N.K.KASHURINA, K.S.VKLKKV

EMBRIOLOGY

Earlyhumandevelopment.Fetal membranes. Comparingembryology

The course of illustrated lectures

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Compized by: *N. K. Kashurina*, Koctor of Medical Science, professor, the Kepartment of Histology, Cytology and Embriology, Crimean State Medical University named after S.I. Georgievskyy.

K.S.Volkov, Koctor of biological Science, professor, Head of the Kepartment of Histology, Cytology and Embriology Ternopil State Medical University named after I.Y.Gorbachevskyy.

Recensents: professor *Maslovskyy S.I.*, Head of the Kepartment Histology, Cytology and Embriology Kharkiv State Medical University.

Professor *Tverdokhlib I.V.* Head of the Kepartment Histology, Cytology and Embriology Kni propetrovsk State Medical University.

This lecture course represents compact text and illustration of early human development and comparing embriology.

The manual presents the relevant information necessary for the medical students to understand origination of cells, tissues and organs.

The chapters are organized to present a systematic and logical approach that explains how embryo develops. The first chapter covers embrionic development beginning with the formation of gamets (progenesis, including oocyte types of chordate animals). The second chapter describes main steep of fertilization. The next chapters introduce embryonic development: implantation of a conseptus, differentiation of derm layers, and formation of the axial organs including notochord, neural tube, and primary gut).

The last part contains clinically orientated material about the fetal membranes (amnion, yolk sac, allantois, chorion, umbilical cord, and placenta).

We are believed that these features will help to emphasize the important tenet of modern day Embriology.

The manual is for medical students and practitioners.

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Content

Embryology

The term "***embryology***" originates from two Greek words: "*embryon*" – embryo and "*logos*" – study or science.

The **value** of the study of embryology to the medical students is fivefold:

1. Embryology gives an understanding of how the different organs and tissue develop from a single cell (zygote) into a complex multicellular organism.

2. Embryology gives a rational explanation of the relationships and position of many normal adult structures.

3. Embryology includes not only the development of the embryo but also the development of the fetus membranes, which connect the fetus to the mother.

A knowledge of the development, relations and properties of these membranes is essential in order to understand obstetrics and as a basis for advances in this subject. Such knowledge is also obviously necessary for the understanding of the physiological relationship between the fetus and the mother.

4. Many pathological conditions can only be understood in the light of normal and abnormal development. Knowledge of the processes of development is essential for the understanding of such defects and for the study of their causes and possible elimination.

5. As the student continues his studies through the basic medical sciences and into the clinical subjects embryology will be appreciated more and more as a great correlator of other morphological disciplines such as anatomy, pathology, physical diagnosis and surgery, and even of many physiological aspects of medicine.

Historicalgleanings

Historically 2 contrasting theory describe the human development.

* The ***theory of preformation*** considered that a pre-existing diversity is already present in the fertilized ovum (or in the sperm) and that future development consists merely in the infolding and rendering visible of this innate diversity.

* The preformation controversy ended in 1775 when Lazano Spallanzani showed that both the ovum and sperm were necessary for initiating the development of a new individual. From his experiments, including artificial insemination in dogs, he concluded that the sperm was the fertilizing agent that initiated the developmental processes.

The ***theory of epigenesis*** considered that during development new cells, tissues and structures appear. In 1759 **CasparFriedrich Wolff** examined unencumbered eggs and proposed the layer concept. His ideas formed the basis of the theory of epigenesis, which states that development results from growth and differentiation of specialized cells.

HeinrichChristianPander discovered the three germ layers of the embryo, which he named the blastoderm.

The **embryological investigations of the past hundred years** have demonstrated that the actual processes of development are of an epigenetic nature, the fertilized egg, possessing a simple form and exhibiting an apparently undifferentiated structure, undergoes a series of developmental changes, which result in the spatial differentiation of the mature organism with its specialized types of cells, tissues and organs.

Modern genetics has shown that the genes located in the chromosomes of the nucleus of the zygote carry the information enabling normal development to occur.

Humandevelopmentalperiods

Human development is continuous process that includes **three main periods**:

- progenesis
- prenatal period
- postnatal period

Progenesis

Progenesis is a period of maturation of specialized generative cells – ***gametes***. This maturation process is called ***spermatogenesis*** in males and ***oogenesis*** (ovogenesis) in female.

Gametogenesis is the process of formation and development of gametes. The number of chromosomes is reduced during meiosis, a special type of cell division that occurs during gametogenesis. Kuring gametogenesis, the chromosome number is reduced by half and the shape of the cells is altered.

The history of male and female gamete formation is different.

· *Spermatogenesis* begins at puberty (13 to 16 years) and continues into old age.

· *ʁogenesis* begins before birth and is completed after puberty (12 to 15 years) and continuous to menopause.

Prenatalperiod

Prenatal (antenatal) period begins when an oocyte (ovum) from female is fertilized by a sperm (spermatozoon) from male with the formation of zygote.

Zygote results from the union of the oocyte and a sperm during fertilization.

Main stages of prenatal period:

· ***Fertilization*** is fusion of a female and male gamete.

· ***Cleavage*** is the series of rapid cell devesions of the zygote with the formation of blastula.

· ***Gastrulation*** is the formative process by which the three germ embryonic layers are established in embryos (ectoderm, endoderm, and mesoderm).

· ***Formation of axial organs***: notochord, neural tube, and primordial gut.

· ***Histogenesis.***

· ***Organogenesis*** with the appearance of recognizable organs or organ primordia.

Human development includes several processes:

- ***growth***
- ***morphogenesis*** is the development of shape, size or other features of different organs that includes interactions and movement of cells
- ***differentiation*** is the formation of cells, tissues and organs that are callable of performing specialized functions

Most developmental changes occur during the embryonic and fetal period.

- The **embryonic period** extends to the end of the 8th week (56 days). The *conceptus* includes all structures that develop from zygote (embryonic part and fetal membranes developing from zygote).
- The **fetal period** extends from 9th week to birth. *Fetus* is the developing human after the embryonic period.

Postnatal period

Postnatal period occurs after the birth and includes infancy, childhood, puberty, adolescence, adulthood.

- ***Infancy*** includes the first year after birth. *Newborn* is infant aged 1 month or less.
- ***Childhood*** is period from 13 month until puberty. During this period primary and secondary teeth are appeared.
- ***Puberty*** is period between the ages of 12 to 15 years, during which secondary sex characteristics develop. Puberty ends in females with the first menstrual cycle.
- ***Adolescence*** is the period from about 11 to 19 years of age; during which rapid physical and sexual maturation occur. There are active ossification (formation of bone), growth of the body and organs. Important changes occur after birth. The brain triples in weight between birth and 16 years.
- ***Adulthood*** is the period of full growth and maturity (18 – 21 years).

The study of human development has been greatly influenced by the knowledge obtained as the result of investigations on

other vertebrate types.

Ontogeny repeats phylogeny. Ontogeny repeats fundamental steps in the ontogenesis of ancestral forms, especially when these steps are of structural or functional importance to the individual (de Beer, 1954).

Gametogenesis

Gametogenesis employs a specialized process of cell division, *meiosis,* which uniquely distributes chromosomes among gametes. Each ***gamete*** thus contains only half the diploid number of chromosomes, known as the ***haploid number***.

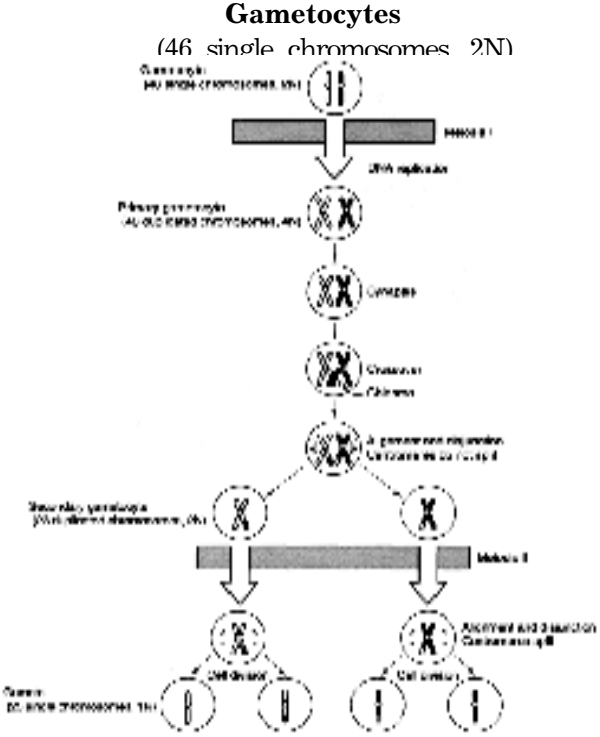


Fig. 1. **Gametogenesis.**

* ***Meiosis*** involves two sequential cell divisions, of which only first is preceded by duplication of chromosomes.

* The **first meiotic division** results in reduction of the chromosome complement to the haploid state and the **second** results in the production of four haploid gametes.

* Unlike the cells produced by mitosis that are genetically identical with the parent cell, the cells produced by meiosis (gametes) are *genetically unique*.

Kifference between meiosis in male and in female

A fundamental difference between meiosis ***in male*** and the equivalent process ***in female*** is that the supply of primary oocyte becomes progressively depleted over a woman's lifetime, whereas the supply of primary spermatocytes is sustained, even in old men.

This is because the spermatogenic cell population is essentially a continuously renewing system that depends on spermatocyte replacement from stem cells.

The ***sperm*** and ***oocyte***, the male and female gametes are ***highly specialized sex cells***. Their structure is adapted to, or determined by the functions they perform.

Consideration of male events

Spermatogenesis is the process of formation and development of specialized male generative cells – spermatozoa or mature sperms.

Spermatogenesis

* At week 3-4 after fertilization primordial germ cells develop within the wall of yolk sac. Primordial germ cells migrate toward the developing testis and are incorporated into the wall of further seminiferous tubules.

* Within the developing gonads primordial germ cells differentiate into *spermatogonia*, which undergo mitosis in late adolescence.

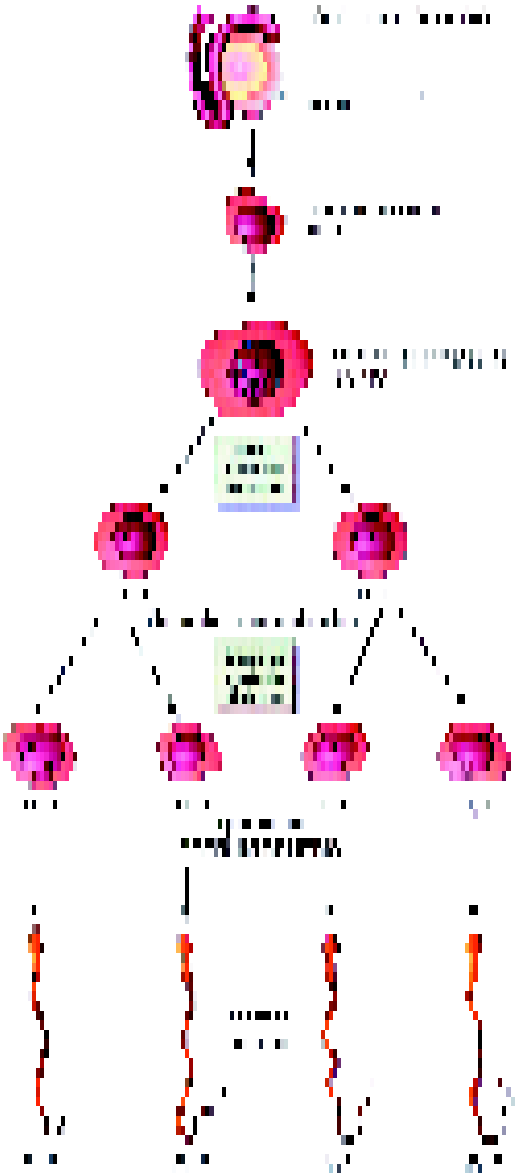


Fig. 2. **Spermatogenesis.**
The number of chromosomes is shown in each stage and includes the sex chromosomes, shown after the comma.

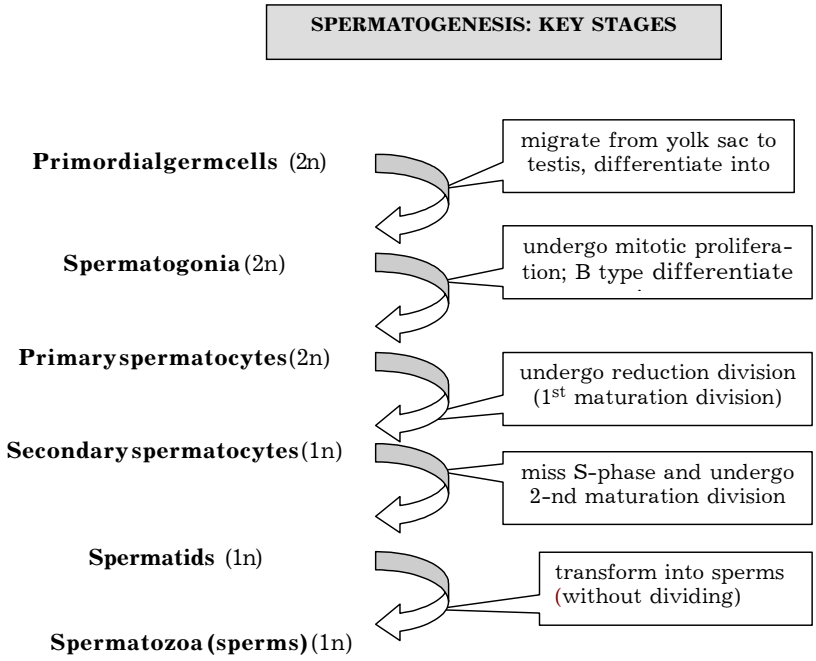
* Spermatogonia, which have been dormant in the seminiferous tubules of the testis since the fetal period, begin to increase in number at puberty. After several mitotic divisions, the spermatogonia grow and give rise to *primary spermatocytes*. The cells of this series are diploid.

