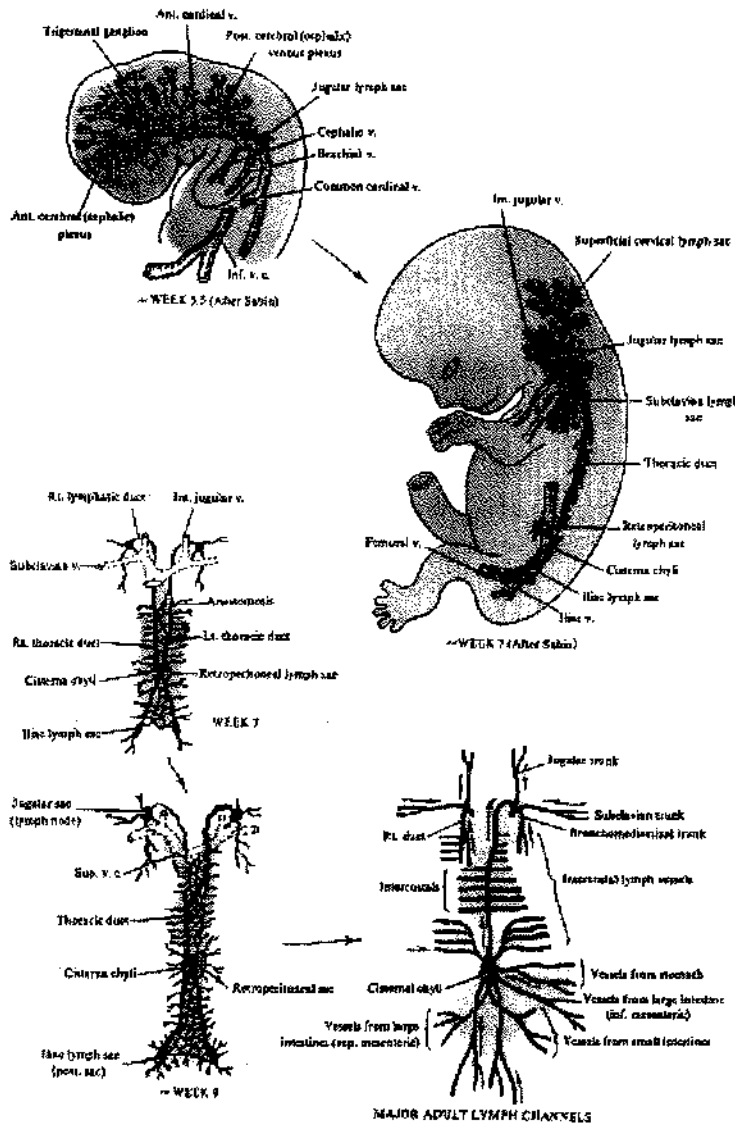


Fig 18.1: **The development of lymphatic system.**

DEVELOPMENT OF SPLEEN AND TONSILS:

The formation of spleen occurs as an aggregation of mesenchymal cells in the dorsal mesogastrium, discussed at length in the development of digestive system.

The formation of palatine tonsils is endodermal in origin, develop from the 2nd pair of pharyngeal pouches and mesenchyme. The tubal tonsils develop from aggregations of lymph nodules around the pharyngeal openings of the pharyngotymanic tubes. The adenoids develop from the aggregation of lymph nodules. However the aggregation of lymph nodules in the root of tongue give rise to the lingual tonsils.

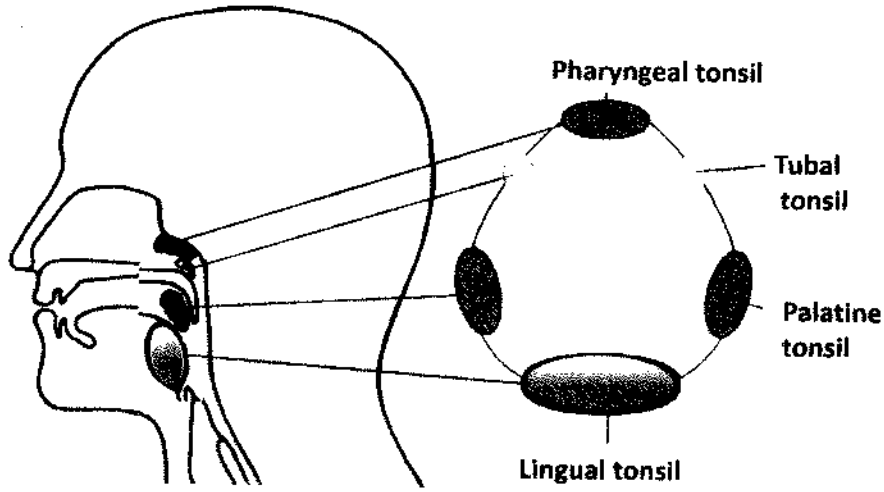


Fig 18.2: **The development of tonsils.**

DEVELOPMENTAL ABNORMALITIES OF LYMPHATIC SYSTEM:

Congenital anomalies of lymphatic system are very rare;

CONGENITAL LYMPHEDEMA:

A condition present at birth in which excess fluid called lymph collects in tissues and causes swelling (edema) in them. Congenital lymphedema is due to a congenital malformation of the lymphatic system.

CYSTIC HYGROMA:

A cystic hygroma is a cyst, or a group of cysts, found mostly in the neck. They are caused by an error in the development of lymph sacs and lymph vessels as the baby develops during pregnancy. By the end of the fifth week of pregnancy, the baby's lymphatic tissues form as lymph sacs.

KEY NOTES!
a- The development of lymphatic system deals with the formation of lymphatic sacs, which are six in number, lymphatic ducts, lymph nodes, lymphocytes and lymphatic organs.
b- Developmental anomalies of lymphatic system are rare, however congenital lymphedema and cyst hygroma occurs sometime.

19

THE DEVELOPMENT OF BODY CAVITIES, DIAPHRAGM AND PRIMITIVE MESENTERIES

LEARNING OBJECTIVES

- GERNERAL INTRODUCTION REGARDING BODY CAVITIES, DIAPHRAGM AND PRIMITIVE MESENTERIES
- THE DEVELOPMENT OF BODY CAVITIES
- THE DEVELOPMENT OF DIAPHRAGM
- THE DEVELOPMENT OF MESENTERIES
- DEVELOPMENTAL ABNORMALITIES RELATED TO CHAPTER
- KEY NOTES

THE DEVELOPMENT OF BODY CAVITIES, DIAPHRAGM AND PRIMITIVE MESENTRIES:

This chapter deals with the formation of intraembryonic coelom, the diaphragm that is the partition between thoracic cavity and abdominal cavity and the development of primitive mesenteries. However at the end of this chapter the developmental anomalies associated with body cavities, diaphragm and primitive mesenteries have also been discussed.

THE DEVELOPMENT OF BODY CAVITIES:

Generally speaking the development of body cavities is associated with the differentiation of the mesoderm into paraxial, intermediate and lateral plate mesoderm.

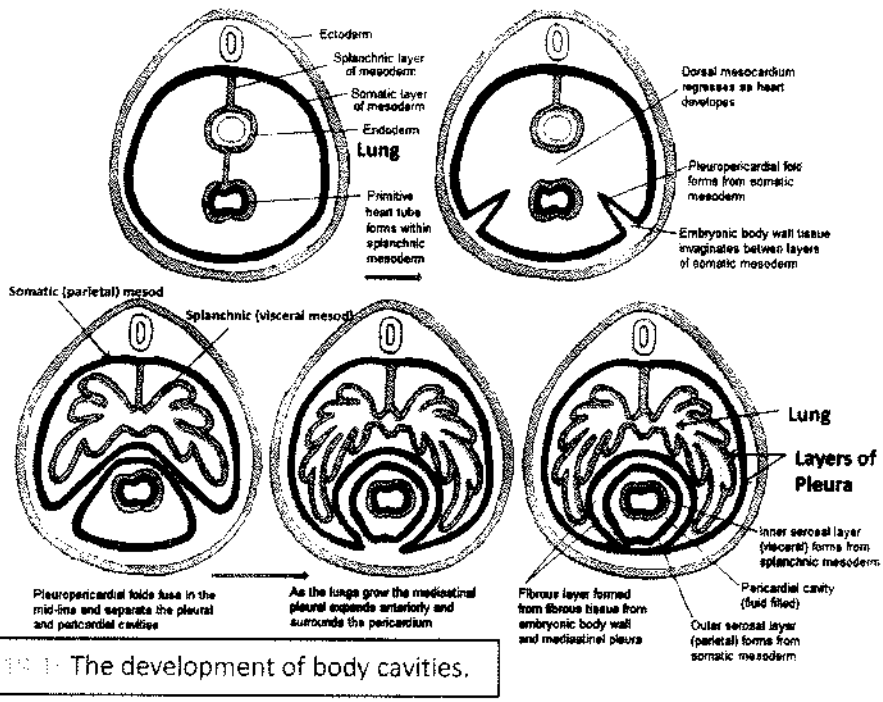


Fig 19.1: The development of body cavities.

After the differentiation process lateral plate mesoderm undergoes further into differentiation by the formation of groove which later on divides the lateral plate mesoderm into two distinct layers known as somatopleure and splanchnopleure. Consequently, approximation of both layers leave a space known intraembryonic coelom. This intraembryonic coelom extends from the thoracic region to the pelvic region. However somatopleure forms the parietal layer of serous membrane which lines the external surface of pleural, peritoneal and pericardial cavities while the splanchnopleure develops into the visceral layer covering the heart, pulmonary structures and abdominal visceras.

Furthermore, the developing embryo undergoes the process of dual foldings and this cavity is eventually divided into the pericardial, pleural, and peritoneal embryonic body cavities. During the fourth week of development the septum transversum grows to separate the pericardial cavity from the pleural cavities. During the sixth week the pleuroperitoneal membranes grow to separate the pleural cavities from the peritoneal cavity. During the seventh week the pleuropericardial membranes separate the pericardial cavity from the pleural cavities. In the adult the pleuropericardial membranes form the fibrous pericardium of the heart.

THE DEVELOPMENT OF DIAPHRAGM:

The diaphragm is the musculotendineous partition that separates the thoracic cavity from the abdominal cavity. It develops from the tissues belong to four origins.

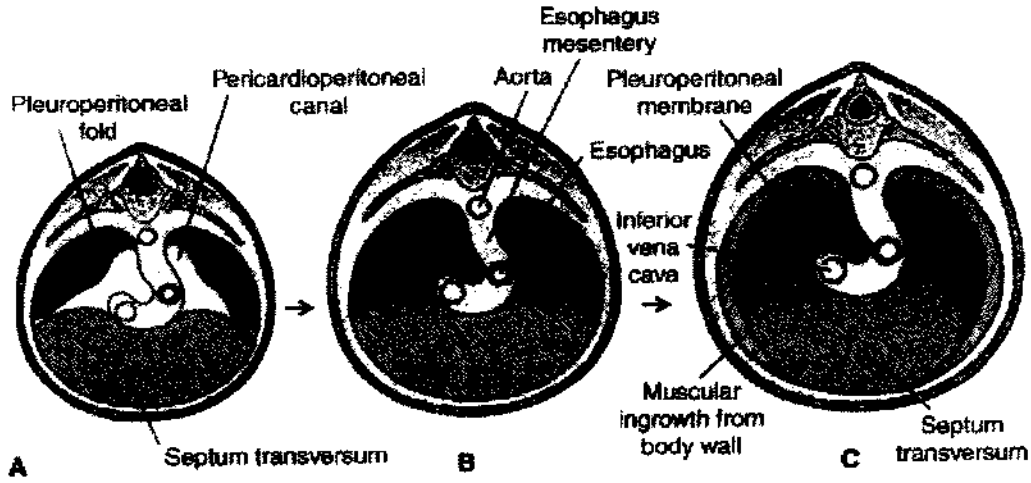


Fig 19.2: The development of diaphragm.