* Primary spermatocytes enter the first reduction meiotic division by undergoing KNA replication after the puberty. Primary spermatocytes complete first meiotic division to form two secondary spermatocytes, which are haploid.

* Without first passing through an S-phase secondary spermatocytes undergo the second meiotic division to form four haploid spermatids.

*** *Maturation* or *spermiogenesis* is the series of changes in spermatids that results in the** formation of **spermatozoa (sperm)**.

* The total *time of sperm formation* (from spermatogonia to spermatozoa) is about 72 days.



Spermatogenesis **is testosterone dependent multistep process, whichcontains***three phases***:**

- spermatocytogenesis
- meiosis
- spermiogenesis (maturation)

Production of spermatozoa from spermatogonia (spermatogenesis) is completed in *64 + 4* or *5* days. Kuring the next *10* days or so, the newly produced spermatozoa passing along the ductus epididymis undergo a maturation process, after which they acquire the capacity for fertilization.

SPERMATκCYTκGENESIS

Spermatocytogenesis is the production of primary spermatocytes from spermatogonia through a series of mitotic divisions.

The spermatogenic stem cells are called *type A spermatogonia*. Under normal circumferences, a subtype of the A spermatogonium that is known as the *pale type A spermotogonium* because its nucleus stains rather lightly, serves as a renewing stem cells. These cells can differentiate during progressive mitotic cycles to become type B spermatogonia.

Type B spermatogonia are differentiating progenitors that give rise to primary spermatocytes but lack the capacity to self-renew.

A third class of spermatogonium has also been identified and known as the *dark type A spermatogonium* because its nucleus stains a little more intensely. It remains out of cycle until the supply of pale type A spermatogonia becomes critically depleted. Hence, it is regarded as a higher-level, "reserve" stem cell that can supplement cell renewal if proliferation of the renewing stem cells is impaired. Kivision of each type B spermatogonium produces two primary spermatocytes, which are larger spherical cells.

The hierarchy of the three types of spermatogonia is therefore:

Kark type A (reserve)

Pale type A (renewing)

▼

▼

Type B (differentiating or progenitor cells)

MEIκSIS

Meiosis consists of two successive divisions that reduce the chromosome number from 46 (44=XY in the male) to 23 (22+X or 22+Y in spermatozoa).

Prophase−I of the first meiotic division lasts for 20-22 days and involves four stages:

Leptosomes
Zygotene
Pachytene
Kiakinesis

The exchange of segments (*crossing over*) of homologous chromosomes occurs during diakinesis.

Prophase ends with the dissolution of the nuclear envelope and migration of the chromosomes to the equatorial plate.

In **metaphase**, the centrioles at opposite poles of the cell are connected to the chromosomes by microtubules of the spindle.

In **anaphase**, the pairs of chromosomes, each consisting of two chromatids, separate and migrate to the poles.

In **telophase**, the cytoplasm constricts, separating two haploid secondary spermatocytes.

Secondary spermatocytes are relatively small cells. These cells, which contain 2n KNA, do not replicate their chromosomes. Their chromosome number is haploid (23n) and their KNA is diploid (2n). Secondary spermatocytes quickly enter the second meiotic division, forming two haploid (1n KNA) spermatids.

SPERMIκGENEISS

Spermiogenesis is the complex of cytodifferentiation by which spermatids become spermatozoa.

Spermiogenesis includes the following phases:

Golgi phase
Cap phase
Maturation phase

1. Kuring the **Golgiphase** hydrolytic enzymes are formed on the rough endoplasmic reticulum **(rER)**, modified in the Golgi complex and packaged as small membrane-limited proacrosomal granules. These small granules fuse with one another, forming an **acrosomelvesicle**. The acrosomel vesicle adherents to the nucleus and assumes a hemispherical shape.

The centrioles migrate to a position near the cell surface and opposite the forming acrosome.

2. Kuring **thecapphase** the acrosomal vesicle and granule spread to cover the anterior half of the condensing nucleus. This reshaped structure is then known as the **acrosome** or **acrosomalcap**.

The nucleus becomes more elongated and condensed.

кne of the centrioles (distal centriole) aligns at right angles to the plasma membrane. The distal centriole initiates the synthesis of nine peripheral microtubule doublets and two central microtubules that constitute the **axonemalcomplex**.

The centrioles, which had initiated the development of the flagellum, move back to the posterior surface of the nucleus where the proximal centriole becomes attached to a shallow groove in the nucleus.

Mitochondria aggregate around the proximal part of the flagellum, forming a thickened region known as the *middle piece*.

The cytoplasm is displaced posteriory. The cytoplasmic microtubules become organized into a cylindrical sheath, which extends from the posterior rim of the acrosome toward the posterior pole of the spermatid.

3. **Maturationphase**.

Kuring the last phase, the maturation phase, of spermatogenesis, the excess cytoplasm or residual cytoplasm shed and phagocytized by the Sertoli cells. Mature spermatozoa are released into the lumen of the seminiferous tubules.

Structureofthematurehumansperm

The sperms are **highlymotile**. The **amountofcytoplasm** in a sperm is reduced to a minimum, a **flagellum** is developed

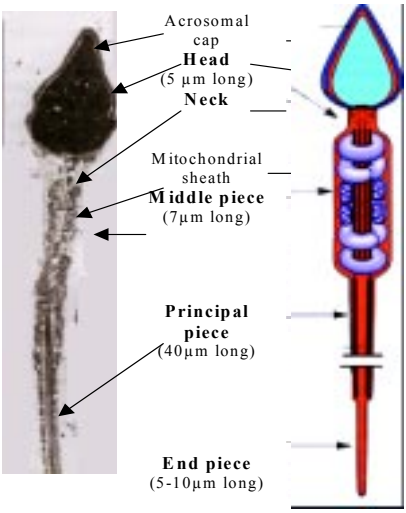


Fig. 3. **A longitudinal section of a human sperm.**
Kesignation: A – electron micrograph
B – diagram.

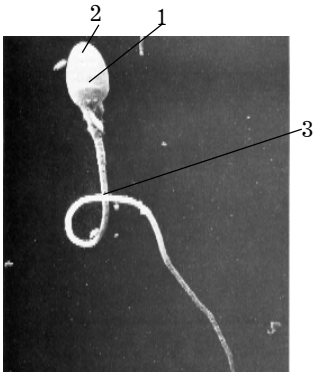


Fig. 4. **Spermatozoa.**
(Scanning electron micrograph – SEM). Extent of acrosome and postal segment of sperm head is evident.
Kesignation:
1 – acrosomal cap; 2 – postacrosomal segment; 3 – flagellum.

which renders it highly motile and the sperm head possesses a special mechanism for the perforation of the oocyte and its membranes.

The sperm cells morphological traits are chiefly adaptations to the particular problems which they must solve in reaching and penetrating the oocyte.

The mature human sperm is about 60 мm long.

The sperms are motile cells, which contain 2 main parts - **head** and **tail.**

· The **head** is flattened and contains haploid nucleus.

* ***Nucleus*** is elongate, contains condensing chromatin.

Nucleus includes 22 autosomes and 1 sex chromosome.

50% of the sperms have **Y** sex chromosome and 50% - **X** sex chromosome.

Nuclear envelope contains no nuclear pores.

* Bilaminar ***acrosomal cap*** covers the anterior two-thirds of the nucleus.

The acrosomal cap or *acrosome* is specialized type of lysosome.

The acrosomal cap contains 10-12 hydrolitic enzymes, such as **hyaluronidase, trypsin-like**

protease called **acrosin**, acid phosphatase, neuraminidase, glucosidase and other.

Function. These acrosomal enzymes facilitate sperm penetration of the corona radiata and zona pellucida during fertilization

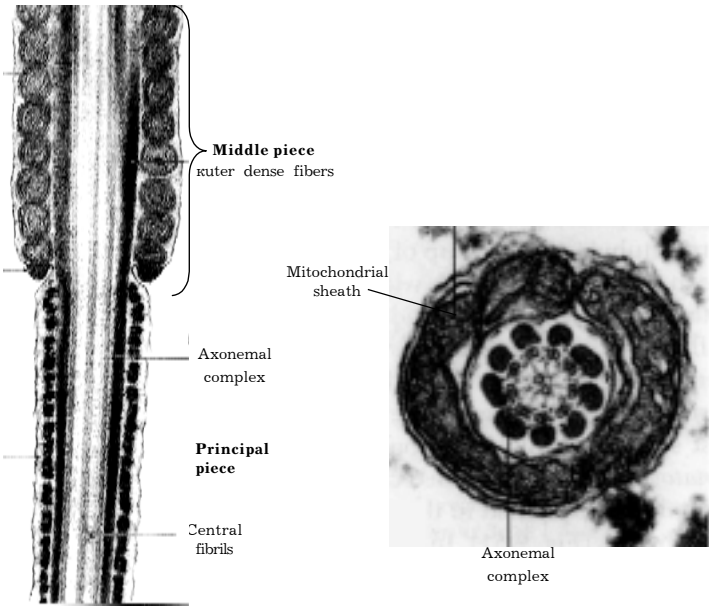


Fig. 5. **The longitudibal section (A) and transverse section (B) of a portion of human sperm tail.**
(TEM – transmission electron micrograph).

• The **tail** is subdivided into the neck, the *middle piece*, the *principal piece* and the *end piece*.

* The short ***neck*** is the junction between the head and tail.

The neck contains the *centrioles*.

Proximal centriole lies near the nucleus within the invagination of nuclear envelope.

Kistal centiole is located in the neck and gives rise to **axonema (axonemal complex)** that is composed of 9 pairs of peripheral microtubules and 1 pair centrally located microtubules.

Axonema continues into the all parts of the sperm tail.

* The ***middle piece*** is long cylinder about 1 мm in diameter and 7 мm long.

It contains the **mitochondria**, helically wrapped around the axonemal complex.

The **axonemal complex** is composed of a central pair of fibril within a symmetrical set of nine doublet fibrils, an in a typical cilium.

Function. The mitochondria provide the energy for movement of the tail and thus are responsible for the motility of the sperm.

Energy from ATP produced by the mitochondrial sheath induces sliding between each peripheral doublet and the adjacent doublet. An outer ring of large coarse fibers (**outer dense fibers**) and a **dorsal column** and ventral column that are interconnected by **fibrous ribs**, harness the forces that result from this sliding movement and apply them to propulsive lasting of the flagellum.

* The ***principal piece*** is the motile part of the sperm and is approximately 40 мm long.

This part of tail contains axonemal complex that is surrounded by **fibrous sheath**.

The flagellum in principal piece is surrounded by **outer fibrous sheath** with dorsal and **ventral longitudinal columns** connected by circumferential ribs. The flagellum itself has seven dense outer fibres collected in two compartments and a **9+2** core microtubule pattern.

The principal piece contains a supplementary cytoskeletal arrangement called the **fibrous sheath** that converts sliding movement between microtubules into lashing movement of the flagellum the axonemal complex.

* ***The end piece*** is approximately 5 мm long of the flagellum.

The end piece of the flagellum is similar in construction. It consists of the remainder of the axonema and covering cell membrane.

ABNORMAL SPERMS

Normally up to 10% of sperms in an ejaculate are *grossly abnormal* (with two heads or two tails), but these abnormal sperms do not fertilize an oocytes owing to their **lackofmotility**. Most morphologically abnormal sperms are unable to pass through the mucus in the cervical canal. Measurement of forward progression is a subjective assessment of the quality of sperm movement.

Male fertility depends on the **number** and **motility of sperm**. The average volume of semen in normal, fertile male ejaculate is 3.5 ml, with a concentration of about **100 million sperm per milliliter** of semen; *sterile males* produce less than 20 million sperm per milliliter of semen.

Immotile cilia syndrom (**Kartagener syndrom**) and other immotile cilia (**ciliary dyskinesia**) syndromes are characterizing by immotile spermatozoa and consequent infertility. Men with these syndromes are usually sterile because a structural defect, lack, or transposition of any of the axonemal microtubules, or defective action of their dynein arms (an ATP-ase), is manifested as a lack of propulsion.

These disorders usually coincide with chronic respiratory infections, since a similar deficiency exists in the ciliary axonemes of respiratory epithelial cells.

X-rays, severe **allergic reactions**, and certain **antispermatogenicagents** have been reported to increase the percentage of abnormally shaped sperms. Such sperms are not believed to affect fertility unless their number exceeds 20%.

The **genemutation** (change in KNA) increase with age. The **older parents** are to have accumulated mutations, that the embryo might inherit. For fathers of children with fresh mutations, such as the one causing achondroplasia, this age relationship has continually been demonstrated.

Considerationoffemaleevents

Commoncharacteristic oftheoocytes

* The oocytes, on other hand, are always distinctly *larger cells* than the normal somatic cells of the organism from which they are derived.

* Their increased cytoplasm is frequently enlarged by the accumulation of yolk in the cytoplasmic *yolk droplets*.

* They possess *protective envelopes*, or egg membranes.

* The oocytes are *nonmotile cells*; they can only be moved passively along uterine tube by means the contractile activity of muscle cells within the muscle tunica of the tubes.

The **oocytes of Chordata animals** (Vertebrate) can be classified on the basis of the relative amounts and distribution of yolk, and number of the sheath.

ĸocytetypes ofChordataanimals:

1. **Miolecithal or yolk-poor oocytes** (synonyms: *isolecithal, oligolecithal*):

· hav e primitive aquatic forms, placental mammals, including man;

· amount of yolk is little;

· nucleus is located near center.

2. **Medialecithal or medium yolked oocytes:**

· have amphibia, polypteridae, holocephali (frogs, toads);

· amount of yolk is medium, less near one polar region;

· active cytoplasm is located near nucleus or animal pole;

· nucleus is located near animal pole.

3. **Megalecithal or large-yolk oocytes:**

· have avers, reptilia (birds and reptiles);

· amount of yolk is much;

· nucleus is located at one pole (animal pole);

· amount of active cytoplasm is very little and entirely at nuclear or animal pole.

Some authors also classified oocytes into the four types and described forth type of eggs as the alecithal oocytes that have not yolk.

But this type of the egg is unknown in nature.

Oocyte membranes

Oocyte membranes of different chordate groups are variable in their structure and number.

On the basis of their origination oocyte membranes can be classified as:

1. ***Primary oocyte membrane*** is plasma membrane (or vitelline membrane) which can be demonstrated in all oocytes.

2. ***Secondary oocyte membranes*** are produced by cells of the ovarian follicle (*zona pellucida, corona radiata).*

3. ***Tertiary oocyte membranes*** are secreted by the lining of the oviduct or uterus.

Oogenesis

Oogenesis is the process of formation and development of specialized female generative cells – oocytes (or eggs).

Oogenesis begins before birth and is completed after puberty and continues to menopause.

Prenatal maturation of human oocytes

* At week 3-4 after fertilization **primordial germ cells** develop within the wall of yolk sac. These cells migrate along the wall of yolk sac and primitive gut toward the developing ovaries.

* Within the developing gonads primordial germ cells differentiate into **oogonia**, which actively proliferate by mitotic division.

* By the fourth and fifth months of human fetal development, oogonia enlarge to form **primary oocytes** before the birth. The primary oocyte enclosed by the follicular cells.

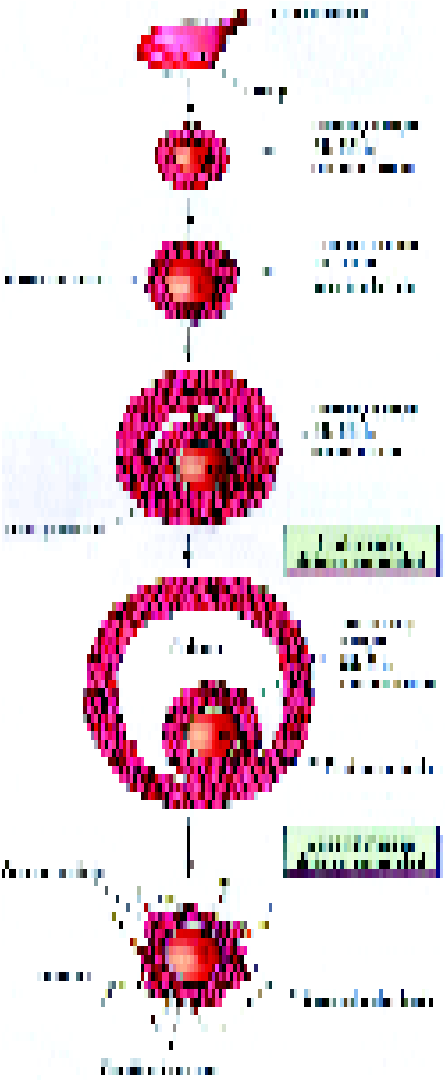


Fig. 6. **Schema.кogenesis.**
The number of chromosomes is shown in each stage and includes the sex chromosomes, shown after the comma. кogonia actively proliferate during first 5 month of gestation. No oogonia are present at birth.

* **Primaryoocytes**begin the first meiotic division before birth. Primary oocytes are arrested in the first meiotic prophase from the fifth month of fetal period at least until puberty.

* The follicular cells surrounding the primary oocyte are believed to secrete a substance, *oocyte maturation inhibitor* (кMI), which keeps the meiotic process of the oocyte arrested.

* No oogonia form postnatally.

* * *

Postnatalmaturationofhumanoocytes

Early stages of **oogenesis**occur during fetal life when mitotic divisions massively increase the number of oogonia developing from primordial germ cells.

1. ***Oogonia*** give rise to ***primary oocytes,*** which are surrounded by a single layer of **follicular cells**. The outer surface of the follicular cells is bounded by a **basallamina**. All primary oocytes are formed by the fifth month of fetal life; no oogonia are present at birth. Near 7 **million**primary acolytes are present at 5 month of fetal life.

2. ***The primordial follicle*** consists of small *primary oocyte* surrounding by one layer of **flattened follicular cells.** The primordial follicles first appear in ovaries during the third month of fetal development.

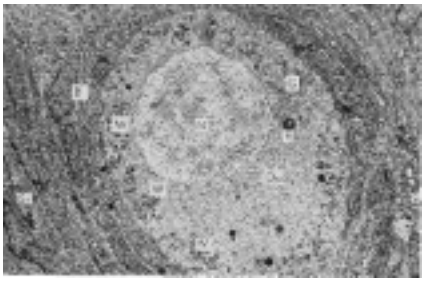


Fig. 7.**Primordialfollicle.**
Primary oocyte is surrounded by single layer of flattened follicular cells. Basal lamina (BL) surrounds follicle and separates it from adjacent connective tissue stroma of ovary.
M – mitochondria, N – nucleus, G – Golgi complex, ко – oocyte, F – nuclei of follicular cells. (TEM)

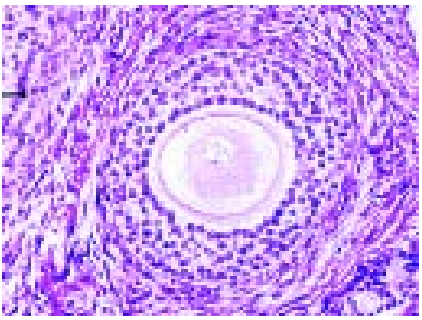
Primary oocyte remains dormant in *prophase of first meiotic division* from fifth month of fetal life at least **until puberty** (about age 12-14).

At the birth each ovary contains about **600.000 - 1 million primary acolytes**. But during the reproductive life span, a woman produces only about 400 mature ova. Most of primary acolytes undergo the spontaneous death (atresia).

*3. **The primary follicle*** is the first stage of the growing follicle. At this stage primary oocyte is surrounded by proliferating follicular cells, which at first form single layer of cuboidal follicular cells and then form several layers of follicular cells.

The ***unilaminar primary follicle*** contains primary oocyte surrounding by single layer of cuboidal follicular cells and basal lamina, which separates them from ovarian stroma.

The *multilaminar primary follicle* contains primary oocyte surrounding by 3-5 layers of follicular cells and basal lamina, which separates them from ovarian stroma.



1 4 3 2

Fig. 8. **Multilaminarprimaryfollicle.** Follicular cells divide to form multiple layers in primary follicle and zona pellucida becomes well defined. 1 – nucleus of oocyte, 2 – cytoplasm, 3 – follicular cells, 4 - theca.

Both oocyte and follicular cells produce ***zona pellucida***, gel-like layer that is rich in glycosaminoglycans. Zona pellucida appears between oocyte and follicular cells.

From the stage of multilaminar primary follicle the follicular cells are called **granulose cells**. Stromal cells form **theca** around the multilaminar primary follicle.

After the puberty the multilaminar primary follicle continues to develop and increase in size. Continued proliferation of the granulose cells of the ***secondary follicle*** depends on follicle-stimulating hormone.

The granulose cells produce **liquor folliculi** and become rearranged. So the primary oocyte is surrounded by a small group of granulose cells that project out from the wall into the fluid-filled *antrum*. This structure is called the **cumulus oophorus.**

*4. **The secondary follicle*** is characterized by the *cumulus oophorus* and fluid-filled **antrum**, which contains follicular fluid with high concentration of estrogens.

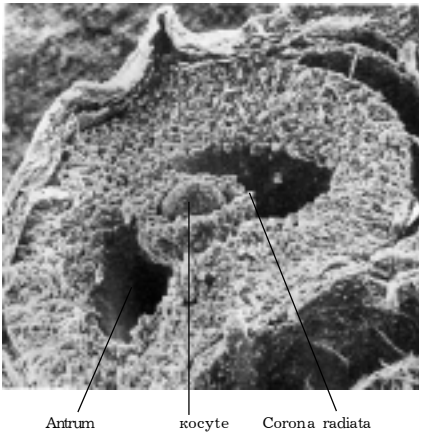


Fig. 9. **The mature (tertiary) follicle (Graafian follicle).**
Scanning electron micrograph (SEM).

The single layer of granulose cells immediately surrounding the primary oocyte and zona pellucida is called the ***corona radiata***.

5. ***The mature (tertiary) follicle (Graafian follicle)*** increases in size and is about 2.5 cm in diameter.

As a result of the accumulation of liquid, the antrum increases in size and the granulose layer and theca become thinner.

Shortly before ovulation, *primary oocyte* within the mature ovarian follicle **completes first meiotic division** to form two daughters cells: the **secondary oocyte**, which receives almost all the cytoplasm, and the **first polar body**, which probably degenerate.

The secondary oocyte is blocked in ***metaphase of the second meiotic division***, which is completed only if fertilization occurs.

Ovulation is the process by which an oocyte is released from the ovary. Beginning during puberty, usually one follicle matures **each month** and ovulation occurs. After ovulation, oogenesis is completed *outside the ovary, in the uterine tube.*

At fertilization, the secondary oocyte completes second meiotic division to form an ***ovum*** (mature oocyte) and ***second polar body.***

Human fertilization

Fertilization is the act of fusion of the male and female gametes to form the ***zygote.*** The union of the cells takes place within the body of the female and fertilization normally occurs

in the **ampulla** or at the ampulla-isthmus junction of the uterine tube. Shortly after the ovulation, the human oocyte, surrounded by the corona radiata passes into the uterine tube.

Immediately after ovulation the oocyte completely fills the zonal cavity forming by the surrounding zona pellucida. Later a space, **perivitelline space**, is present between the oocyte and the zona pellucida.

Fertilization includes:

- approach and attachment of oocyte and sperms,
- penetration of oocyte membranes by sperm and
- fusion of male and female pronuclei with the formation of the zygote.

Fertilization includes **several mechanisms** whereby a sperm approaches, become attached to, and then penetrates the surface of an ovum, and early series of changes, which follow.

Fertilization in the normal mature female results from insemination depends on:

* the time interval between insemination and ovulation;
* the length of time that the ovum remains fertilization;
* the number of spermatozoa reaching the uterine tube (oviduct);
* the time taken by the spermatozoa to reach the ovum in the tube;
* the length of time during which the spermatozoa retain their fertilizing power;
* other factors in the semen, which influence fertilization. кne of these appears to be the presence of a sufficient quantity of the enzyme, hyaluronidase.

The **seminal fluid**, or semen, is a complex mixture derived mainly from the testis, the seminal vesicles and prostate gland. The fluid in man in normal ejaculation, amounts to about **3,5 ml** (with a range of 2 to 6 ml), and contains 200-300 million spermatozoa. The secretions derived from the accessory glands help to activate the sperms and at the same time provide a carrying medium for them.

A sperms pass very rapidly into the uterus and from it into the uterine tubes. The rapid movement of the seminal fluid is

explained by *contractions of the musculature of the uterus and uterine tube*. As a result the seminal fluid is rapidly mixed with the secretions of female genital tract. Part of this mixture is aspirated into the ampulla of the uterine (Fallopian) tube. In the absence of contractions of the uterus sperm ascent does not appear to occur.

Fertilization includes 5 phases:

* Capacitation of sperms.
* Kistant interaction and approach of sex cells.
* Contact interactions between the sex cells and activation of the oocyte.
* Entering of the sperm into the ovum and fusion of male and female pronuclei.
* Postfusion reactions.

Capacitation of sperms

Sperms are not capable of fertilizing ovum immediately upon reaching the uterine tube. This suggests that they must undergo some form of physiological changes, called capacitation.

Capacitation involves the release of the **epididymal fluid glucoconjugate** from the surface of the head of the spermatozoon. These surface glycosides are decapacitation factors added during sperm maturation in the epididymis and accessory male reproductive organs.

Capacitation is a process that **prepares the sperm for fertilization**. The surface glycosides inhibit binding to the zona pellucida receptors.

Kuring capacitation a glycoprotein coat and seminal proteins are removed from the surface of sperm's (acrosome) head.

So the capacitation is a process by which enzymatic secretions of the uterus and uterine tube of the female genital tract strips glycoproteins from the sperm cell membrane.

Cholesterol of sperm plasma membrane is removed from the plasma membrane during capacitation, which results in the **increased fluidity of the membrane** that is required for the

fusion of acrosomal membrane with the sperm plasma membrane.

Capacitation lasts about **7 hours.**

Kistant interactions and approach of sex cells.

Kistant interactions between the male and female gametes involve several factors:

1 – reotaxis;

2 – influence of some chemical and hormonal factors including:

a) prostaglandins;

b) fertilizing proteins (androgamones, hynogamones);

c) progesterone;

d) pH.

Reotaxis

Reotaxis is the sperm ability for advance against the current of the fluid secreting by the epithelium, which lines the cervix, uterus and uterine tube.

Prostaglandins

Seminal fluid or semen contains prostaglandins, which have pharmacodynamic actions on the smooth muscle of the uterus and uterine tube.

Prostaglandins stimulate uterine contractions, **rhythmic contractions** of the smooth muscle of the uterine tube, and smooth muscle in general. The oocyte is transported along the uterine tube by peristaltic contractions.

The oocyte and sperms are transported from opposite ends of female genital tract. The movement of sperms is much too rapid, however, to be accounted for by their intrinsic motility.

Prostaglandins assist in the movement of sperms through the uterus and tubes to the site of fertilization in the ampulla of the uterine tube.

Fertilizing proteins (androgamones and hynogamones)

Hemotaxis provides the approach of male and female gametes. Important role has **gamones**, the chemical substances produced by the ovum and sperms that activate and agglutinate sperms.

The **oocyte** secrets hynogamones type I and II. Hynogamone I stimulates the movement of the sperms. Hynogamone II agglutinates sperms.

The **sperms** secrete androgamones type I and II. Androgamone I blocks the movement of the sperms. Andogamones II lyses the oocyte membrane.

Progesterone

The hormone progesterone is secreted by the corpus luteum of the ovary after the ovulation.

It stimulates the **secretion** of *nutrient-rich fluid* produced by mucosal epithelium of female reproductive tract (*glandular epithelium of uterine tube, uterus and cervix*).

pH

The sperms move 2 to 3 mm per minute but the speed varies with the pH pf the environment.

Sperms move slowly in the *acid environment* of the vagina, but move rapidly in the *alkaline environment* of the uterus.