1. The septum transversum: It develops the central tendon of the diaphragm.
2. The pleuroperitoneal membranes: It contributes only a small amount to the adult diaphragm.
3. The dorsal mesentery of the esophagus: It forms the crura and median portion of the diaphragm.
4. The body wall: It forms the peripheral region of the diaphragm.

Initially, the diaphragm develops at the level of cervical somites 3-5 however, it descends to the level of L_1 as the embryo grows. As it moves, it takes along its innervation, which explains why the phrenic nerve arises from cervical roots three, four, and five.

THE DEVELOPMENT OF PRIMITIVE MESENTERIES;

1. FORMATION AND DERIVATIES OF DORSAL MESENTERY:

The approximation of splanchnopleuric mesoderm of the opposite sides form the dorsal mesentery. It derives the following structures.

c- Gastrosplenic Ligament

d- Gastrophernic Ligament

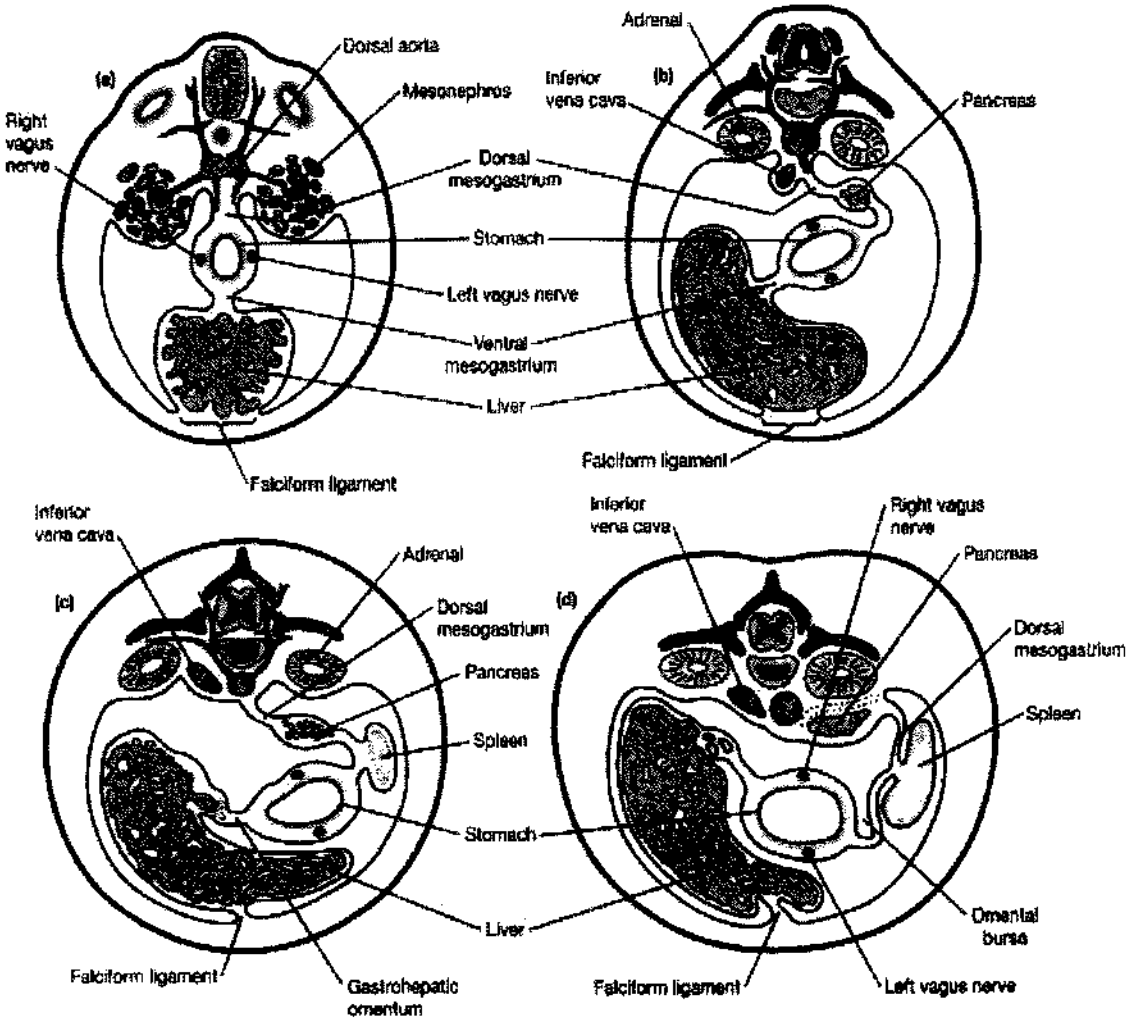


Fig. 19.3: Different derivatives of dorsal mesentry.

e- Greater omentum

f- Linorenal Ligament

g- Mesenteries of small and large intestines.

5. FORMATION AND DERIVATIVES OF VENTRAL MESENTERY:

The mesoderm of septum transversum forms the ventral mesentery. Its derivatives are given as under;

a- Lesser omentum
b- Falciform ligament
c- Coronary ligament of liver
d- Triangular ligament of liver.

DEVELOPMENTAL ABNORMALITIES:

1. CONGENITAL HIATAL HERNIA:

It occurs when the diaphragm, the muscle that separates the chest from the abdomen, fails to close during prenatal development. This opening allows contents of the abdomen (stomach, intestines and/or liver) to migrate into the chest, impacting the growth and development of the lungs.

2. UMBILICAL HERNIA:

This type of hernia is due to the weakness of abdominal muscles which surrounds the umbilicus. Due to this hernia a soft skin covered protrusion expel out through the umbilicus.

3. ESOPHAGEAL HIATAL HERNIA:

In this type of hernia, esophagus (food pipe) goes through the hiatus and attaches to your stomach. In a sliding hiatal hernia, your stomach and the lower part of your esophagus slide up into your chest through the diaphragm.

4. DIAPHRAGMATIC HERNIA:

It is a birth defect in which there is an abnormal opening in the diaphragm. The diaphragm is the muscle between the chest and abdomen that helps you breathe. The opening allows part of the organs from the belly to move into the chest cavity near the lungs.

5. GASTROSCHISIS:

It is a birth defect of the abdominal (belly) wall. The baby's intestines are found outside of the baby's body, exiting through a hole beside the belly button. The hole can be small or large and sometimes other organs, such as the stomach and liver, can also be found outside of the baby's body.

KEY NOTES!
a- This chapter deals with the formation of body cavities, diaphragm and the primitive mesenteries. b- Intraembryonic coelom is formed from the differentiation of lateral plate mesoderm. c- Diaphragm develops from the four sources; the septum transversum, the pleuroperitoneal membrane, dorsal mesentery of the esophagus and the body wall. d- Dorsal mesentery is formed by the fusion of splanchnopleuric mesoderm while ventral mesentery is formed by the septum transversum. e- Regarding developmental anomalies this chapter includes; congenital hiatal hernia, umbilical hernia, gastroschisis, esophageal hernia etc.

20

THE DEVELOPMENT OF OPTHALMIC SYSTEM

LEARNING OBJECTIVES

- GENERAL INTRODUCTION OF THE DEVELOPMENT OF OPTHALMIC SYSTEM
- THE FORMATION OF LENS
- THE FORMATION OF CILIARY BODY
- THE FORMATION OF IRIS
- THE FORMATION OF CORNEA
- THE FORMATION OF CHOROID AND SCLERA
- THE FORMATION OF VITEROUS BODY
- THE FORMATION OF AQUEOUS CHAMBER
- THE FORMATION OF EYE LID
- THE FORMATION OF LACRIMAL GLAND
- DEVELOPMENTAL ABNORMALITIES OF THE OPTHALMIC SYSTEM
- KEY NOTES.

THE DEVELOPMENT OF OPTHALMIC SYSTEM:

This chapter deals with the formation of eye and its associated structures. The development of the eye begins to appear when the optic groove express in the neural fold of head. The formation of eyes takes place from four constituents;

1. Neuroectoderm of the forebrain
2. Surface ectoderm of the head
3. Mesoderm between the previous two layers
4. Neural crest cells.

✓ When the optic groove appear on the 22nd day of gestation it marks the formation of the eye and slowly this groove grows inward to form the vesicular structure known as the optic vesicle.
Later on this optic vesicle soon dilates and lengthens to form the hollow and double walled cup structures known as optic stalks and optic cups respectively. Moreover the optic vesicles approximates the sides of head and induce the surface ectoderm to form the thickenings known as optic lens placodes.

✓ The Neuroectoderm differentiate into the retina, posterior layers of iris and the optic nerve. The derivatives of the surface ectoderm are the lens of eye and the corneal epithelium. The fibrous and vascular coats of the eye are formed by mesoderm between the neuroectoderm and the surface ectoderm. However the neural crest cells first migrate to mesenchyme and then differentiate to form the choroid, sclera and corneal endothelium. The formation of the eye is entirely the genetic signalling process.

THE DEVELOPMENT OF RETINA:

The development of retina takes place from the walls of optic cup, as a bud from the forebrain. The walls of the optic cup soon differentiate into the two functionally distinct layers; the outer layer of optic cup which is thin becomes the pigment layer of retina while

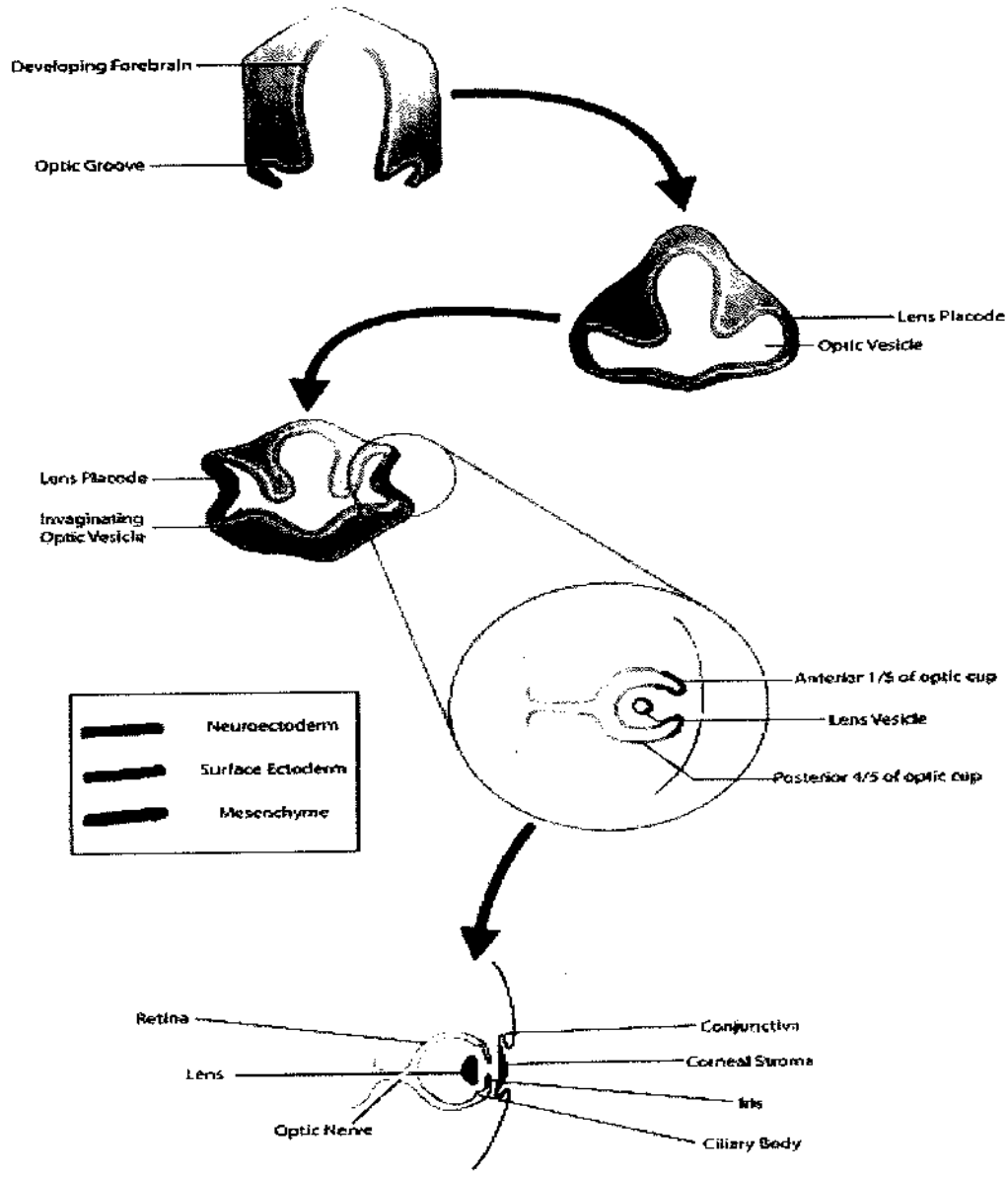


Fig 20.1: Initial stages in the development of an eye.

the inner layer which is thick becomes the neural retina of the eye. Initially in the embryonic life the two layers are separated by interretinal space which later on disappears and both layers approximate to each other. Moreover under the influence of developing lens, the inner layer divides to form the neuroepithelium. Similarly cells of this layer form the neural retina which contains photoreceptors and cell bodies of the neuron.

Furthermore the cavity of the optic stalk is gradually obliterated as the axons of the many ganglion cells to form optic nerve. Optic nerve is surrounded by three sheaths the outer one is dural sheath, the intermediate sheath which is formed by arachnoid matter and the inner sheath which is formed by the pia matter and it is the vascular sheath.

THE FORMATION OF LENS:

The formation of the lens takes place from the lens placodes, shortly after its formation the formation of posterior wall begin to lengthens anteriorly and fill the lumen of optic vesicle. By the end of 7th week the first formed lens fibres reach to the anterior wall of the lens vesicle. After this secondary lens fibres add continuously till it reach the complete development.

THE FORMATION OF CILIARY BODY:

The ventral portion of the optic cup forms the epithelium of the ciliary body which is wedged shaped extension of choroid. However the non-visual retina is the extension of neural retina. The connective tissue and ciliary smooth muscle develops from the mesenchyme which is present at the edge of optic cup.

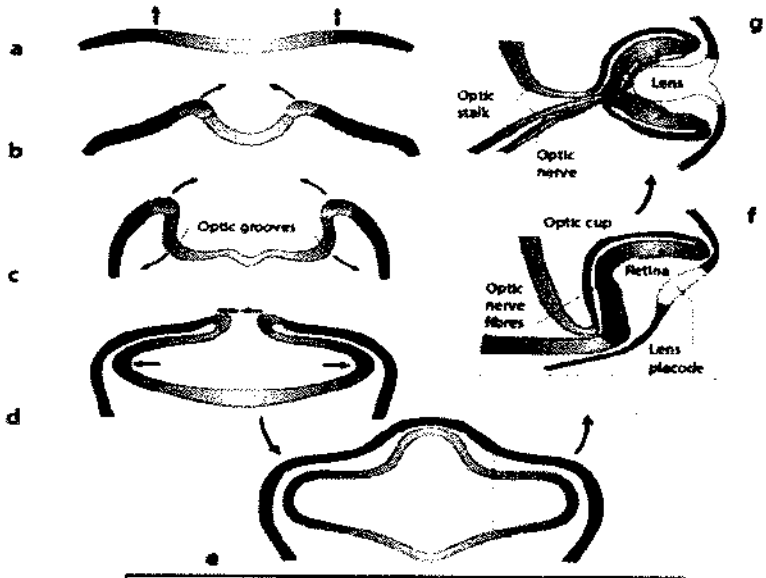


Fig 20.2. **Formation of optic groove and lens**

THE FORMATION OF IRIS:

The iris is formed by the rim of the optic cup which invaginates and covers the lens. The dilator papillae and sphincter papillae muscles of the iris are derived from neuroectoderm of the optic cup. They appear to arise from the anterior epithelial cells of the iris. The smooth muscles result from a transformation of epithelial cells into smooth muscle cells.

THE FORMATION OF CORNEA:

The formation of cornea is of dual origin and induced by the lens vesicle. The surface ectoderm forms the corneal epithelium and underlying mesenchyme differentiates to form the dense connective tissue which is called as substantia propria of cornea.

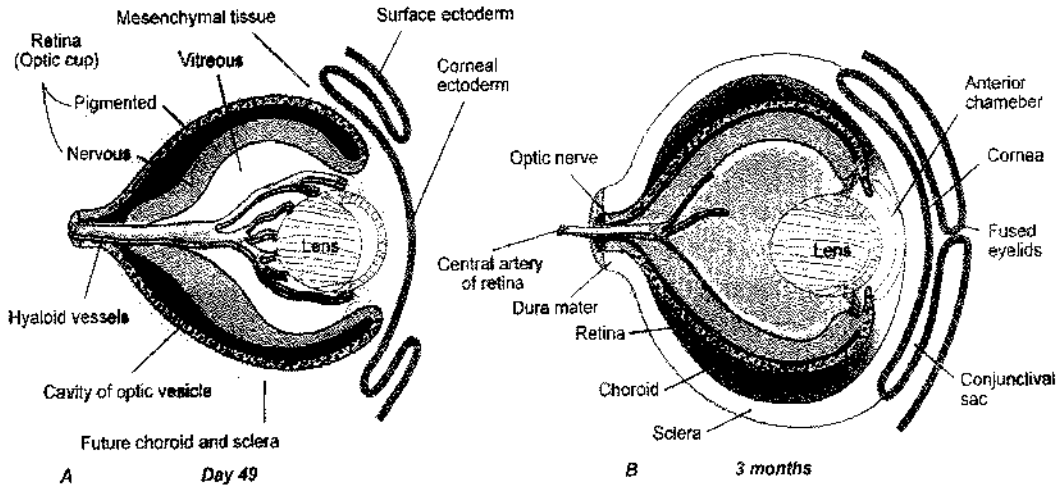


Fig 20.3: Depiction of different structures of an eye.

THE FORMATION OF CHORIOD AND SCLERA:

By the interaction of mesenchyme and the layers of the optic cup double membranous structure is formed. Outer layer which is vascularized is known as the choroid and the inner layer which is of fibrous manifestation is known as the sclera. Toward the rim of optic cup, the choroid modified to form the cores of choroid process.

THE FORMATION OF VITEROUS BODY:

The colloid portion of the vitreous body is derived from the mesenchyme and that enters into the optic cup while vitreous humour is derived from the inner wall of the optic cup and epithelium of ciliary body. The hyaloid membrane surround the vitreous body.

THE FORMATION OF AQUEOUS CHAMBER:

In eyes there are two chambers which contains the aqueous humour the anterior chamber which is formed by the mesenchyme between the surface ectoderm and developing iris while the posterior chamber develops as a split l the mesenchyme posterior to the developing iris and anterior to the developing lens. The pupil is the communicating link between posterior and the anterior chamber. Ciliary body secretes the aqueous humour and it fills the anterior and posterior chamber.

THE FORMATION OF EYE LIDS:

The ectodermal folds form the eyelids. They approximate towards each other and adhere till 8th week of gestation however it does not open until 26th week.

THE FORMATION OF LACRIMAL GLANDS:

The surface ectoderm forms the bud like structures which later on develop into the lacrimal glands. These solid buds recanalize to give rise the ducts and alveoli of the gland.

EMBRYOLOGICAL TID BITS!
The lacrimal glands at birth do not function fully at birth hence infant does not produce tear when it cries.

DEVELOPMENTAL ABNORMALITIES OF THE OPTHALMIC SYSTEM:

1. Coloboma:

   A coloboma describes conditions where normal tissue in or around the eye is missing at birth. Coloboma comes from the Greek word that means "curtailed." The eye develops quickly during a fetus' first three months of growth.

2. Cyclopia:

   Cyclopia is a rare birth defect that occurs when the front part of the brain doesn't cleave into right and left hemispheres. The most obvious symptom of cyclopia is a single eye or a partially divided eye.

3. Detachment of retina:

   Retinal detachment describes an emergency situation in which a thin layer of tissue (the retina) at the back of the eye pulls away from the layer of blood vessels that provides it with oxygen and nutrients. Retinal detachment is often accompanied by flashes and floaters in your vision.

4. Microphthalmia:

   Microphthalmia is a disorder in which one or both eyes are abnormally small, while anophthalmia is the absence of one or both eyes. These rare disorders develop during pregnancy and can be associated with other birth defects.

5. Anophthalmia:

   It is the medical term for the absence of one or both eyes. Both the globe (human eye) and the ocular tissue are missing from the orbit.

6. Congenital aniridia:

   Aniridia is the absence of the iris, usually involving both eyes. It can be congenital or caused by a penetrant injury. Isolated aniridia is a congenital disorder which is not limited to a defect in iris development, but is a panocular condition with macular and optic nerve hypoplasia, cataract, and corneal changes.

7. Persistent pupillary membrane (PPM)

   It is a condition of the eye involving remnant of fetal membrane that persist as strands of tissue crossing the pupil. The pupillary membrane in mammals exists in the fetus as a source of blood supply for the lens.

8. Congenital glaucoma:

It is the condition in which the intraocular pressure increases because there is a birth defect in the development of the angle of the eye as a result of poor development of the eye. This means that the aqueous humor cannot flow out normally, so the intraocular pressure increases and leads to optic nerve damage.

9. Edema of the optic disc:

Optic disc edema refers to the ophthalmoscopic swelling of the optic disc with a concurrent increase in fluid within or surrounding the axons. While unilateral disc edema is more common, bilateral disc edema can occur.

10. Congenital ptosis:

Ptosis (eyelid drooping) in infants and children is when the upper eyelid is lower than it should be. This may occur in one or both eyes. Eyelid drooping that occurs at birth or within the first year is called congenital ptosis.

11. Crytophthalmos:

It is a very rare congenital defect in which the eyelids are absent and replaced by a continuous layer of skin over a microphthalmic eyeball, resulting in an absence of palpebral fissure. Eyelashes may or may not be present. The cornea is fused with the overlying skin into one structure.

KEY NOTES!

A- The very first indication of the development of eye is the formation of optic groove which later on converted into optic vesicles and induce the formation of lens placodes .As lens placodes thicken to form the lens pit and optic vesicle invaginates to form the optic cup. The formation of retina takes place from the two layers of optic cup. The retina, optic nerve fibres, epithelium, ciliary body and muscle of the iris develops from the neuroectoderm of the forebrain.

B- The eyes are sensitive to teratogenic effects of infectious agents. Moreover congenital cataract and glaucoma maybe the result of intrauterine hazardous.