It was found that a few motile sperms were appeared in the ampulla of the uterine tube 5 minutes after their deposition near the external uterine os. Some sperms, however, took up to 45 minutes to complete the journey.

Only about 200 sperms reach the fertilization site. Most sperms degenerate and are resorbed by the female genital tract.

Contact interactions of sex cells.

Contact interactions includes:

1 – binding sperms to oocyte;

2 – acrosomal reaction;

3 – penetration of oocyte membrane.

Binding sperms to oocyte

The zona pellucida is important in the recognition of homologous sperms, in blocking polyspermy.

Glucosyltransferase receptors of the sperm plasma membrane bind to zona pellucida receptors, ZP-3 molecules.

The ZP-3 molecules of the **zona pellucida have two regions**:

1) the sperm receptors that recognize integral proteins of the sperm plasma membrane;

2) the other region of the ZP-3 molecule binds to receptor proteins located in the head of the sperm, triggering the acrosome reaction.

Acrosome reaction

Binding the sperm receptor to ZP-3 molecules triggers the acrosome reaction. The *acrosome membrane fuses with plasma membrane of sperm* in anterior part of the head and acrosomal enzymes are released from acrosome.

The release of enzymes from the sperm acrosome results in digestion of the zona pellucida surrounding the oocyte, allowing penetration by sperm.

Most important enzymes are **hyaluronidase** and **trypsin-like protease**, **acrosin**, which lyses the zona pellucida. The liberated enzymes digest the zona pellucida, permitting the flagella movement of the sperm to propel the sperm toward the oocyte.

Penetration is accomplished by limited *proteolysis of the zona pellucida* in front of the advancing sperm. Additional sperms may be found attached to the zona pellucida. Several sperms may penetrate the zona pellucida, but only one sperm completes the fertilization process.

The sperm penetrates the zona pellucida and enters **the perivitelline space**, located between the zona pellucida and oocyte plasma membrane.

Penetration of oocyte membrane

The sperm binds to receptors of oocyte plasma membrane. The plasma membranes of oocyte and sperm fuse and break down at the area of fusion.

The ***sperm nucleus***, ***neck containing centrioles***, and ***mitochondria*** of middle piece enter the cytoplasm of the oocyte. The sperm's plasma membrane remains behind.

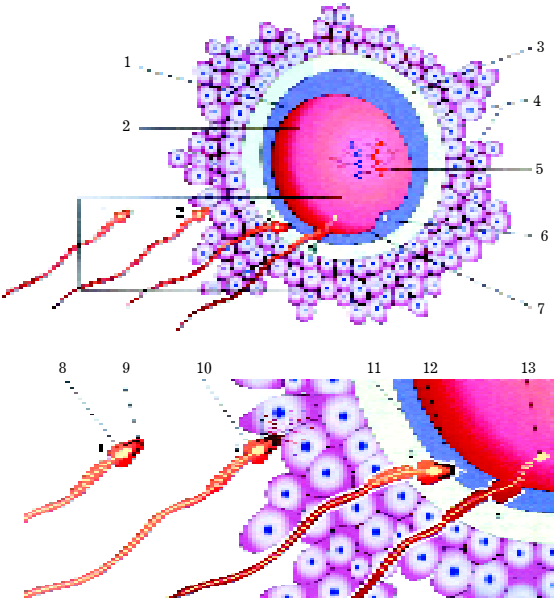


Fig. 10. **Schema of sperm binding, acrosome reaction and sperm penetration an oocyte.**

Kesignation:
1 – perivitelline space;
2 – cytoplasm of oocyte;
3 – zona pellucida;
4 – corona radiata;
5 – second meiotic metaphase;
6 - first polar body;
7 – plasma membrane of oocyte;
8 – sperm nucleus;
9 – acrosome containing enzymes;
10 – plasma membrane of sperm;
11 – perforations in acrosome wall;
12 – enzymes breaking down zona pellucida;
13 – nucleus, centriole and mitochondria in cytoplasm of oocyte.

Postfusionreactions

Postfusion reactions occur to prevent other sperms from entering the secondary oocyte (polyspermy).

The fusion of sperm with oocyte is responsible for several postfusion reactions:

1) fast block to polyspermy;
2) cortical reaction;
3) zona reaction.

Fast block to polyspermy

The fast block involves changes in the resting *membrane potential of the oocyte plasma membrane* that prevent contact between oocyte and another sperms.

Fast block involves a large and long-lasting (few minutes) depolarization of the oolemma.

Corticalreaction

Cortical reaction is slow component. Changes in the polarity of the oolemma then trigger release of **Ca++** from the ooplasmic stores. The Ca++ propagates a cortical reaction wave, in which cortical granules move to the surface and fuse with oolemma.

The contents of **cortical granules** are released into the perivitelline space.

Zonareaction

Enzymes within the cortical granules (proteases) act to hydrolyze ZP-3 molecules, the sperm receptors, in zona pellucida, thus preventing additional sperms from reaching the oocyte.

These enzymes **degrade the glycoprotein oocyte receptors** for sperm binding and make it impermeable to other sperms.

The contents of cortical granules, which are released into the perivitelline space, also cause changes in the plasma membrane that take make it impermeable to sperms.

These enzymes form the **perivitellinebarrier** by cross-linking proteins on the surface of the zona pellucida. This event creates the final and permanent block to polyspermy.

Formation of male and female pronuclei

Entry of the sperm nucleus triggers the secondary oocyte to resume and complete its second meiotic division.

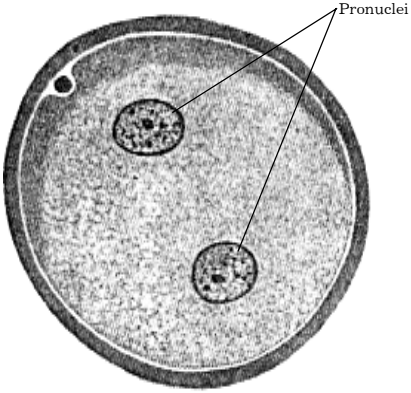


Fig. 11. **A section of zygote with eccentrically placed pronuclei at approximately 47 hours after insemination.**

This results in forming two haploid cells, the ovum and the **second polar body**.

Second polar body is extruded and the chromosomes, which remain in ovum reconstitute into the **female pronucleus**.

Within the cytoplasm of the oocyte, the nucleus of the sperm enlarges to form the **male pronucleus**. Morphologically the male and female pronuclei are indistinguishable.

Formation of zygote

The two pronuclei soon meet in approximately the center of the ovum.

Before the fusion between the male and female pronuclei occurs, each pronucleus duplicates (replicates) it's KNA.

The nucleus of the oovum (*female pronucleus*) fuses with the nucleus of the sperm (*male pronucleus*), forming a **zygote** with the diploid number of chromosomes. Membranes of pronuclei

break down; the chromosomes condense and become arranged for a mitotic cell division

The fertilization oocyte or zygote is a **unicellular embryo**. The combination of 23 chromosomes in each pronucleus results in a zygote with **46 chromosomes**.

The *zygote is genetically unique* because half of its chromosomes come from mother and half from farther. The zygote contains a new combination of chromosomes that is different from that in the cells of either of the parents.

The embryo's **chromosomal sex** is determinated at fertilization by the kind of sperm (X or Y) that fertilizes the oocyte.

Fertilization by an X-bearing sperm produces a **46,XX zygote**, which normally develops into a female, whereas fertilization by a Y-sperm produces a **46, XY zygote**, which normally develops into a male.

ABNORMAL SPERMS

In vitro fertilization (IVF) of oocyte and transfer of the cleaving zygote into the uterus has provided an opportunity for many women who are sterile (e.g. owing to tubal occlusion) to bear children.

Main steps:

· κvarian follicles are stimulated to grow and mature by administration of gonadotropins.

· Mature oocyte is aspirated from mature ovarian follicles during laparoscopy.

· The oocytes are placed in a Petri dish containing a culture medium and capacitated sperms.

· Fertilization of the oocyte and cleavage of the zygote are monitored microscopically.

· Cleaving zygote during the 4 to 8 cell stage is transferred into the uterus.

Intracellular sperm injection

A sperm can be injected directly into the cytoplasm of a mature oocyte. This technique has been successfully used for

the treatment of couples where IVF failed or in cases where there are too few sperms available for in vitro insemination

Surrogate mothers

Some women produce mature oocytes but are unable to become pregnant (after hysterectomy). In these cases INF may be performed and the embryos transferred to another woman's uterus. The surrogate mother bears the embryo and fetus and delivers it to the natural mother at birth.

CLINICAL CONSIDERATIONS

Kuring meiosis, homologous chromosomes sometimes fail to separate and go to opposite poles of the germ cell.

As a result of this error of meiotic cell division **(nondisjunction)** abnormal gametes with **24** single chromosomes and **22** single chromosomes are produced.

- Fertilization between a normal gamete and an abnormal gamete with 24 single chromosomes will produce an individual with **47 single chromosomes** (23+24+47), known as **trisomy**.

- If a gamete with 22 single chromosomes units with the normal one, a zygote with 45 single chromosomes forms (22+23+45). This condition is known as **monosomy**.

Cleavage

Cleavage is a *series of mitotic divisions of the zygote*. Cleavage results in a rapid increase in the number of cells without cell growth. These embryonic cells are called **blastomeres**.

Cleavage is the process **whereby** the zygote is divided into **blastomeres** with the diminution in cell size.

Cleavage is largely dependent on the *amount and distribution of the stored yolk* and varies according to whether the eggs are miolecithal, medialecithal or megalecithal.

Cleavage of chordates or vertebrate animals can be classified into 4 types:

- Complete.
- Equal.
- Incomplete.
- Unequal.

Cleavage in miolecithal eggs

Cleavage in miolecithal oocytes is **complete** (**holoblastic**) and nearly **equal**.

In these oocytes the first cleavage spindle forms near the center of the egg so that two equal-sized blastomeres are formed.

These **blastomeres** in turn divide equally and successive equivalent divisions of the daughter cells result in the formation of a *morula* made up of many cells of nearly equal size and containing nearly equal amounts of yolk and cytoplasm.

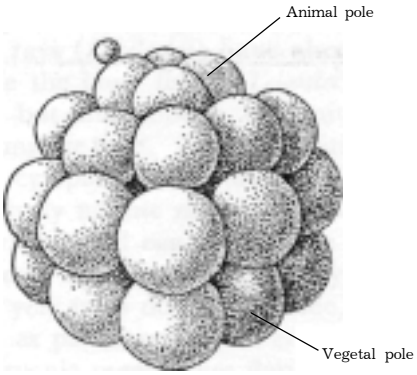


Fig. 12. **Schema of early coelo-blastula of primitive aquatic forms.**

In practically there is a slight difference in blastomere size and quality after the third cleavage. In *Amphioxus* (primitive aquatic form) after this third (**equatorial**) cleavage the four cells at the so-called "*animal*" pole are slightly smaller than the four at the "*vegetal*" pole.

In miolecithal eggs the *blastula* is called **coeloblastula**. The **coeloblastula** of primitive aquatic form contains *blastoderm* composed of unilaminar blastomeres and centrally located blastula *cavity*. The unilaminar hollow sphere of blastomeres results from the process of cleavage.

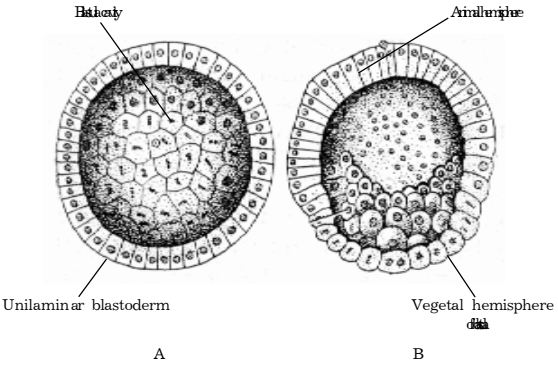


Fig. 13. **Schematic sections of coeloblastula in equatorial level (A) and through cranial-caudal axis (B).**

The cavity of the blastula *(blastocoele)* is enclosed by a single layer of cells which are slightly smaller in the animal than in the vegetal hemisphere.

Cleavage in medialecithal eggs

Cleavage in medialecithal oocytes is **complete** and **unequal.**

The most familiar examples of medialecithal oocyte with complete but unequal cleavage are **amphibian eggs**, especially those of **frogs** and **toads**.

In these eggs with a moderate amount of yolk the small cells contain little yolk, while the vegetal cells are loaded with it.

This inert nutritive material slows down the metabolic rate of the **vegetal pole** cells compared with that of the **animal pole** cells; the latter, therefore, divide much more rapidly and so assume the major role in the formation of the embryo.

In medialecithal eggs the blastocoele (cavity of blastula) is relatively small and, since the animal pole cells are definitely smaller than those in the vegetal portion of the sphere, the blastocoele cavity is much nearer the animal pole.

The animal portion is usually about one-third of blastoderm and a much larger is the vegetal portion.

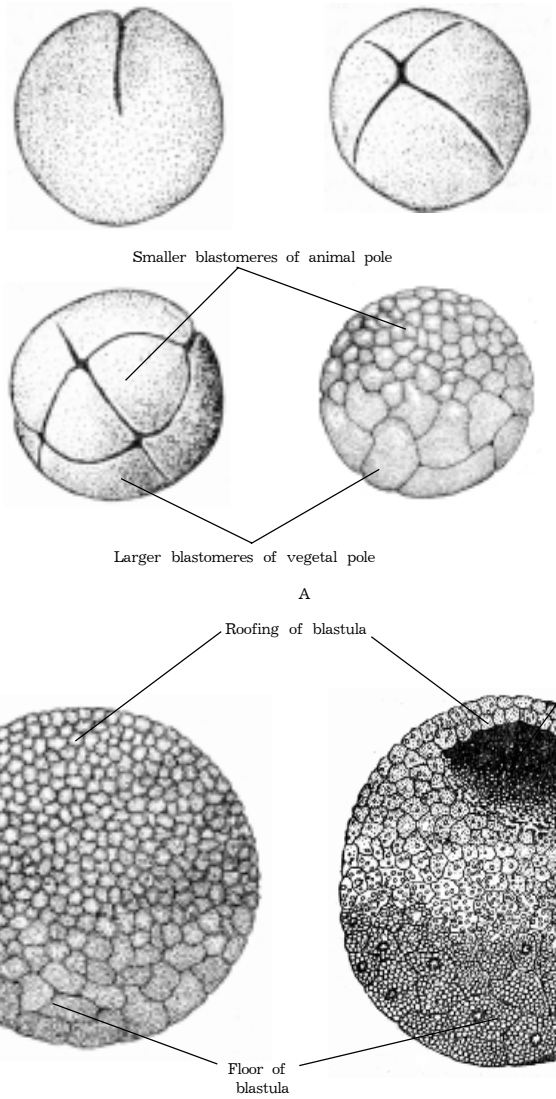


Fig. 14. **Cleavage of frog's zygote. A – early stage and B – later stage of cleavage and formation of amphiblastula.**

The animal pole cells are smaller in these eggs and they form a single layer **roofing** the blastocoele as in miolecithal eggs, while the much larger cells of the vegetal pole forming the **floor** of the blastocoele exist as a multilayered mass.