21

THE DEVELOPMENT OF AUDITORY SYSTEM

LEARNING OBJECTIVES

- GENERAL INTRODUCTION OF THE DEVELOPMENT OF OPTHALMIC SYSTEM
- THE DEVELOPMENT OF INTERNAL EAR
- THE DEVELOPMENT OF MIDDLE EAR
- THE DEVELOPMENT OF EXTERNAL EAR
- THE ABNORMALITIES ASSOCIATED WITH THE DEELOPMENT OF AUDITORY SYSTEM
- KEY NOTES

THE DEVELOPMENT OF AUDITORY SYSTEM:

This chapter deals with the formation of auditory apparatus and associated developmental anomalies; for the sack of description, the development of auditory system has been classified into the following three sections.

1. The development of internal ear; which comprises of the vestibulochochlear organ that functions in hearing and balance.
2. The development of middle ear; which comprises of the three small auditory ossicles and internal layers of the tympanic membranes which in turn are connected to the oval widows of the internal ears by the ear ossicles.
3. The development of external ear; which comprises of the ear auricle, external acoustic meatus and external layer of the tympanic membrane.

1. THE DEVELOPMENT OF INTERNAL EAR:

✓ Early in the fourth week of gestation the formation of internal ear begins to express, when the surface ectoderm on the each side of rhombencephalon thickens and forms the otic placodes which later on invaginates soon and form the auditory vesicles. Afterwards the auditory vesicles differentiate to give rise the ganglion cells for vestibulochochlear ganglia. The vesicle soon loses its connection with the surface ectoderm, and a diverticulum grows from the vesicles and elongates to form the endolymphatic duct and sac. Two regions of otic vesicle differentiated at this stage; the ventral part is known as the saccular part which forms the saccule and cochlear duct. While the dorsal part of the vesicle forms the utricular part that give rise the small endolymphatic ducts, utricle and semicircular ducts.

- ✓ Regarding saccule, cochlea and the organs of corti, at the lower end of saccule an outgrowth that is known as the cochlear duct appears approximately at 6th week of development which crosses the surrounding mesenchyme by forming the spiral loop and this spiral loop makes 2- 3 turns by the eighth week of development. Soon after this the cells of cochlear duct differentiate to the organs of corti. The function of organs of corti is the transduction and electrical signalling for the process of hearing.
- ✓ Moreover the mesenchyme around the cochlear duct modifies into the cartilage which undergoes vacuolization and forms the two perilymphatic spaces known as the scala vestibuli and the scala tympani. Medially the cochlear duct separates from the vestibule by the membrane however laterally it is attached by spiral ligament.

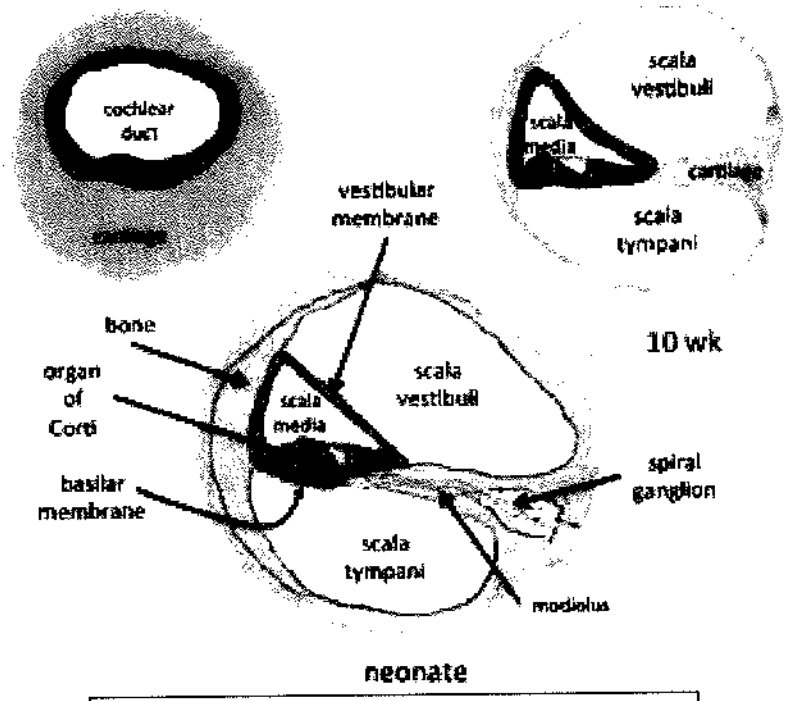


Fig 21.1: Initial stages in the development of ear.

- ✓ The constitution of the organ of corti takes place from the sensory and the tectorial cells which are formed by the differentiation of the epithelial cells of the cochlear duct. The differentiation of the cochlear epithelium give rise to the inner groove that is the presumptive spiral limbs and the outer ridge which forms the outer and inner hair cells. The organ of corti receives the stimulus and transmitted to the spiral organ and then to the nervous system by eighth cranial nerve.

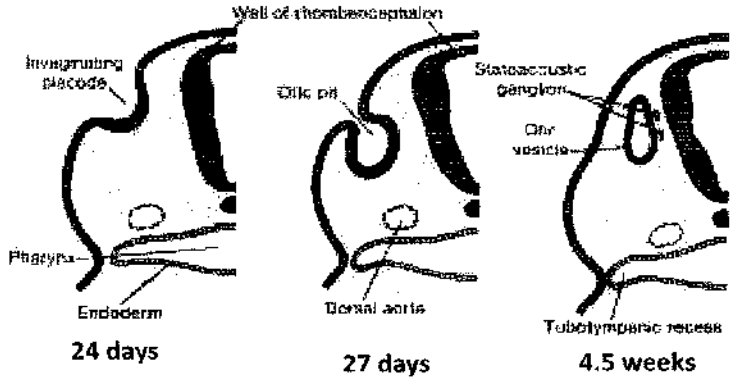


Fig 21.2: The development of internal ear.

2. THE DEVELOPMENT OF MIDDLE EAR:

- ✓ The formation of middle ear takes place from the 1st pharyngeal pouch by the appearance of endodermal diverticulum on the primitive pharynx. The 1st pharyngeal pouch expands to develop into tubotympanic recess. Afterwards, the proximal part of the tubotympanic membrane give rise the pharyngotymanic tube while distal part becomes the tympanic cavity which gradually covers the ear ossicles. The tubotympanic membrane flattens and approximate with the mesoderm and ectoderm of the 1st pharyngeal pouch to form the tympanic membrane.
- ✓ Moreover the formation of incus, malleus and stapes takes place from 1st and 2nd pharyngeal arch respectively.

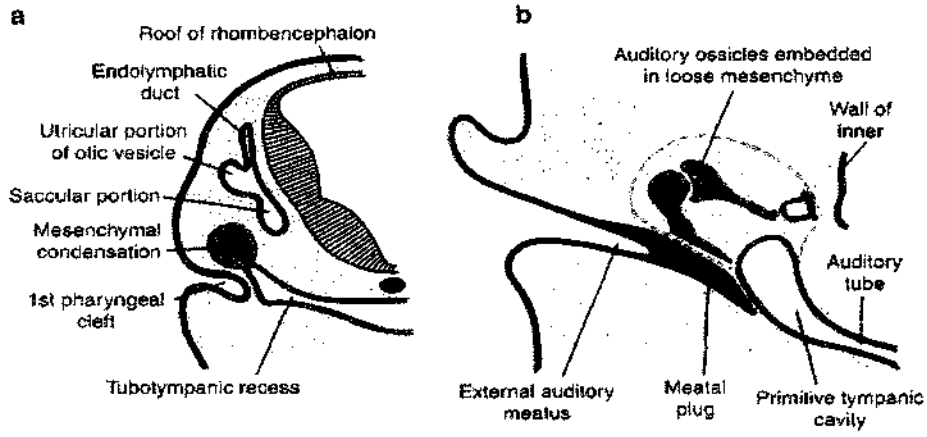


Fig 21.3: The development of middle ear.

3. THE DEVELOPMENT OF EXTERNAL EAR:

- ✓ The formation of external ear takes place from the six mesenchymal swellings known as auricular hillocks that develop around the dorsal end of 1st and 2nd pharyngeal groves. The swellings called as auricular hillocks later on coalesce to form the auricle of ear.
- ✓ The formation of the external acoustic meatus takes place from the first pharyngeal clef. The pharyngeal cleft is the ectodermal groove which continues to grow inward and medially until it reaches to the first pharyngeal pouch.
- ✓ The developmental sources of the tympanic membrane are the ectoderm of the auditory meatus, the endodermal lining of the tympanic cavity and intermediate layer of connective tissue. However its primordia develops from the first pharyngeal membrane.

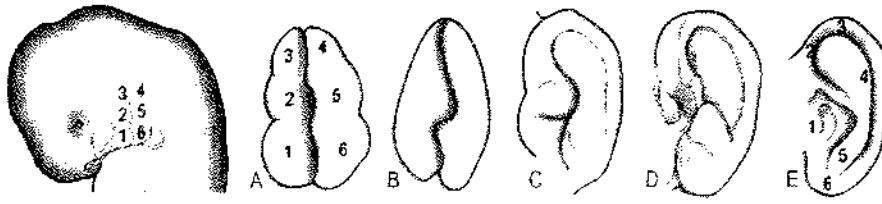


Fig 21.4: The development of external ear.

THE ABNORMALITIES RELATED WITH THE DEVEOPMENT OF AUDITORY SYSTEM:

1. CONGENITAL DEAFNESS:

   It is the loss of hearing present at birth or loss that may develop later but is due to genetic causes or other influences that affected the fetus while it was in utero (in the womb). The distinction between congenital and acquired deafness specifies only the time that the deafness appears.

2. AURICULAR ABNORMALITIES:

   Auricular abnormalities include the auricular appendages, absence of the auricle, microtia, the periauricular sinuses and fistulas, atresia of the external acoustic meatus, absence of external acoustic meatus and congenital cholesteatoma.

3. AURICULAR APPENDAGES:

   These are the skin tags that are common and results from the formation of accessory auricular hillocks. The appendages usually appear anterior to the auricle, more often unilaterally or bilaterally. The appendages which often has narrow pedicles, consist of skin, but they may contain some cartilage.

4. ANOTIA:

   It describes a rare congenital deformity that involves the complete absence of the pinna, the outer projected portion of the ear, and narrowing or absence of the ear canal. This contrasts with microtia, in which a small part of the pinna is present.

5. MICROTIA

   It is a congenital deformity where the pinna (external ear) is underdeveloped. A completely undeveloped pinna is referred to as anotia. Because microtia and anotia have the same origin, it can be referred to as microtia-anotia. Microtia can be unilateral (one side only) or bilateral (affecting both sides).

6. PERIAURICULAR SINUSES AND FISTULAS:

   The periauricular sinus is a benign congenital malformation of the periauricular soft tissues. It is also termed as periauricular pit, preauricular fistula, preauricular tract and periauricular cyst. It has an estimated incidence of 0.1–0.9% in the general population.

7. EXTERNAL AUDITORY CANAL ATRESIA:
It is also known as congenital aural atresia, is characterized by complete or incomplete bony atresia of the external auditory canal (EAC), often in association with a dysplastic auricle and an abnormal middle ear cavity or ossicles.

8. CONGENITAL MIDDLE EAR CHOLESTEATOMA:
It is defined as a keratinizing epithelial rest that occurs behind an intact tympanic membrane without a prior history of infection or trauma. Although its cause is unknown, several theories have been proposed to explain its origin.