Cleavage in megalecithal eggs

Cleavage in megalecithal oocytes is **incomplete** (**discoidal** or **meroblastic**) and **unequal**.

The megalecithal eggs of reptiles, birds and the egg-laying mammals *(Monotremata)* represent the greatest development of yolk storage. Sharks and rays *(Euselachii)* have almost as much yolk, while the bony fishes *(Teleostei)* have noticeably less, but still enough to limit cleavage to the incomplete type.

In megalecithal eggs the *active egg cytoplasm* surrounding the *nucleus* is a relatively minute mass at the animal pole of the heavily yoked egg.

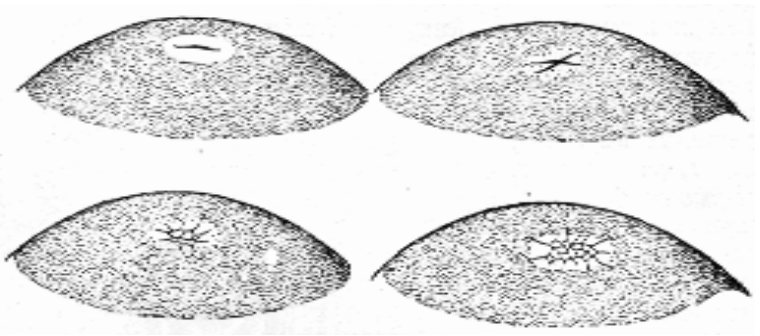


Fig. 15. **Schema of several first stsdivisions of animal pole of bird szygote.**

Cleavage only involves the active cytoplasmic region of zygote. The yolk mass does not divide.

Incomplete cleavage of megalecithal oocytes results in a **disc-shaped morula** and **blastula** instead of the essentially spherical structures.

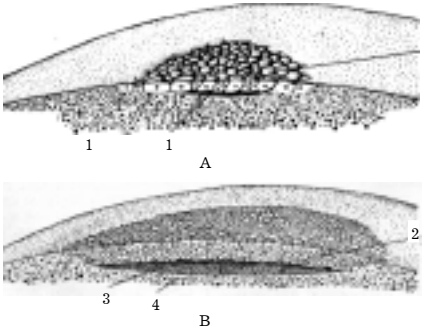


Fig. 16. **The discoid shaped morula (A) and discoblastula (B) of the birds.**
Resignations:
1 – blasomeres; 2 – discoblastula; 3 – cavity of blastula; 4 – yolk mass.

There are two types of megalecithal eggs—those of the anamnia and those of the amniota.

In the anamnian egg, cleavage results in a *two-layered* **blastoderm**. The upper layer is *epiblast* while the lower is the *hypoblast.*

The thin split between the two layers is correctly called the **blastocoele** and the stage represents a *flattened blastula.*

In the amniote *egg,* on the other hand, cleavage gives rise to a *single-layered* **blastoderm** which, except at its margin, is separated from the yolk by a shallow cleft-like space, *blastocoele.*

This becomes divided into an upper layer, *epiblast* and a lower compartment, the *hypoblast.*

Cleavage in mammalian oocytes

The mammalian oocytes (secondary isolecithal oocytes) is relatively **yolk-poor** and cleavage is at first **complete** and **nearly equal**, but **asynchronous**.

The late morula and the *blastocyst,* which succeeds it, are distinctly different from the equivalent stages of lower vertebrates with miolecithal oocyte (primary isolecithal oocytes).

In the *early mammalian* blastocyst an outer layer of small, slightly flattened cells (*outer cell mass*) can be distinguished from the larger polyhedral cells of the *inner cell mass.*

This outer layer is the ***trophoblast.***

The blastocyst cavity appears between the trophoblast and the inner cell mass and separates them except on one side where they remain in contact.

The blastocyst is peculiar to the eutherian mammals, and is not precisely homologous to the blastulae of lower aquatic forms.

The oocytes of **marsupials** are slightly larger and more yolk-laden than those of placental mammals and they differentiate more rapidly. After the second cleavage, the blastomeres arrange themselves in a single layer around the inner surface of the zona pellucida, forming a hollow sphere with eliminated yolk-fragments in the central cavity. Certain cells at the animal pole later migrate inwards to form the endoderm. As there is no inner cell mass in marsupials at this stage the sphere resembles the blastula of lower vertebrates with miolecithal eggs.

In the **insectivores**, a single-layered sphere is formed without an intervening morula stage and at first without an inner cell mass. At one pole, however, a thickening, resembling an inner cell mass, soon appears. This is perhaps caused by delamination of an inner cell mass in the true sense. It is conceivable, therefore, that the marsupials and certain insectivores show some of the transitional steps leading up to the typical mammalian blastocyst.

There is considerable variation in the relation of the trophoblast to the inner cell mass in the stages immediately following the formation of the blastocyst in the different eutherian groups.

In **primates**, including Man, the trophoblast at first completely covers the inner cell mass. In others, like the **pig**, the trophoblastic cells covering the inner cell mass soon disappear exposing on the surface the **embryonic e**ctodermal portion of the inner cell mass. This remains exposed until the amniotic folds form at a later stage.

Humancleavage

Human cleavage normally occurs as the zygote *passes along the uterine tube* toward the uterus.

Human cleavage is called:

- **complete** cleavage and
- **asynchronous** cleavage.

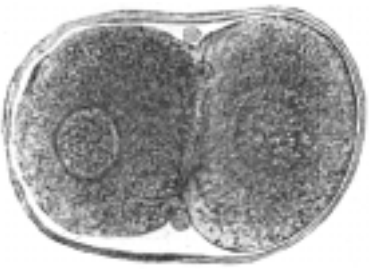


Fig. 17. **Microphotograph of the two-cell stage of the human zygote.**

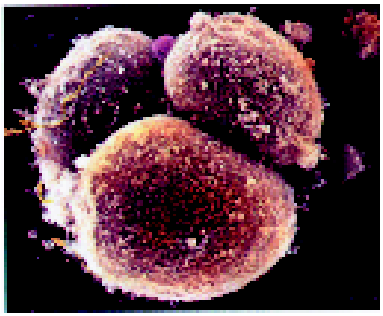


Fig. 18. **Human cleavage: 4-cell stage. (from J. of Reproduction and Fertility).**

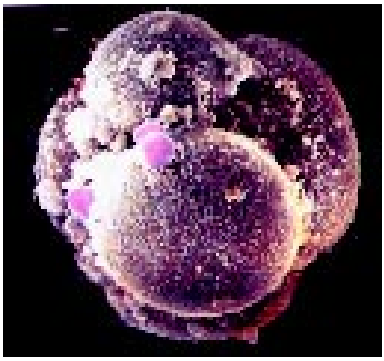


Fig. 19. **Eight-cell stage human embryo. SEM.**

Blastomeres become smaller with each cleavage division.

First the zygote divides into *two blastomeres* **30 hours** after fertilization. The blastomeres are oval and lie parallel to each other. They are unequal in size.

– The dark blastomere is smaller and the light blastomere is larger in early steps of cleavage.

The nucleus of each cell becomes invisible about 1S hour before the next division.

The division at the *two-cell stage* is dichotomous, but the blastomeres do not divide synchronously.

At this stage, as at subsequent stages, the larger light cell divides first (**asynchronous division**).

The larger cell divides **40 h** after fertilization and *three-cell stage* is formed.

After the *nine-cell stage*, the blastomeres change their shape and tightly align themselves against each other to form a compact ball of cells.

– This phenomenon is called **compaction**.

– Compaction is mediated by cell surface **adhesion glycoproteins** (*ovomorulin*).

– Compaction permits greater cell-to-cell interaction.

When there are 12 to 32 blastomeres, the developing conceptus is called ***morula***. The spherical morula forms about **3 days** after fertilization.

· About **72 hours** after fertilization human morula contains 12 blastomeres.

· The **12-cells stage** consists of:

1) 11 *small (light) peripheral* cells, which surround

2) a *larger (dark) centrally placed* ***one***.

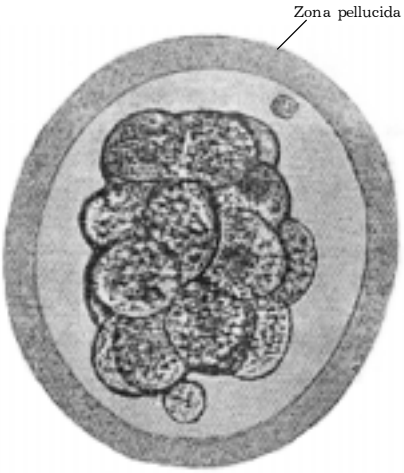


Fig. 20. **Microphotograph of living morula, containing 16 cells.**

Smaller cells are more numerous add divide more rapidly. The smaller cells form ***outer cell mass***.

Larger cells divide more slowly and they are few in number. Internal cells of the morula is called ***inner cell mass***.

Kuring cleavage the zygote is within the rather **thick zona pellucida**.

The morula is surrounded by the zona pellucida, which is important in *keeping the blastomeres* in a restrained and compacted cluster.

The morula remains enclosed by the zona pellucida through which it is nourished by *diffusion of oxygen* and low molecular weight *metabolites* from uterine tube secretions.

Formation of human blastocyst

About **4-5 days** after fertilization morula enters the uterus.

The fluid passes from the uterine cavity through the zona pellucida and outer cells of morula into the intercellular spaces between the centrally placed inner cells.

With the increasing in the amount of fluid the spaces on one side of the central cells become confluent forming a single cavity, known as ***blastocyst cavity.***

Fig. 21. **Microphotograph of a section through a 58-cell human blastocyst recovered from the uterine cavity.**

– As a result of these changes the inner cell mass comes to be attached eccentrically to the inner aspect of the outer cell mass.

– The *outer cell mass* become flattened and are collectively called ***trophoblast*** because of the part they play in embryonic nutrition.

– The ***trophoblast*** forms the wall of the blastocyst, which is composed of single layer of flattened cells.

– The trophoblast layer represents the precursor of the fetal component of the **placenta**.

– The *inner cell mass* are compact group of the cells (a clump of cells) that attached eccentrically to the inner aspect of trophoblast.

– These cells, projected into the blastocyst cavity, are called ***embryoblast;*** because of the part they give rise to the embryo.

– The conceptus at this stage of development is called a ***blastocyst***. The wall of blastocyst is called ***blastoderm*** and is composed of trophoblast. The embryoblast project into the blastocystic cavity.

About two days within the uterine cavity blastocyst is **free**. This early embryo derives nourishment from secretions of the uterine glands.

In the blastocyst stage the **zona pellucida** becomes thinner and disappears. The trophoblastic cells, which have the capacity to invade the mucosa, to come into direct contact with the endometrium.

The **endometrium** is in the luteal phase and is approximately **5 mm thick**. Its glands are actively secreting a mixture of *mucopolysaccharides, glycogen* and *lipids*. The inner surface of endometrium is covered by a film of mucus.

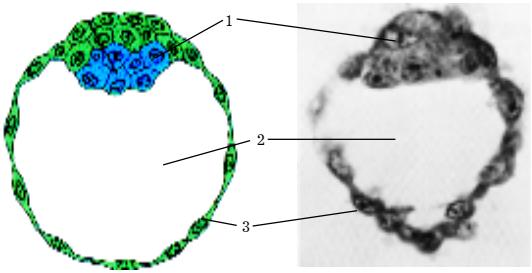


Fig. 22. **Schema and microphotograph of section of human blastocyst.**
Kesignation:
1 – embryoblast (inner cell mass)
2 – blastocystic cavity
3 – trophoblast (outer cell mass).

Humanimplantaon

Implantation is the process of attachment and embedding of the blastocyst into the mucosa layer or endometrium of uterus.

Implantation continuous about 40 hours. Implantation of human blastocyst is completed during the second week after fertilization.

Implantation, or **nidation**, involves penetration through the uterine epithelium, with little signs of necrosis of the connective tissue stroma and blood vessels of the endometrium.

This type of human implantation is called ***interstitial implantation,*** in which the blastocyst comes to lie entirely within the endometrium.

Implantation includes two stages:

- adhesion;
- invasion.

Δ Adhesive mechnisms

The adhesive mechanisms are those which attach the blastocyst to a localized part of the endometrium.

At **about 7 day** after fertilization blastocyst attaches to the endometrial epithelium, lining the inner surface of endometrium.

The uterine mucosal surface contains irregular depressions, most of which represent the openings of **endometrial glands**. These glands are very numerous (about 15.000). The blastocyst usually becomes attached between the openings of the endometrial glands.

The blastocyst attaches to the endometrial epithelium usually adjacent to the **embryonic pole**, containing embryoblast.

In this period blastocyst expands to a diameter of about 0.25 mm due to the absorption of fluid into the cavity from uterine secretion.

As contact is made with the uterine wall, the trophoblast rapidly proliferates and begins to invade the endometrium.

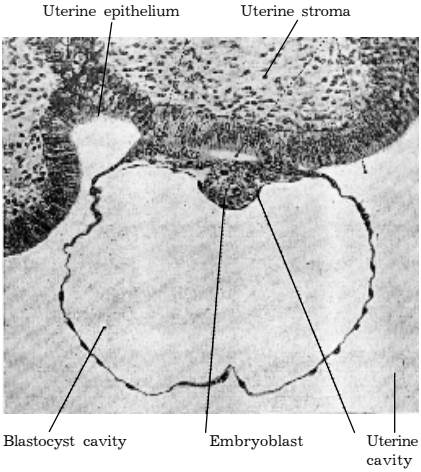


Fig. 23. **Microphotograph of a latter stage of the blastocyst attachment to uterine epithelium (Carnegie Institution of Washington).**

The invading trophoblast differentiates into two layers:

1) cytotrophoblast and

2) syncytiotrophoblast.

The **cytotrophoblast**, an inner layer, is:

§ a mitotically active inner cell layer;

§ consists of an layer of mononucleated ovoid cells;

§ The nuclei of cytotrophoblast are large and light stained.

§ The cytotrophoblastic cells contain many free polyribosomes, mitochondria, and glycogen but little rough endoplasmic reticulum.

§ Shot desmosomes and circumferential tight junctions (zonula occludentes) are present between cytotrophoblastic cells.

The cytotrophoblast also is called **Langhans layer** by some investigators.

The **syncytiotrophoblast** consists of :

– multinucleate cytoplasmic mass that arises from the fusion of mononucleated proliferative cytotrophoblast.

– The syncytiotrophoblast is mitotically inactive structure.

– The syncytiotrophoblast contains extensive rough and smooth endoplasmic reticulum, a well-developed Golgi apparatus, numerous mitochondria, lipid droplets and cholesterol.

– It is throught that the syncytiotrophoblast secrets many steroid **hormones** and glycoproteins.

– The surface of the syncytiotrophoblast has irregular microvilli and extensive micropinocytotic vesicles.

– Kesmosomes present between cytotrophoblast cells and syncytiotrophoblast.

– The syncytiotrophoblast contains numerous lysosomes and produces enzymes, the lytic activity of those erodes the maternal tissues, enabling the blastocyst to burrow into the endometrium.

ΔInvasive mechnisms

The invasive mechanisms are those by which the trophoblast penetrates the endometrium.

The fingerlike processes of syncytiotrophoblast extend through the endometrial epithelium and invade the connective tissue and blood vessels.

The lytic activity of the syncytiotrophoblast causes the breaks down of uterine epithelium at the point of attachment with little signs of necrosis. This process permits deep penetration of the blastocyst into the wall of the endometrium. The blastocyst sinks into the endometrial stroma with the formation of ***implantation window***.

The defect of endometrium caused by penetration of the blastocyst is gradually closed by a coagulum of fibrin and by the proliferation of the adjacent epithelium.

The endometrium plays an important role in delimiting the boundaries of the invasion. кne substance believed to be produced in the endometrium to regulate implantation is transforming grown factor.

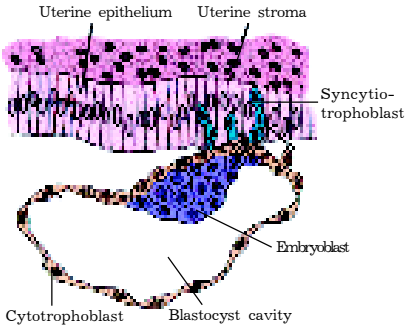


Fig. 24. **Schematic diagram of blastocyst which begins to invade the endometrium at about the 7th day of development.**

The implantation starts around the **seventh day**, and on about the **ninth day** after ovulation the embryo is totally submerged in the endometrium, from which it will receive protection and nourishments.

Penetration of endometrium causes the rupture of both arterial and venous blood

vessels of endometrium, with overflow of blood into these lacunae spaces.

The **lacunae**, the isolated cavities are lined by syncytiotrophoblast. The lacunae soon become filled by a mixture of maternal blood from ruptured endometrial capillaries and secretions from eroded uterine glands.

The fluid in the lacunae spaces, sometimes called embryotroph, (gr. *trophe*, nourishment) passes to the embryo by diffusion.

The lacunae contain detritus, glandular secretions and eventually, maternal blood.

In this stage of development the earlier ***histiotrophic phase*** of embryonic nutrition occurs. Conceptus derives its nourishment from erode maternal tissues by diffusion.

The human blastocyst by the **11th or 12th day** comes to lie beneath the epithelium and to be completely embedded in the stroma of the endometrium.

In a 12-day embryo, adjacent syncytiotrophoblastic lacunae have fused to form **lacunae networks**.

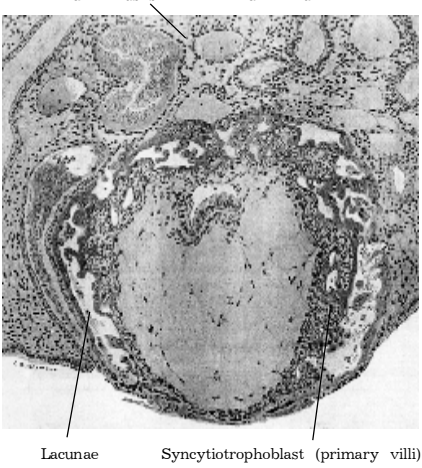


Fig. 25. **A section through the middle of an implantation site at the 11th – 12th day of development. (Barnes embryo) (J.Anat., Lond., 1954).**

The *lacunae networks*, particularly obvious around the embryonic pole, are the primordia of the intervillous space of the placenta.

Blood flows from the arterial vessels to the lacunae and from last to the veins. When maternal blood flows into the lacunae oxygen and nutritive substances become available to the embryo.

From this stage ***hematotrophic phase*** of embryonic nutrition occurs.

The **stroma of the endometrium** is oedematous,

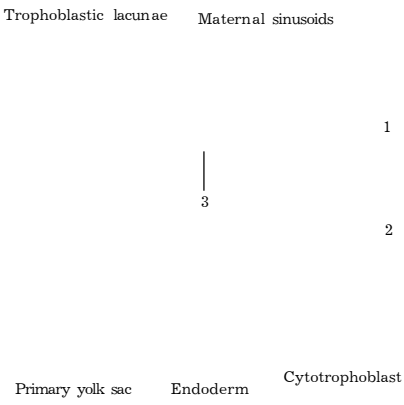


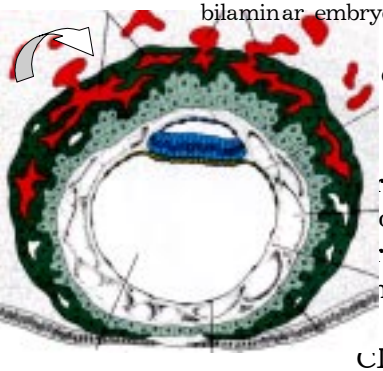
Fig. 26. **Schema of section through the middle of an implantation site at the 11th – 12th day of development.**
Kesignation:
1 – amnion; 2 – epiblast of bilaminar embryonic disk; 3 – hypoblast of bilaminar embryonic disk

especially at the implantation site, the glands are actively secreting glycogen and mucus.

Stroma cells are transformed ***into decidual cells*** that accumulate glycogen and lipids.

The trophoblast has differentiated into **syncytiotrophoblast** and **cytotrophoblast** and give rise to primary **chorionic villi**.

The intercommunicating lacunae contain some maternal blood. The endometrium surrounding the implanted blastocyst is edematous and there is hemorrhage into a uterine gland in contact with the syncytiotrophoblast



ontrol of implantation

control of implantation is exercised by the **one** and **estrogens**.

otrophoblast produces hormone – human **ophin**, which enters the maternal blood and monal activity of corpus luteum.

CLINICAL CONSIDERATIONS

Implantation of blastocyst usually occurs in the endometrium of the uterus, usually superiorly in the body of the uterus, slightly more often on the posterior than on the anterior wall.

Implantation of a blastocyst can be detected by ultrasonography and highly sensitive radioimmune assays of hCG as early as the end of the second week.

Extrauterine implantation

Blastocyst may implant outside the uterus. These implantation is called extrauterine implantation and result in ectopic pregnancies.

The ectopic pregnancy includes:

1) **Tubal pregnancy.** About 95-97% of ectopic implantations occur in the uterine tube. Most ectopic pregnancies are in the ampulla and the isthmus of the uterine tube.

Also tubal pregnancy contains intramural (uterine) tubal pregnancy.

The incidence of tubal pregnancy varies from 1 in 80 to 1 in 250 pregnancies, developing on the socioeconomic level of the population.

There are several causes of tubal pregnancy, but they are often related to factors that delay or prevent transport of the zygote to the uterus:

- mucosal adhesions in the uterine tube
- pelvic inflammatory disease

2) **Abdominal pregnancy.** Blastocyst may implant in the ampulla or on fimbriae of uterine tube and may be expelled into peritoneal cavity.

3) **Cervical implantation** occurs if blastocyst implant into the uterine cervix. Some of these pregnancies are not recognized because the conceptus is aborted during early stage of development.

Results of ectopic pregnancy

Ectopic tubal pregnancies usually results in rupture of the uterine tube and hemorrhage into the peritoneal cavity during the first 8 weeks, followed by death of the embryo.

Abortion of an embryo from the isthmus of the uterine tube often results in extensive bleeding.

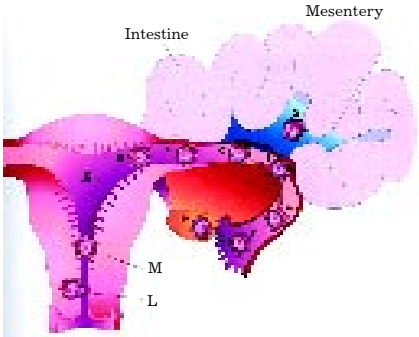


Fig. 27. **Schematic diagram of implantation sites of blastocyst.**
Kesignation:
X – typical normal site of implantation in the posterior wall of the uterus; A, B, C, K, E, F – tubal implantation; G – abdominal implantation; M – implantation at internal os; L – cervical implantation.

When blastocyst implant in the intramural part of the tube, it may develops into fetus before expulsion occurs.

Spontaneous abortion of an early embryo in the uterine tube may results in abdominal implantation of the conceptus (in the ovary or in other organs or on mesenteries).

Usually, an abdominal pregnancy creates a series condition because the placenta attaches to abdominal organs and causes intraperitoneal bleeding.

Gastrulation

Gastrulation is the process that establishes the three definitive germ embryonic layers: ectoderm, endoderm, and mesoderm.

Gastrulation of chordate or vertebrate animals can be classified into 4 types:

- Invagination.
- Epiboly.
- Kelamination.
- Migration.

Invagination

Gastrulation of **miolecithal oocytes** (or eggs) results in the establishment of the **invagination.**

The *vegetal hemisphere* of the blastula invaginates into the *animal hemisphere*, thus obliterating the blastocoele and forming a new cavity, the *gaslrocoele,* lined by the invaginated cells,

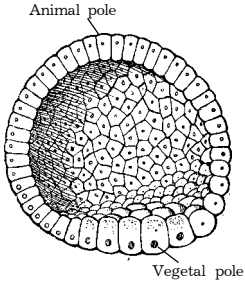


Fig. 28. **The blastocyste**

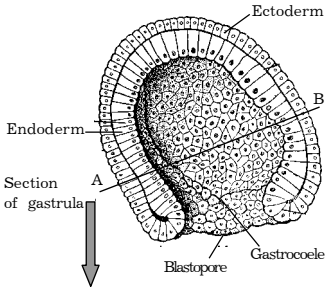


Fig. 29. **The blastocyste with blastopore**

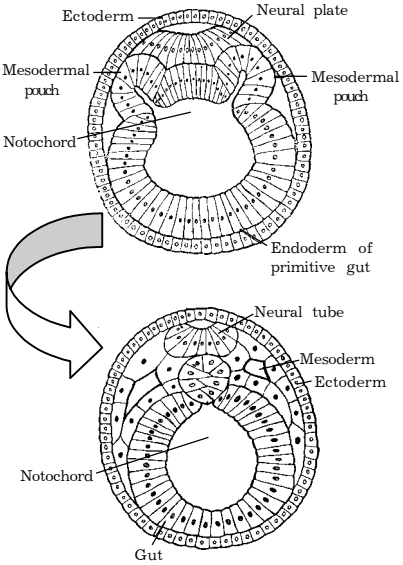


Fig. 31. **Schema showing the gastrulation and notochord-mesoderm formation of primary miolecithal oocytes of primitive aquatic forms.**

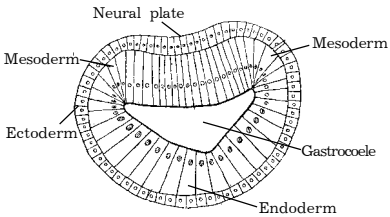


Fig. 30. **The blastocyste with notochord-mesoderm formation**

which constitute the endoderm and the notochord-mesoderm (the mesoderm and notochord).

The outer layer of cells is now the ectoderm. The circular opening, where the latter is continuous with the invaginated endoderm, is the ***blastopore***.

The invaginated vegetal hemisphere cells form **endoderm**, approximately the lower two-thirds of the lateral sides of the elongating gastrocoele or primitive gut. These cells also form **notochord-mesoderm**, upper third of the sides of the primitive gut, consisting of small yolk-free cells.

The notochord-mesoderm along the midline of the roof of the gastrocoele evaginates dorsal ward, separates from the gut, and forms a solid notochord.

At the same time lateral diverticula arise from the lateral part of the chorda-mesoderm on either side of the notochord evagination. The pouches enlarge, separate from the primitive gut, and give rise to the mesoderm.

Epiboly

Gastrulation in the **medialecithal oocytes** is typified by that of the frog. The process of spreading, or overgrowth, by the animal pole cells, is called ***epiboly***.

In the frog the relatively great size and slow cleavage rate of the blastomeres in the vegetal two-thirds of the blastula is the cause of differences in its gastrulation.

The *smaller cells of the animal pole* proliferate and surround the *larger cells of the vegetal pole*.