KEY NOTES!
A- This chapter deals with study of the development of the auditory apparatus which is divided into the formation of the external, middle and internal ear.
B- This chapter also discusses the developmental abnormalities related with auditory apparatus which include the congenital deafness and abnormalities of the auricle.

22

THE DEVELOPMENT OF INTEGUMENTARY SYSTEM

LEARNING OBJECTIVES

- GENERAL INTRODUCTION OF THE DEVELOPMENT OF INTEGUMENTARY SYSTEM
- DEVELOPMENT OF THE SKIN
- THE DEVELOPMENT OF EPIDERMIS
- THE DEVELOPMENT OF DERMIS
- THE DEVELOPMENT OF SKIN GLANDS
- THE DEVELOPMENT OF NAIL
- THE DEVELOPMENT OF HAIR
- THE DEVELOPMENT OF TEETH
- ABNORMALITIES RELATED WITH THE DEVELOPMENT OF INTEGUMENTARY SYSTEM
- KEY NOTES

THE DEVELOPMENT OF INTEGUMENTARY SYSTEM:

This chapter deals with the formation of skin which is medically known as integument and its appendages which includes the sweat glands, hairs, nails, teeth, erector pili muscles, mammary glands and the sebaceous glands.

DEVELOPMENT OF THE SKIN:

Skin is the complex and largest organ of the body and it clothes the whole host of structures present inside the body. On the basis of histochemical manifestation skin has dual origin as it consists of two distinct layers.

1. The epidermis which is superficial layer of skin and it is a derivative of surface ectoderm.
2. The dermis which lies underneath the epidermis and have the mesenchymal origin which in turn form the irregularly arranged dense connective tissue.

1. THE DEVELOPMENT OF EPIDERMIS:

The formation of epidermis is episodic process. Initially, single layer of epidermal cells cover the embryo. Afterwards in the 5th week of gestation proliferation of the epithelium cells take place which later on undergoes the process of flattening to form the periderm or epitrichium. The periderm later on continuously divide and undergoes the process of keratinization, desquamation and replacement by the new cells of basal origin. With further proliferation of cells in the in the basal layer a third layer is form in the intermediate zone. Lastly by the end of fourth month, the epidermis acquires its definitive arrangement and skin can be marked as quadri layered structure.

1. The stratum germinativum: It is the basal layer of the skin and it is continuously proliferating layer of cells. This layer forms the irregularities in the skin and reduces the smoothness. Therefore, the fingerprint considered as the consequence of basal layer proliferation.
2. The stratum spinosum: It is the spinous layer of the skin comprises of the polyhedral cells containing tonofibrils.
3. The stratum granulosum: This layer has the granular appearance which contains the keratohyalin granules in the cells after modification.
4. The horny layer: It is the layer consist of scale like epidermal cells and it is the combination of stratum lucidum and corneum.
5. The epidermis is invaded by the mesenchymal cells which in turn form the neural crest cells that form the melanocytes that secretes melanin pigment which give colour to the body.

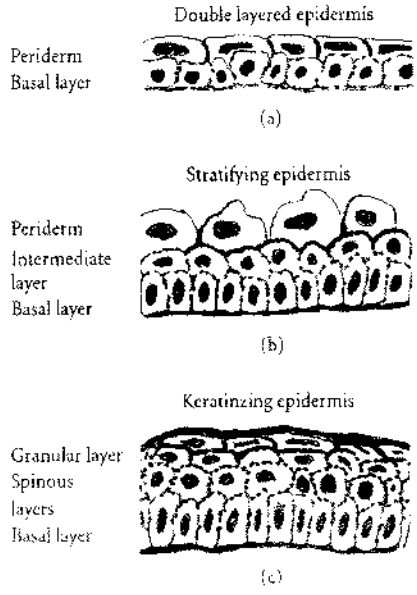


Fig 22.1. The epidermis

THE DEVELOPMENT OF DERMIS:

The dermis is of mesenchymal origin, which is formed by the mesoderm. Connective tissue formation mostly takes place from the lateral mesoderm albeit some of it is derived from the dermatomal somites. The dermal papillae is formed by the epidermal ridges. The blood vessels in the dermis begin as simple endothelium lined structures that undergoes the process of vasculogenesis.

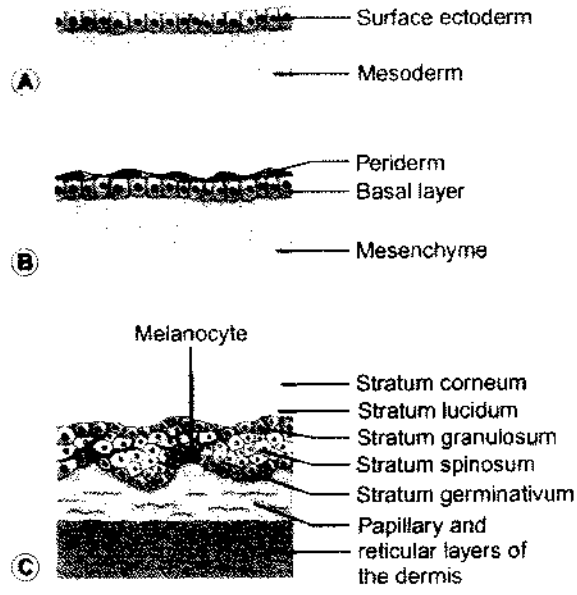


Fig 22.2: **Different layers of skin.**

THE DEVELOPMENT OF GLANDS:

The glands are formed from the epidermis however it grows into the dermis. Three of the most important integumentary glands are discussed here.

DEVELOPMENT OF THE SEBACEOUS GLAND:

The development of sebaceous glands occurs as the epithelial outgrowth from the both sides of the root sheath of hair follicles these outgrowths grows inward and envelops into the dermal connective tissue. Afterwards the outgrowth branch to form the primordial glandular alveoli which starts to secrete the sebum.

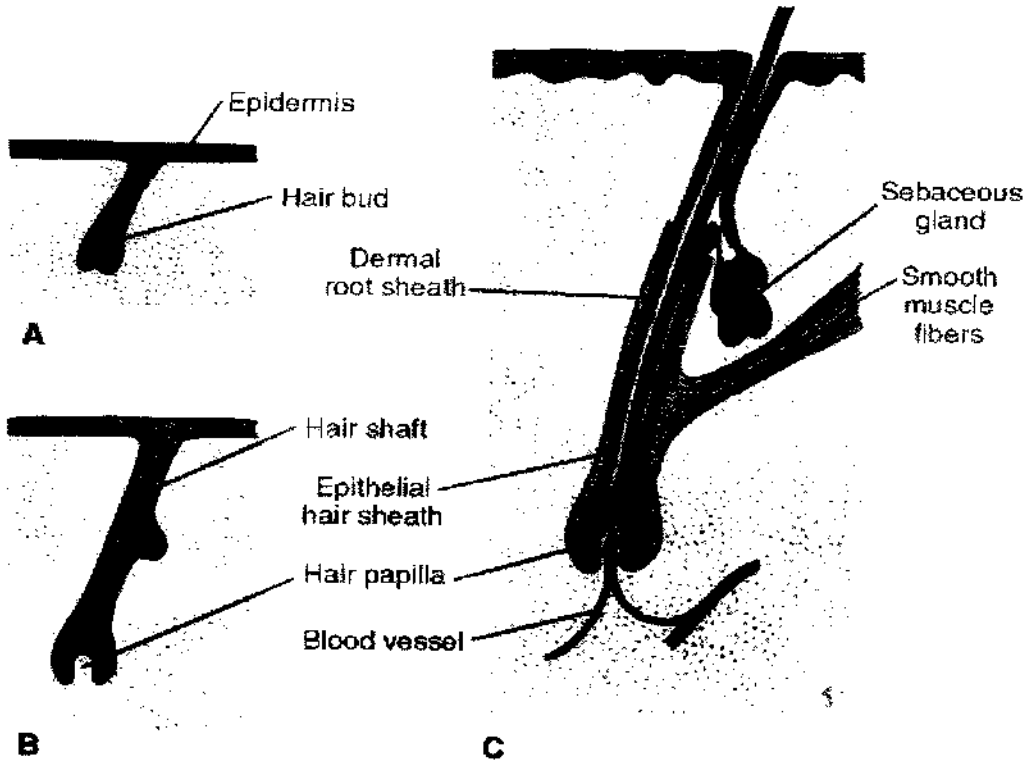
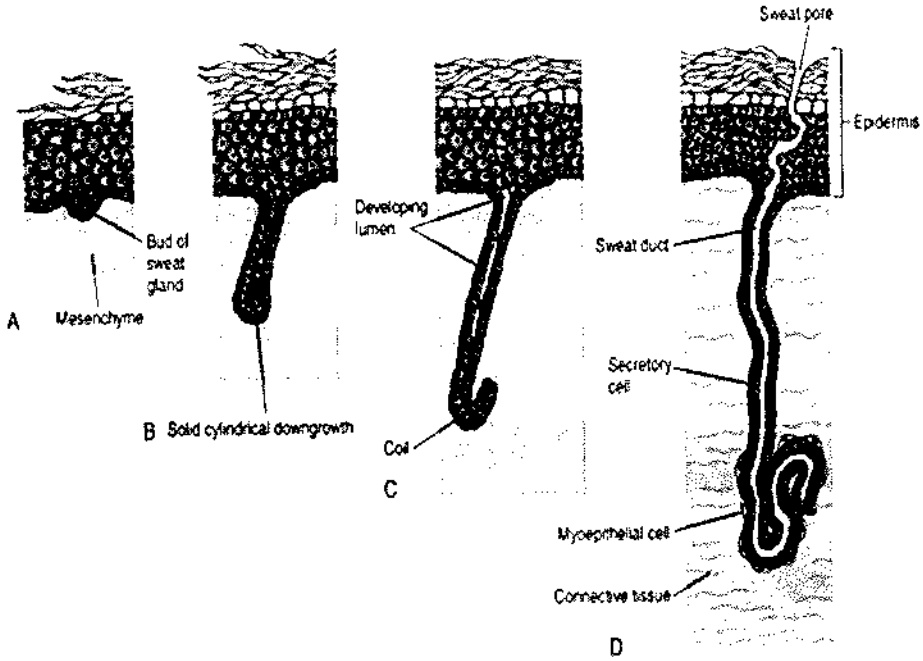


Fig 22.3: **Development of sebaceous glands.**

DEVELOPMENT OF SWEAT GLAND:

The development of sweat glands starts as the epidermal outgrowth which invade into the mesenchyme and elongates to form the tubular channels of the gland. The peripheral part of the glands differentiate to form the cells of secretory origin known as the myoepithelial cells.