At the same time, the animal pole cells of the advancing margin are progressively invaginated so those appear a new cavity, the *gastrocoele*.

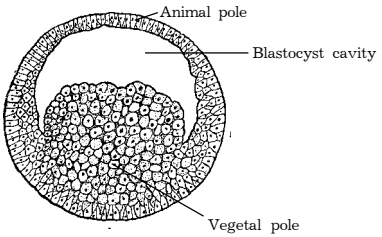


Fig. **The epibolyot**

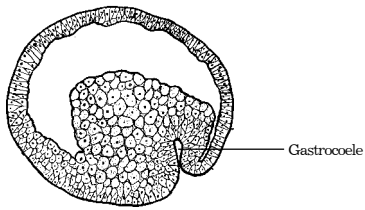


Fig. **The invagination**

The gastrocoele is partially lined by animal pole cells (**notochord-mesoderm**) in addition to the heavily yolked cells of the original vegetal pole (**endoderm**). The former will give origin to the mesoderm and notochord.

The animal pole cells, which are never invaginated, will in later stages form the definitive **ectoderm** and **neural plate**.

With continued development the periphery of the invaginated

notochord-mesoderm extends ventrally on the lateral side of the endoderm.

The mesodermal pouches are not formed by evagination from the notochord-mesoderm. The *mesodermal sheet* merely *extends ventrally between the endoderm and the overlying ectoderm.*

Kifferentiation of the mesodermal somites, lateral plate mesoderm and coelom is typical of that of most vertebrates.

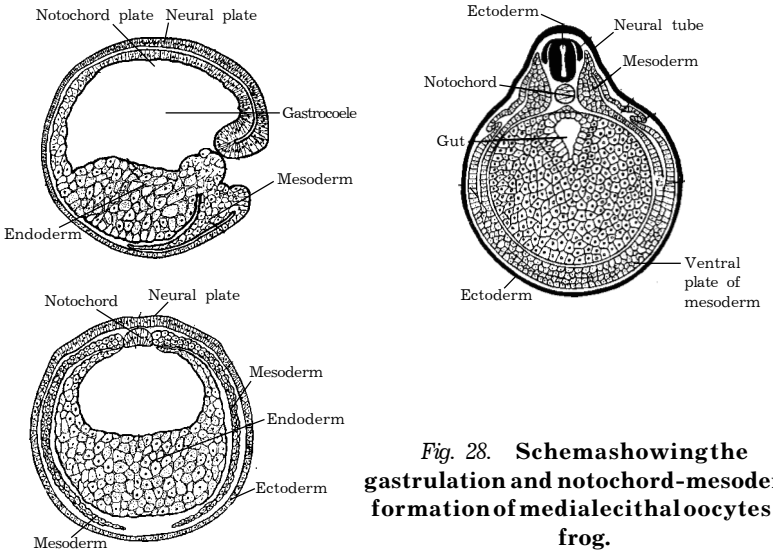


Fig. 28. **Schemashowingthe gastrulation and notochord-mesoderm formationofmedialecithaloocytesof frog.**

Kelaminationandmigration

The presence of large amounts of yolk in the **megalecithal oocytes** modifies not only cleavage but also the processes of gastrulation.

At blastula stage the cleavage cells form a **blastoderm** three or four cells thick, separated by cavity from the centrally placed yolk and continuous with it at the periphery.

The blastodisc (**discoblastula**) is a relatively small area on the yolk mass.

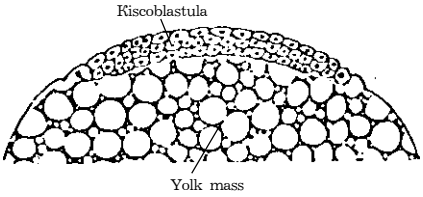


Fig. **The blastodisc**

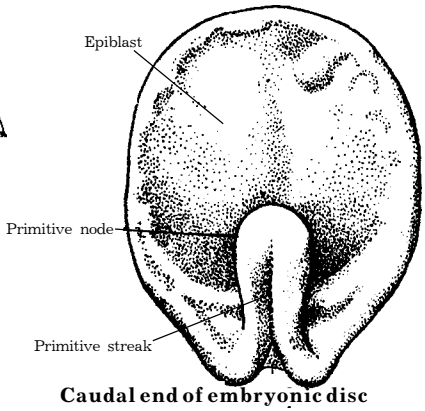


Fig. **The primitive streak formation of the embrio disc**

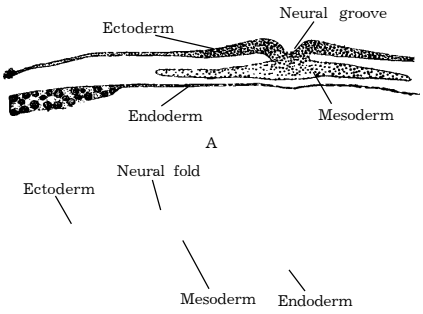
Under the blastoderm, cells separate from the surface cells by delamination and organize to form a complete sheet of endoderm.

The **two-layered disc** begins to overgrow the yolk.

At the same time a small depression forms on surface of disc *near the caudal margin.*

There is a convergence of surface cells towards this area and a short **primitive streak** is formed, from which the notochord and mesoderm arise.

rated laterally from the streak lie between **ndoderm** and are, therefore, **mesoderm**. end of the streak the **notochord** arises.



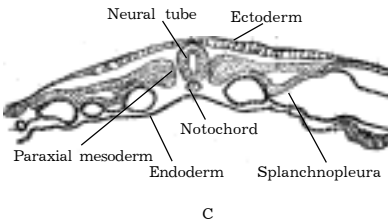


Fig. 29. **Schema showing the gastrulation and notochord-mesoderm formation of megalecithal oocytes of avers.**

A. Formation of mesoderm

B. Formation of neural tube

C. Kifferentiation of mesoderm

Humangastrulation

Human gastrulation includes two main processes:

1) **Kelamination**, which establishes bilaminar embryonic disk composed of two layers, the epiblast and hypoblast**.**

2) **Migration**, which establishes three-laminar embryonic composed of ectoderm, mesoderm and endoderm.

These three germ layers give rise to all tissues and organs of the adult, the fetal membranes including fetal portion of placenta.

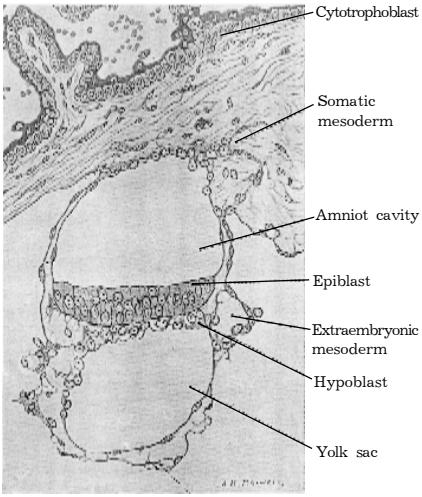


Fig. 30. **A transverse section through the bilaminar embryonic disk.** Extraembryonic mesoderm fills the blastocyst cavity and forms the wall of two small new cavities: amnion and yolk sac.

Gastrulation begins in the same time as implantation. The morphological changes occur in the embryoblast.

A. The early phase of gastrulation begins at **7.5 day** after fertilization.

The embryoblast differentiates into two distinct cellular layers:

1 – the dorsal layer – epiblast

2 – the ventral layer – hypoblast

The **epiblast** is the thicker (upper, dorsal) layer and consists of high columnar cells.

The **hypoblast** is the thinner (lower, ventral) layer consisting of small cuboidal cells adjacent to blastocyst cavity (exocoelomic cavity).

The epiblast and hypoblast form a flat, ovoid-shaped disk known as the **bilaminar embryonic disk.**

The **first phase of gastrulation** is the separation by morphogenetic movements (delamination) of the hypoblast, presumptive endodermal cells, from the surface layer, epiblast, that contains presumptive ectoderm, notochord and mesoderm.

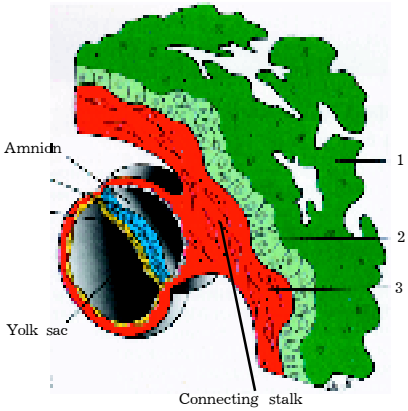


Fig. 31. **The end of second week of development.** Formation of amnion and yolk sac that are separated by bilaminar embryonic disk consisting of epiblast (blue) and hypoblast (yellow). Arrows show these layers. Extraembryonic mesoderm (red -3) lines the inner aspect of cytotrophoblast (2) and covers amnion (somatopleure), and yolk sac (splanchnopleure). Also it forms connecting stalk. Syncytiotrophoblast covers chorionic villi (dark green).

The **second phase of gastrulation** begins at **14-15day** after fertilization and establishes three germ embryonic layers with the formation of primitive streak, primitive node, notochord, mesoderm and neural tube.

B. In the second stage of gastrulation there is a migration of epiblast cells to a limited axial region of the posterior portion of the embryonic disc to form the **primitive streak**.

The process of formation of third germ embryonic layer is more in the nature of a migration of epiblast cells than a specific proliferative process.

Gastrulation at second week and early part of the third week is characterized by:

– development of extraembryonic mesoderm;
– appearance of the primitive streak;
– development of the notochord;
– formation of the intraembryonic mesoderm.

Development of the extraembryonic mesoderm

During the week 2 a new layer, extraembryonic mesoderm develops.

* Origination. Extraembryonic mesoderm is composed of loosely arranged cells, which are derived from epiblast. These migrating cells fill the space of blastocystic cavity.

* Location. Extraembryonic mesoderm fills the blastocyst cavity and forms the wall of two small new cavities:

1 – primary amniotic cavity;
2 – primary yolk sac.

Primary amniotic cavity is located between the epiblast and inner aspect of cytotrophoblast.

Primary yolk sac is located under the hypoblast.

The bilaminar embryonic disk lies between two cavities - the amniotic cavity and cavity of primary yolk sac.

The **extraembryonic mesoderm**

subdivides into two parts:

1. extraembryonic somatic mesoderm;
2. extraembryonic visceral mesoderm.

Extraembryonic somatic mesoderm (somatopleure) lines the trophoblast (inner surface of cytotrophoblast) and covers the amnion, and forms the **connecting stalk**.

Extraembryonic visceral mesoderm (splanchnopleure) covers the yolk sac.

The fluid-filled cavity surrounds the amnion and yolk sac, except where they are attached to the trophoblast by connecting stalk, is called **extraembryonic coelom**.

Extraembryonic somatic mesoderm, lining the inner aspect of cytotrophoblast, and two layer of trophoblast (cytotrophoblast + syncytiotrophoblast) constitute the **chorion**.

The extraembryonic coelom is now called the **chorionic cavity.**

Fomation of the primitive streak

In a human embryo of **15th day** the primitive streak appears at the caudal end of the embryonic disc. The primitive streak results from the proliferation and migration of the cells of the epiblast to the median plane of the embryonic disc.

These cells form a thickened linear band of epiblast. In this area epiblast cells proliferate, dividing more frequently then elsewhere in epiblast. A narrow **primitive groove** develops in the primitive streak.

Cranial end of primitive streak forms a **primitive node**, known as Hensen's node.

Some of the cells of primitive node form an invagination, a small depression, which is called the **primitive pit**, surrounded by a slightly elevated area.

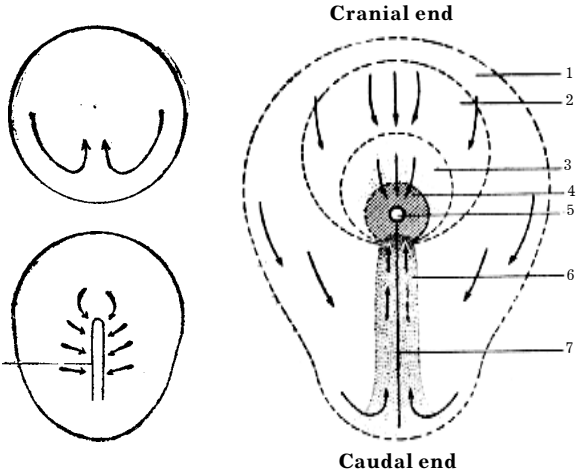


Fig. 32. **Schema illustrates the migration of epiblast cells during the formation of primitive streak.**

Resignation:

1 – epiblast; 2 – material of neural plate; 3 – material of notochord; 4 – primitive node; 5 – primitive pit; 6 – primitive streak; 7 – primitive groove

Cells of primitive pit migrate in the axial region between epiblast and hypoblast and give rise to the **notochord**.

Development of the intraembryonic mesoderm (embryonic mesoderm)

The term intraembryonic mesoderm describes the germ layer that forms during **week 3** (gastrulation) in contrast to the extraembryonic mesoderm, which forms during week 2.

Shortly after the primitive streak appears, cells leave its deep surface and migrate in lateral direction between the epiblast and hypoblast.

Migrating cells actively proliferate and move laterally and cranially, alone the midline. This new forming cellular layer is called **intraembryonic (embryonic) mesoderm.**

The intraembryonic mesoderm progressively extends laterally until it reaches the margins of embryonic disc in each side eventually. There, these mesodermal cells continue with the extraembryonic mesoderm, which covers the amnion and yolk sac.

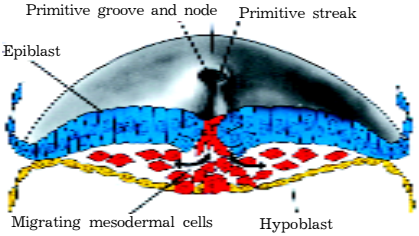


Fig. 33. **Dorsal surface of embryo at 16th day of development.** Cells of primitive streak migrate between epiblast and hypoblast laterally and give rise to intraembryonic mesodermal cells.

Some cells of intraembryonic mesoderm migrate cranially. Here they meet cranilly to form the cardiogenic mesoderm in the **car–diogenic area**, where the primordium of the heart begins to develop at the end of the third week.