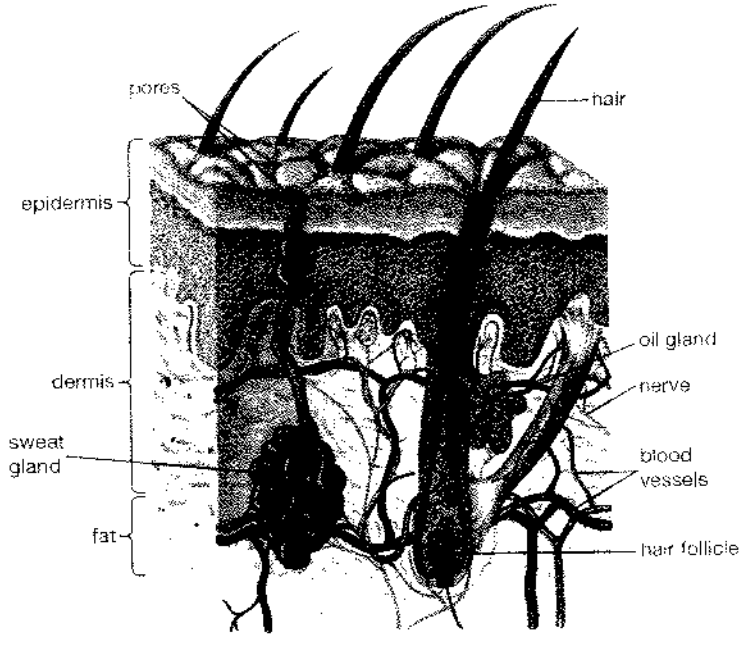


Fig 22.4: Development of sweat glands

DEVELOPMENT OF THE MAMMARY GLAND:

The development of the mammary glands starts to appear in the sixth week of gestation. Mammary glands are the modified sweat glands. Initially the mammary ridges appear which

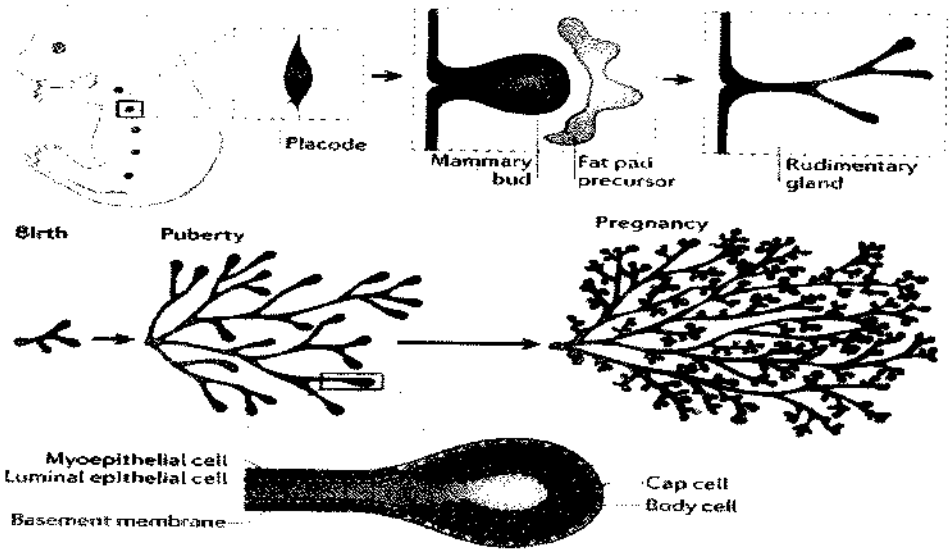


Fig 22.5: Development of mammary glands.

later on develops into the glandular structures. The glands formed from the sprouting down growths called as mammary buds which form the 15 to 20 cords. Afterwards it undergoes the process of recanalization to form the lactiferous tubules. These lactiferous tubules drains into the epithelial modification known as nipples. At this stage mammary glands in both sexes are identical.

THE DEVELOPMENT OF NAIL:

Nails develop from the epidermal thickenings known as bail fields which develops at the apex of digits. Nail fields continue to grow proximally and dorsally until the final attainment.

THE DEVELOPMENT OF HAIR:

From the stratum germinativum a solid epidermal growth starts to appear known as the hair. At the caudal end hairs have invaginations known as hair papillae. The dermal root sheath is formed by the surrounding mesenchyme. Erector pili muscles are also of mesenchymal origin. The first hair which is formed know as lanugo hairs.

THE DEVELOPMENT OF TEETH:

Teeth develops as the interaction of ectoderm and the mesoderm. There are two sets of teeth for the life.

1. Primary dentition
2. Secondary dentition.

STAGES OF TOOTH DEVELOPMENT:

There are three stages of tooth development;

Bud stage:

Dental lamina form the dental buds which are ten in numbers. These teeth are of deciduous origin and sheds at the age of seven. Permanent set of tooth develops during the fetal period however the 2nd and 3rd permanent tooth develops after birth.

Cap stage:

By the invagination of mesenchyme tooth becomes the cap like structure and its ectodermal part is known as enamel organ while inner part is known as dental papillae.

Bell stage:

By the differentiation of enamel organ tooth becomes the bell like structure. The mesenchymal cells of dental papillae forms the odontoblasts. These odontoblasts differentiates to form predentin that by the process of calcification becomes dentin. Cells of inner enamel epithelium forms the ameloblast which produces enamel. The vascular mesenchyme envelops the developing tooth to form the dental sac which forms the cementum and periodontal layer.

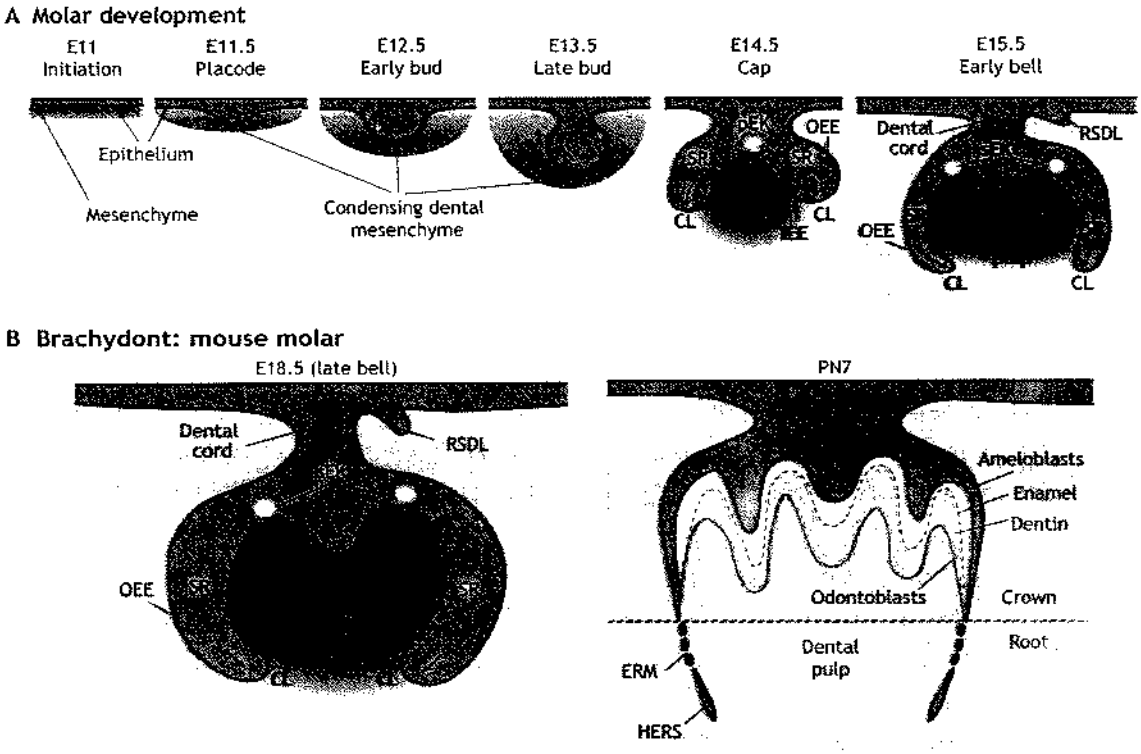


Fig 22.6: Different stages in development of tooth.

ABNORMALIIES RELATED WITH THE DEVELOPMENT OF INTEGUMENTARY SYSTEM:

1. ICHTHYOSIS:

Ichthyosis is a family of genetic skin disorders characterized by dry, thickened, scaly skin. The more than 20 types of Ichthyosis range in severity of symptoms, outward appearance, underlying genetic cause and mode of inheritance (e.g., dominant, recessive, autosomal or X-linked).

2. CONGENITAL ECTODERMAL DSPLASIA:

It is a group of disorders in which two or more of the ectodermally derived structures; the skin, sweat glands, hair, nails, teeth and mucous membranes develop abnormally. Each person with an ectodermal dysplasia may have a different combination of defects.

3. INTEGUMENTARY ANJIOMAS:

Red moles, or cherry angiomas, are common skin growths that can develop on most areas of your body. They're also known as senile angiomas or Campbell de Morgan spots. They're usually found on people aged 30 and older. The collection of small blood vessels inside a cherry angioma give them a reddish appearance.

4. ALBINISM:

It is a genetic condition where people are born without the usual pigment (color) in their bodies. Their bodies aren't able to make a normal amount of melanin, the chemical that is responsible for eye, skin, and hair color. So most people with albinism have very pale skin, hair, and eyes.

5. GYNECOMASTIA:

It is an enlargement or swelling of breast tissue in males. It is most commonly caused by male estrogen levels that are too high or are out of balance with testosterone levels.

6. ATHELIA:

It is a condition in which a person is born without one or both nipples. Although athelia is rare overall, it's more common in children who are born with conditions such as Poland syndrome and ectodermal dysplasia.

7. AMASTIA:

It refers to a rare clinical anomaly in which both breast tissue and nipple are absent. Amastia can be either isolated or complicated with other syndromes such as ectodermal dysplasia, syndactaly (Poland's syndrome) and lipoatrophic diabetes.

8. POLYTHELIA AND POLYMASTIA:

It refers to the presence of an additional nipple alone while polymastia denotes the much rarer presence of additional mammary glands.

9. APLASIA OF BREAST:

A rare condition wherein the normal growth of the breast or nipple never takes place. They are congenitally absent. There is no sign whatsoever of the breast tissue, areola or nipple.

10. INVERTED NIPPLES:

Inverted nipples are nipples that point inward or lie flat, rather than pointing out. It's also called retracted nipples. It can happen in one breast or both. However, if it starts to happen later in life, it could be a sign of a medical problem that needs to be checked by a doctor.

11. HYPERTRICHOSIS:

It is excessive hair growth over and above the normal for the age, sex and race of an individual, in contrast to hirsutism, which is excess hair growth in women following a male distribution pattern. Hypertrichosis can develop all over the body or can be isolated to small patches.

12. APLASTIC ANONYCHIA:

Congenital absence of nails is a rare disorder. Anonychia results from failure of nail fields to form or from failure of the proximal nail folds to form nail plates.

13. ENAMEL HYPOPLASIA:

It is a defect of the teeth in which the enamel is deficient in amount, caused by defective enamel matrix formation. Defects are commonly split into one of four categories, pit-form, plane-form, linear-form, and localized enamel hypoplasia.

14. DENTIGEROUS CYST:

It also called follicular cysts, are slow-growing benign and non-inflammatory odontogenic cysts that are thought to be developmental in origin. On imaging, they usually present as a well-defined and unilocular radiolucency surrounding the crown of an unerupted or impacted tooth within the mandible.

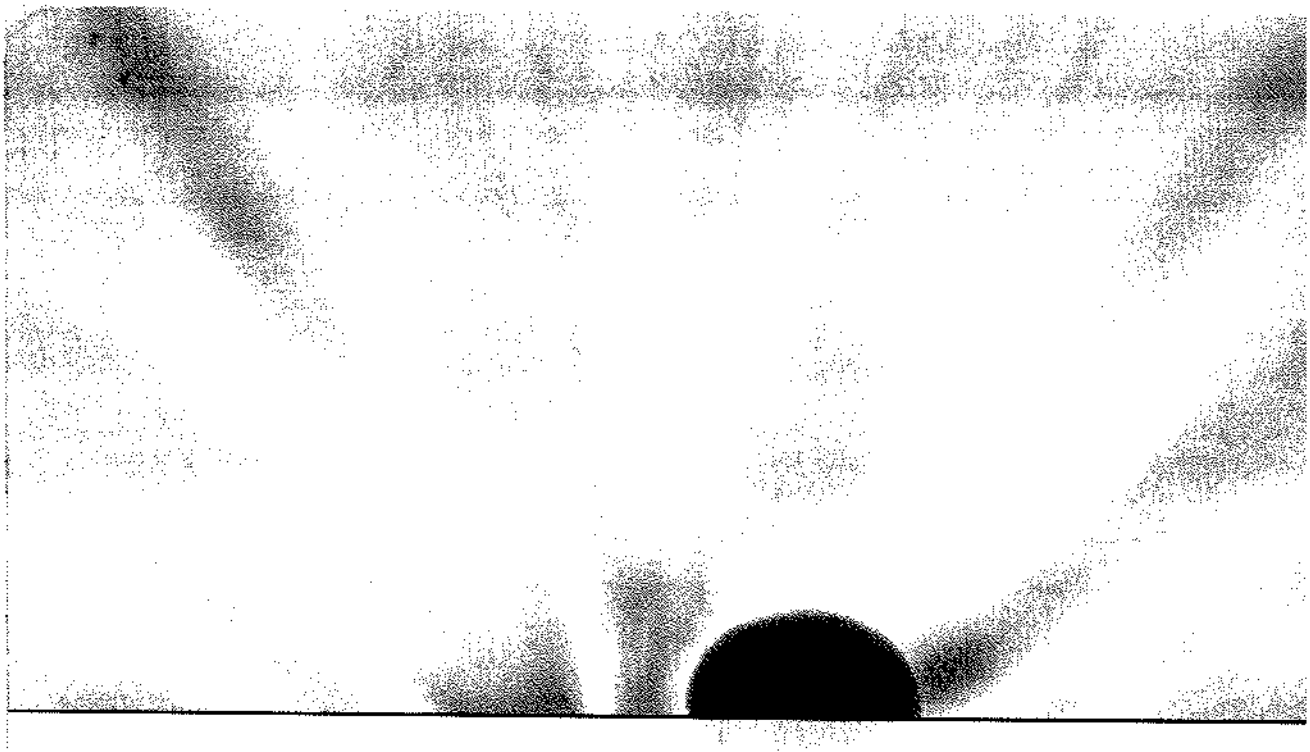
15. AMELOGENESIS IMPERFECTA:

It is a disorder of tooth development. This condition causes teeth to be unusually small, discolored, pitted or grooved, and prone to rapid wear and breakage. Other dental abnormalities are also possible.

16. DENTINOGENESIS IMERFECTA:

This condition causes the teeth to be discolored (most often a blue-gray or yellow-brown color) and translucent. Teeth are also weaker than normal, making them prone to rapid wear, breakage and loss.

KEY NOTES!
a- The integument and its appendages are derived from the ectoderm, mesenchyme and neural crest cells.
b- Hairs are derived from the downgrowths of the epidermis into the dermis. The first hairs are known as lanugo hairs and it sheds before birth and shortly thereafter replaced by coarser hair.
c- Most of the sebaceous glands develop as the outgrowths from the sides of hair follicle while sweat and mammary glands develop as the downgrowth of epidermis into dermis.
d- Birth defects of skin are mainly the disorders of pigmentation and keratinization.



SECTION - D
THE PATHOLOGICAL EMBRYOLOGY

23 THE DISEASES OF INFANCY, BIRTH AND CHILDHOOD

LEARNING OBJECTIVES

- GENERAL INTRODUCTION
- CONGENITAL ANOMALIES
- PREMATURE BIRTH DEFECTS
- INBORN DISORDERS OF METABOLISMAND OTHER GENETICAL ERRORS
- TUMOR AND TUMOR LIKE LESIONS OF INFANCY AND CHILDHOOD
- KEY NOTES.

THE DISEASES OF THE INFANCY, BIRTH AND CHILDHOOD

This chapter deals with the pathological manifestation of the congenital anomalies. It also focuses the three main causes behind the congenital anomalies. These are genetical, environmental and multifactorial. The basic aim behind discussing this chapter is to know how the greatest mortality occurs during the first year of life and dying progressively until the middle adolescence commences. The causes of mortality also depend on the age, with congenital anomalies, premature births and sudden death of infants associated with sudden infant death syndrome is on top of the list during the first year of postnatal life.

CONGENITAL ANOMALIES:

These anomalies are the morphologic defects mostly present at birth, however occasionally it becomes apparent later in life. It has been estimated that 20% of the fertilized ova are so much anomalous that they do not have ability to be morphed into a viable conceptus.

CAUSES OF CONGENITAL ANOMALIES:

Mostly the causes of congenital anomalies are idiopathic however in 20 to 60 % of cases these are of genetical, environmental and multifactorial manifestation.

GENETIC CAUSES:

Two of the genetic causes are worthy to discuss here these are;

1. Chromosomal abnormalities which are present in the minor proportion; it occurs in live born infants only in 10% to 20% of the cases however 80% to 90% of the fetuses with this sort of abnormality die in the uterus. The aberration are not of familial manifestation

albeit these are cytogenetic origin which arises during the process of gametogenesis. The most frequent examples of these type of anomalies are;

a- Turner syndrome:
It is a condition that affects only females, results when one of the X chromosomes (sex chromosomes) is missing or partially missing. Turner syndrome can cause a variety of medical and developmental problems, including short height, failure of the ovaries to develop and heart defects.

b- Klinefelter syndrome:
It is a genetic condition in which a boy is born with an extra X chromosome. Instead of the typical XY chromosomes in men, they have XXY, so this condition is sometimes called XXY syndrome. Men with Klinefelter usually don't know they have it until they run into problems trying to have a child.

c- Down syndrome:
It is a condition in which a child is born with an extra copy of their 21st chromosome hence its other name, trisomy 21. This causes physical and mental developmental delays and disabilities.

d- Patau syndrome:
It is a syndrome caused by a chromosomal abnormality, in which some or all of the cells of the body contain extra genetic material from chromosome 13. The extra genetic material disrupts normal development, causing multiple and complex organ defects.

e- Edwards syndrome:
It is also known as trisomy 18, is a genetic disorder caused by the presence of a third copy of all or part of chromosome 18. Many parts of the body are affected. Babies are often born small and have heart defects.

2. Single gene mutations:
These type of anomalies are usually rare but follow Mendelian patterns of inheritance; many of them involve loss of function in genes that derive the process of development. For example: the hedgehog signaling pathway and holoprosencephalic developmental defects.

ENVIORNMENTAL CAUSES:

The environmental causes of the congenital anomalies include;

a) Viruses: The effects of the viruses are related with developmental period at time of infection. For example;
   1. Cytomegaloviruses is a virus which infect the fetus frequently. The risk of its infection is greatest during the second trimester of pregnancy. As organogenesis is usually completed during this time so congenital malformations are rare however central nervous system infection may results into microcephaly, mental retardation, deafness etc.
   2. Congenital rubella syndrome is also may also occur during the 16th week of gestation. It can cause heart defects, cataracts, deafness, mental retardation etc.

b) Drugs and chemicals: These substances may also cause congenital anomalies; most frequent substances that can cause teratogenesis are;
   1. Folate antagonists
   2. Androgenic hormones
   3. Anticonvulsants
   4. 13- cis retinoic acid
   5. Thalidomide.
      a. Alcohol: It is most commonly used teratogen which cause the structural anomalies, as well as cognitive and behavioral defects, these are known as fetal alcohol spectrum disorders. It affects the infant as; growth retardation, atrial septa; defects, maxillary hypoplasia, microcephaly etc.
      b. Maternal diabetes: the malformations associated with diabetic mother are cardiac anomalies, neural tube defects and maternal hyperglycemia induced fetal hyperinsulinemia which causes increased body fat, muscle mass and organomegaly.
      c. Radiation: It also affects the developing embryo. During the process of organogenesis high doses of radiation can cause the skull defects, microcephaly, spina bifida, blindness etc.

MULTIFACTORIAL CAUSES:

The pathological diseases during the process of embryogenesis may arise due to the interaction of environmental factors with the mutated genes. For example;

1. Congenital hip dislocation
2. Neural tube defects.

EMBRYOLOGICAL PATHOGENESIS OF CONGENITAL ANOMALIES:

From the above mentioned agents everyone is able to insult the normal process of embryogenesis and starts the pathogenesis. A given agent can have significantly different consequences depending on what is encountered.

- ✓ Any insult during the first three weeks of gestation either kills many of the cells and results into the abortion or injure the limited number of cells that can be recovered by fetus without much lose.
- ✓ During the 3rd week to 9th week embryo is so much sensitive that any insult affect the process of organogenesis.
- ✓ Any insult during the fetal period can affect the growth of embryo.

CAUSES OF CONGENITAL ANOMALIES
1. Genetic a- Chromosomal abnormalities b- Mendelian inheritance
2. Environmental a- Placental infections Cytomegalovirus Rubella virus Toxoplasmosis Human immunodeficiency virus Syphilis b- Drugs and chemicals Alcohol Thalidomide Androgenic hormones Phenytoin 13- cis retinoic acid Warfarin folic acid antagonists c- Maternal disease states Diabetes Endocrinopathies Phenylketonuria d- Irradiations
3. Multifactorial influences
4. Idiopathic manifestations

PREMATURE BIRTH DEFECTS:

After the congenital malformations the second leading cause of neonatal mortality is the premature births. There are two types of babies which are count in this category;

1. Preterm babies: Those who born before 37 weeks of gestation are considered as preterm babies.
2. Post term babies: those who born after 42 weeks of gestation are considered as post term babies.

   In addition to this, those babies who fail to grow normally are also at significant risks however those who are underweight has also severe medical consequences.

CAUSES OF PREMATURE BIRTHS:

The major causes of premature births are given as under;

1. PRETERM BIRTHS:

   Generally speaking, the preterm births are due to placental inflammation and metalloproteinase activation. These can cause;

   a- Premature rapture of placental membranes
   b- Malnutrition
   c- Smoking
   d- Preterm labor
   e- Gestational vaginal bleeding.

2. INTRAUTERINE INFECTIONS:

   Below are given some intrauterine infections which are due to the infections of different particles. These infectious particles activate the toll like receptors which in turn deregulate the prostaglandin production, leading to the contraction of uterine smooth muscles.

   a- Chorioamnionitis
   b- Funistis
   c- Mycoplasma hominis
   d- Gardenella vaginalis
   e- Trichomonas and chlamydia
   f- Organisms having ureaplasma urealyticum.

3. UTERINE FIBROIDS:

   Uterine fibroids formed as the result of following consequences;

   a- Uterine abnormalities
   b- Placental abnormalities
   c- Cervical abnormalities.

4. MULTIPLE GESTATION:
   Multiple gestation includes the twin pregnancy.

CAUSES OF THE RESTRICTED GROWTH:

There are three main causes which predisposes restricted growth of the fetus; these are fetal, placental and maternal.

1. FETAL CAUSES:
   Fetus can proportionally be affected despite there is no maternal issue. The causes behind this issue are;
   a- Chromosomal abnormalities
   b- Congenital anomalies
   c- Congenital infections.

2. PLACENTAL:
   Extensive growth of fetus during the 3rd trimester of embryogenesis requires the formation of placenta. Defects in the development of placenta can cause disproportionate growth retardation. The causes includes;
   a- Placenta previa
   b- Placental thrombosis and infarctions
   c- Placental infections
   d- Multiple gestation
   e- Placental mosaicism
   f- Placental abruption
   g- Umbilical placental vascular abnormalities.

3. MATERNAL CAUSES:
   Maternal issues can have severe consequences for the CNS dysfunction, hearing impairment, visual impairment and learning disability. The causes are;
   a- Smoking and drug addiction
   b- Hypertension
   c- Narcotic and alcohol intake
   d- Preeclampsia
   e- Malnutrition.

Premature births can lead to respiratory distress syndrome, sepsis, intraventricular haemorrhage, necrotizing enterocolitis.

RESPIRATORY DISTRESS SYNDROM:

It is the most common lung disease in premature infants and it occurs because the baby's lungs are not fully developed. The more premature the infant, the more likely it is for the baby to have RDS. RDS is caused by not having enough surfactant in the lungs.

SEPSIS:

It is a potentially life-threatening condition caused by the body's response to an infection. The body normally releases chemicals into the bloodstream to fight an infection. Sepsis occurs when the body's response to these chemicals is out of balance, triggering changes that can damage multiple organ systems.

INTERVENTRICULAR HAEMORRHAGE:

It is bleeding into the brain's ventricular system, where the cerebrospinal fluid is produced and circulates through towards the subarachnoid space. It can result from physical trauma or from hemorrhagic stroke.

NECROTIZING ENTEROCOLITIS:

It is a medical condition where a portion of the bowel dies. It typically occurs in newborns that are either premature or otherwise unwell. Symptoms may include poor feeding, bloating, decreased activity, blood in the stool, or vomiting of bile.

PERINATAL INFECTIONS:

Those type of infections which are typically acquired either transcervically or transplacentally.

TRANSCERVICAL INFECTIONS:

The type of infection which has ascending transmission mostly the infections are of bacterial or viral manifestation. The transmission of infections mostly occur through cervicovaginal route however sometimes it may also occurs in the consequence of amniotic fluid inhalation or at parturition by passing through an infected birth canal. Clinical symptoms associated with this type of infection are; sepsis, meningitis and pneumonia.

TRANSPLACENTAL INFECTION:

This type of infection exhibits the transmission through placental barrier therefore it is known as transplacental infection. Most parasitic and viral infections as well as some bacterial infections transmit through fetal bloodstream via chorionic villi. Infection may occur at any time during embryogenesis however the time of parturition it is the most frequent. Clinical

symptoms associated with this type of infection are; encephalitis, fever, chorioretinitis, myocarditis, hepatosplenomegaly, pneumonitis and skin lesions.

FETAL HYDROPS:

It is a serious fetal condition which is defined as abnormal accumulation of fluid in two or more fetal compartments that includes ascites, pleural effusion, pericardial effusion, and skin edema. In some patients, it may also be associated with polyhydramnios and placental edema.

IMMUNE FETAL HYDROPS:

It is most usually a complication of a severe form of **Rh incompatibility**, which can be prevented. In this condition, mother who has Rh negative blood type makes antibodies to her baby's Rh positive blood cells, and these antibodies have propensity to cross the placenta. The Rh incompatibility causes a plethora of red blood cells to be destructed, therefore it is also known as **hemolytic disease of the newborn**. The problems associated with this condition includes total body swelling. However severe swelling can interfere with the physiology of organs.

NON IMMUNE FETAL HYDROPS:

It is a form of fetal hydrops which is a severe fetal condition as the excessive accumulation of fetal fluid within the fetal extravascular compartments and body cavities, and is the end-stage of a wide variety of disorders. Various causes of this type of fetal hydrops are given as under in tabulated form;

CAUSES OF NON IMMUNE FETAL HYDROPS
1. CARDIOVASCULAR CAUSES Tachyarrhythmia Cardiac malformations High output failure
2. THORACIC CAUSES Diaphragmatic hernia Cystic adenomatous malformation
3. CHROMOSOMAL CAUSES Turner syndrome Down's syndrome Edward's syndrome.

4. TWIN GESTATION Twin to twin transfusion
5. FETAL ANEMIA Homozygous alpha thalassemia Parvovirus Immune hydrops
6. GENITOURINARY TRACT MALFORMATIONS Tumors
7. GENETIC AND METABOLIC DISORDERS
8. INFECTIONS Syphilis Cytomegalovirus Toxoplasmosis.

INBORN DISORDERS OF METABOLISM AND SOME OTHER GENETICAL ERRORS:

In this section four main disorders have been briefly explain. These four disorders are;

1. Galactosemia
2. Phenylketonuria
3. Cystic fibrosis
4. Sudden infant syndrome.

1. GALACTOSEMIA:

It refers to "galactose in the blood". It is a group of inherited disorders that impair the ability of body to process and produce energy from a sugar called galactose. When people with galactosemia ingest foods or liquids containing galactose, it is not digested and the undigested food particles build up in the blood. Galactose is present in many foods, including all dairy products, many baby formulas, and some fruits and vegetables. The impaired ability to process galactose can be due to the deficiency of any of 3 enzymes, caused by mutations in different genes. There are 3 main types of galactosemia which are distinguished based on their genetic causes, signs and symptoms, and severity:

a- Classic galactosemia: It is due to the deficiency of galactose 1- phosphate uridyltransferase which is caused by mutation in GALT gene.

b- Glactokinase deficiency: It is type 2 galactosemia which is due to the deficiency of galactokinase 1 caused by the mutation in GALK1 gene.

c- Galactoepimerase deficiency: It is type 3 galactosemia which is due to the deficiency of UDP- galactose 4 epimerase enzyme cause by mutation in GALE gene.

2. PHENYLKETONUREA:

It is an inborn error of metabolism that is due to phenylalanine hydroxylase deficiency. It results in decreased metabolism of the amino acid phenylalanine. Untreated, phenylketonuria can lead to intellectual disability, seizures, behavioral problems, skin disorders and mental disorders.

3. CYSTIC FIBROSIS:

It is a type of hereditary disease that affects the lungs and digestive system. The body produces thick and sticky mucus that can affect the lungs and obstruct the pancreas. Cystic fibrosis can be life-threatening therefore people with the condition tend to have a shorter than normal life

CAUSES OF CYSTIC FIBROSIS:

Cystic fibrosis is an inherited condition. This is due to inheritance of the defective gene from both of their parents. The defective gene contains codes for producing a protein that controls the flow of salt and water outside of the organs, including the lungs and the pancreas.

In Cystic Fibrosis the balance of salt is disturbed that leads to small quantity of salt and water outside of the cells and the production of thick mucus. People with only one copy of the defective gene are called carriers. They do not have the condition or its symptoms. To have the disease, both parents must be carriers.

4. SUDDEN INFANT DEATH SYNDROME:

This is the unexplained death. It occurs when the baby is sleeping. The perfect reason of this disease is unexplained yet however there are some factors which helps to explain it.

The combination of physical and sleep environmental factors can make an infant more vulnerable to SIDS. These factors vary from child to child.

Physical factors:

Physical factors associated with SIDS include.

A- Brain defects. Some infants are born with problems that make them more likely to die of SIDS. In many of these babies, the portion of the brain that controls breathing and arousal from sleep hasn't matured enough to work properly.

B- Low birth weight. Premature birth or being part of a multiple birth increases the likelihood that a baby's brain hasn't matured completely, so he or she has less control over such automatic processes as breathing and heart rate.

C- Respiratory infection. Many infants who died of SIDS had recently had a cold, which might contribute to breathing problems.

Sleep environmental factors:

The items in a baby's crib and his or her sleeping position can combine with a baby's physical problems to increase the risk of SIDS. Examples include:

a- Sleeping on the stomach or side. Babies placed in these positions to sleep might have more difficulty breathing than those placed on their backs.

b- Sleeping on a soft surface. Lying face down on a fluffy comforter, a soft mattress or a waterbed can block an infant's airway.

c- Sharing a bed. While the risk of SIDS is lowered if an infant sleeps in the same room as his or her parents, the risk increases if the baby sleeps in the same bed with parents, siblings or pets.

d- Overheating. Being too warm while sleeping can increase a baby's risk of SIDS.

Risk factors

Although sudden infant death syndrome can strike any infant, researchers have identified several factors that might increase a baby's risk. They include:

- Sex. Boys are slightly more likely to die of SIDS.
- Age. Infants are most vulnerable between the second and fourth months of life.
- Race. For reasons that aren't well-understood, nonwhite infants are more likely to develop SIDS.
- Family history. Babies who've had siblings or cousins die of SIDS are at higher risk of SIDS.
- Secondhand smoke. Babies who live with smokers have a higher risk of SIDS.
- Being premature. Both being born early and having a low birth weight increase your baby's chances of SIDS.

Maternal risk factors:

During pregnancy, the mother also affects the baby with risk of SIDS, especially if she:

A- Is younger than 20
B- Smokes cigarettes
C- Uses drugs or alcohol
D- Has inadequate prenatal care

TUMOR AND TUMOR LIKE LESIONS OF INFANCY AND CHILDHOOD:

Both the benign and malignant tumors occur in the infancy and childhood however the benign tumors are more frequent than malignant.

BENIGN TUMORS AND TUMOR LIKE LESIONS:

1. HETEROTOPIA:
   It is the presence of normal tissue at abnormal location. For example pancreatic tissue in the stomach wall.

2. HAMARTOMAS:
   It is a noncancerous tumor made of an abnormal mixture of normal tissues and cells from the area in which it grows. It can grow on any part of the body, including the neck, face, and head. In some cases, hamartomas grow internally in places such as the heart, brain, and lungs.

3. HEMANGIOMAS:

It is a benign tumor made up of blood vessels. There are many types of hemangiomas, and they can occur throughout the body, including in skin, muscle, bone, and internal organs. Most hemangiomas occur on the surface of the skin or just beneath it.

4. LYMPHATIC TUMORS:

Lymphoma is a cancer of the lymphatic system, which is part of the body's germ-fighting network. The lymphatic system includes the lymph nodes (lymph glands), spleen, thymus gland and bone marrow. Lymphoma can affect all those areas as well as other organs throughout the body.

5. FIBROUS TUMORS:

These are benign fibrous growths that occur rarely in the general population (5 to 6 per 1 million per year) but frequently in one of the familial cancer predisposition conditions known as familial adenomatous polyposis (FAP) or Gardner syndrome.

6. TERATOMA:

It is a rare type of tumor that can contain fully developed tissues and organs, including hair, teeth, muscle, and bone. Teratomas are most common in the tailbone, ovaries, and testicles, but can occur elsewhere in the body. Teratomas can appear in newborns, children, or adults. They're more common in females.

MALIGNANT TUMORS:

Histologically and biologically childhood malignancies differs from the adulthood in the following aspects;

1. Incidence and type of tumor
2. Teratogenesis and oncogenesis
3. Prevalence of underlying familial and genetic aberrations
4. Cytodifferentiation.
5. Survival and cure rates.

TYPES OF MALIGNANT TUMORS:

1. Hematopoietic system: leukaemia and some lymphomas.
2. Retina: retinoblastoma
3. Bone : oestrogenic sarcoma, edwing sarcoma
4. Soft tissues: rahbdomyosarcoma
5. Adrenal medulla: medulloblastoma
6. Central nervous system: astrocytoma, neuroblastoma and ependydoma
7. Kidney : Wilm's tumor

WILMS' TUMOR:

It is a rare kidney cancer that primarily affects children. It is also known as nephroblastoma, it is the most common cancer of the kidneys in children. Wilms' tumor most often affects children ages 3 to 4 and becomes much less common after age 5.

KEY NOTES!
This chapter deals with the pathological disease which occur before birth or after birth as well as it deals with the disorders of childhood. Regarding birth defects, these are the structural abnormalities present at the time of birth. Birth defects may be single or multiple and have minor or major consequences. Pathological diseases of embryogenesis are due to genetics, environment, infectious or idiopathic causes.