As a result of the formation of intraembryonic mesoderm bilaminar embryonic disc becomes **trilaminar disc**.

External form of the embryo at presomite period

This period extends from the time of appearance of the primitive streak until the differentiation of the **first somite**.

The embryonic body at the **14th or 15th** day after fertilization consists of a bilaminar disc of epiblast and hypoblast lying between the amniotic and the yolk sac cavities.

In the caudal half of the disk the **primitive streak** can be seen in the midline as a linear thickening which terminates cranially in the **primitive** (Hensen's) **node**.

The presence of the primitive streak together with the **notochord** confers an obvious bilateral symmetry on the disk.

Caudally the primitive streak does not quite reach the hinder edge of the disk, being separated from it by the cloacal membrane.

With further growth the embryonic disk increases in size, especially in the cranio-caudal axis, and the primitive streak and node appear to be carried in a caudal direction since the streak and the area lateral to it grow relatively slowly, while the area cephalic to the primitive node grows rapidly.

During this process of caudal migration of the primitive streak the embryonic disk elongates and changes its shape, becoming first oval, then pear-shaped.

At the same time the embryonic disc develops **head** and **tail folds** and bulges slightly upwards into the amniotic cavity.

Towards the end of the presomatic period of development a broad, a **neural groove** appears in the **neural plate** region of the embryonic disc cranial to the primitive node.

Fomation of the notochord

Kuring the formation of the intraembryonic mesoderm notochord develops. The small depression, called **primitive pit** forms in the center of the primitive node.

The **notochordal process** elongates by invagination of cells from the primitive pit.

The notochordal process is now a cellular tube that extends *cranially* from the primitive node to the prechordal plate *between epiblast* and *hypoblast*.

Beginning at the cranial end of the embryo, the notochordal cells proliferate and the notochordal plate infolds to form the rod-shaped notochord.

Notochord is a **solid cylinder cord** located in the midline of the embryonic disc between the ectoderm and endoderm.

At the end of the 4th week notochord is in its final position between endoderm and ventral aspect of the neural groove or neural tube.

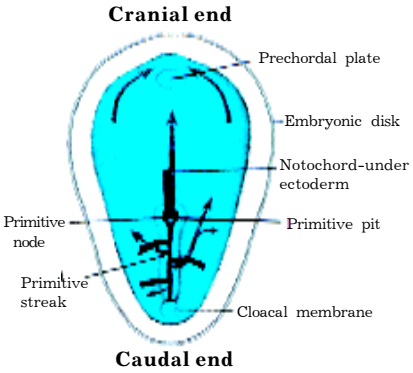


Fig. 34. **Kevelopment of notochordal process.** The notochordal process elongates by invagination of cells from primitive pit and extends cranially from primitive node.

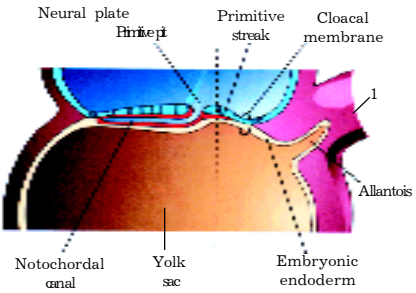


Fig. 35. **Formation of notochordal canal.** The opening of notochordal canal rapidly disappears and remains of notochordal process form a solid cord. (1 – connecting stalk).

The notochord degenerates and disappears as the body forms, but it persists as the **nucleus pulposus** of each **intervertebral disc**.

Notochord is important for the following:

1. Notochord induces the overlying embryonic ectoderm to differentiate into the neural plate, the primordium of the nervous system.
2. Notochord serves as the basis for development of the axial skeleton (bones of head and vertebral column).
3. Notochord induces the formation of vertebral bodies.
4. Notochord provides changes involving endoderm. Endoderm is involved in the formation of the future digestive system, respiratory system, central parts of the urogenital system and pharyngeal pouches.

CLINICAL CRNSIKERATIRNS

1. Sacrococcygeal teratoma.

· is tumor that arises from remnants of the primitive streak, which normally degenerates and disappears;

· is derived from pluripotent cells of the primitive streak and often contains various types of tissue (e.g. bone, nerve, hair);

· occurs more commonly in female infants;

· usually becomes malignant during infancy and must be removed by age 6 months.

2. Chordoma.

· is a tumor that arises from remnants of the notochord;

· may be found either intracranially or in the sacral region;

· may be either benign or malignant.

After the formation of primitive streak, intraembryonic mesoderm and notochord, remainder of epiblast is called ectodermal germ layer (**ectoderm**).

After the formation of the extraembryonic endodermal layer, lining the inner surface of secondary yolk sac, remainder of hypoblast is called **endodermal germ layer** (**endoderm**).

* **Prechordal plate** (prochordal plate) is a small circular area of columnar endodermal cells located in cranial part of embryonic disk.

Prechordal plate is firmly attached to the overlying ectoderm.

These fused germ layers form the oropharyngeal membrane, located at the future site of the oral cavity (mouth).

* Caudal to the primitive streak there is a circular area known as the **cloacal membrane**, which indicates the future site of the anus.

*The embryonic disk remains bilaminar at the **oropharyngeal** and **cloacal membranes** because the embryonic ectoderm and endoderm are fused at the sites, thereby preventing migration of mesodermal cells between them.

Fomation of the neural tube (neurulation)

- At the *beginning* of the **third week** of development the ectodermal germ layer has a shape of a flat disc.

Under the inductive influence of the notochord, the ectodermal disc changes in form and give rise to the nervous system.

Signaling molecules appear to involve members of the transforming growth factor-β (TGF-β) family, which includes activin and fibroblast growth factors (FGFs).

- At the *end of the third week* of development, as the notochord develops, the embryonic ectoderm over it thickens to form an elongated slipper-shaped plate that is called **neural plate**. Neural plate formation induces the signaling molecules (activin, FGFs), produced by the developing notochord.
- **Neural plate** appears cranial to the primitive node and dorsal to the notochord and mesoderm adjacent to it. As notochord elongates cranially, the neural plate extends cranially as far as the oropharyngeal membrane.
- *About the 18th day* of development, the neural plate invaginates along its central axis to form a longitudinal median **neural groove**, which has **neural folds** on each side.

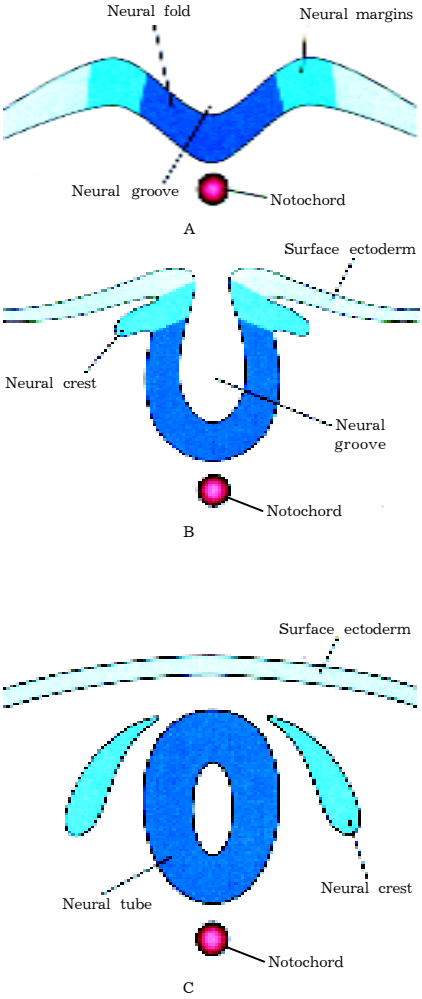


Fig. 36. **Schematic diagram of transverse sections of embryo at various stages of neural tube formation.**
A – Early neural groove stage; B – Late neural groove stage; C – Neural tube and neural crests stage

Gradually the **neural folds** approach each other in the midline, where they fuse. This fusion begins in the region of the future neck (in the region of the fourth to sixth pairs of somites). Fusion of the neural folds proceeds in cranial and caudal directions. As a result of the fusion a tube-like structure, the **neural tube**, is formed.

At the cranial and caudal ends of the embryo neural tube remains temporarily openings at the both ends. The lumen of the neural tube, **neural canal**, communicates freely with the amniotic cavity.

The cranial opening, the rostral (anterior) **neuropore**, closes on about 25-27 day, and the caudal (posterior) neuropore 2 days later.

The wall of the neural tube thickens to form the **brain** and the **spinal cord**.

The neural canal of the neural tube is converted into the **ventricular system** of the brain and the **central canal** of the spinal cord.

The neural tube soon separates from the surface ectoderm and the free edges of the ectoderm fuse so that this layer becomes continuous over the neural tube.

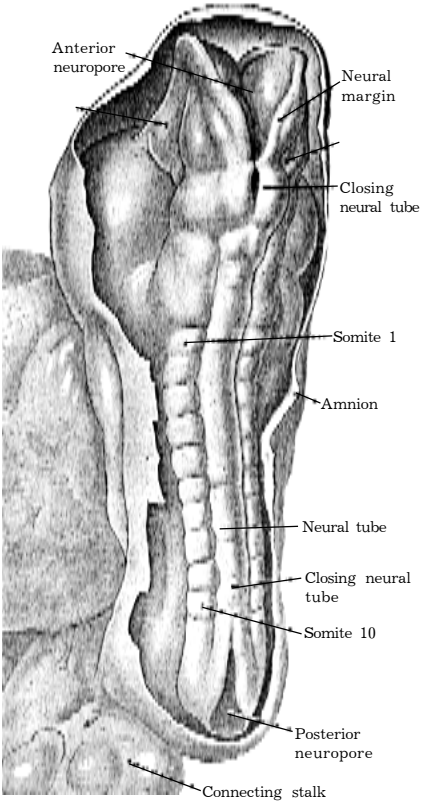


Fig. 37. The dorsal aspect of a reconstruction of human embryo at about the 23 day of development.

11. Some cells of the neural folds migrate dorsolaterally on each side of the neural plate.

They soon form a flattened irregular mass, the **neural crest**, between the neural tube and the overlying surface ectoderm. The neural crest soon separate into right and left parts that migrate to the dorsolateral aspects of the neural tube.

Neural crest cells give rise to following:

1). **Pseudounipolar ganglion cells** of the spinal ganglia (dorsal root ganglia).

2). **Multipolar ganglion cells** of autonomic ganglia.

3). The nervous cells of **cranial ganglia** V, VII, IX and X also partly derived from neural crests cells.

4). Neuralemmal **Schwann cells** in peripheral nervous system.

5). **Meningeal coverings** of the brain and spinal cord (the pia mater and arachnoid's mater).

6). Chromaffin cells of **suprarenal medulla**.

7). **Pigment cells**.

8). **Parafollicular cells** (calcitonin-producing C cells) of thyroid gland.

Differentiation of the germ layers

In normal development the cells of three primary germ layers (ectoderm, mesoderm, and endoderm) make specific contributions to the formation of different tissues and organs. These germ layers formed during gastrulation give rise to all tissues and organs.

Differentiation of the mesodermal germ layer

The mesoderm germ layer forms a thin sheet of loosely arranged tissue on each side of midline.

By approximately the **17th day**, as the notochord and neural tube form, the intraembryonic mesoderm on each side close to the midline proliferates to form a thick, longitudinal column known as **paraxial mesoderm**.

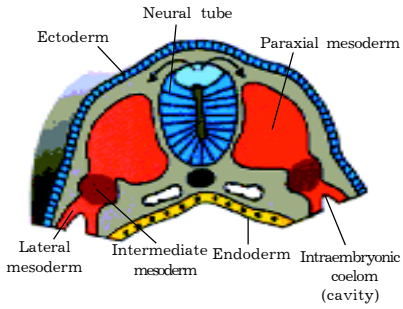


Fig. 38. **Schema illustrated subdividing of intraembryonic mesoderm into the paraxial, intermediate and lateral mesoderm.**

More laterally, the paraxial mesoderm continuous into the **intermediate mesoderm**, which gradually thins into the layers of **lateral mesoderm** (or lateral mesoderm plate).

The **lateral mesoderm** divides into two layers:

1) the **somatic** (or parietal) and **2) splanchnic** (or visceral) mesoderm layers.

The somatic and splanchnic mesoderm layers together line a newly formed cavity, the **intraembryonic coelom**,

Development of somites

The **somite period**, which extends approximately from **20th to 30th day** of human development, is characterized by the formation of **somites.**

· Toward the end of the third week the paraxial mesoderm differentiates and begins to divide into paired cuboidal bodies, the **somites** (gr. *soma*, body).

· The blocks of paraxial mesoderm are located *on each side of the neural tube.*

· Each somite consists of mesodermal cells arranged in concentric whorls around the center of the unit. Each consists at first of epitheliod cells.

· The somites are triangular on transverse section with *medial*, *ventral* and dorso-lateral walls.

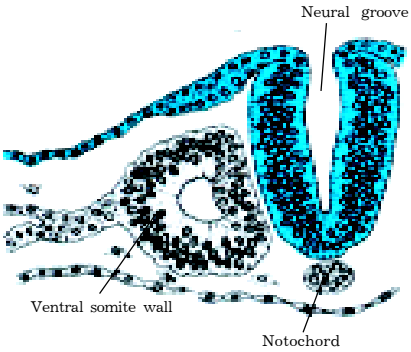


Fig. 39. **Schema of early stage of paraxial mesoderm development. Mesoderm cells are arranged around a small cavity.**

The first pair of somites appears at the end of the third week a short distance caudal to the cranial end of the notochord. From here, new somites appear in craniocaudal sequence at a *rate* of approximately *three pairs per day.*

The somites increase in number as development progress, new ones being added caudally until the end of the fifth week, **generally 42 to 44** (4 occipital, 8 cervical, 12 thoracic, 5 lumbar, 5 sacral, 8-10 coccygeal) are formed.

During this period of development, the age of the embryo is expressed in number of somites.

By the beginning of the *fourth week*, **paraxial mesoderm** cells forming the ventral and medial walls of the somite lose their compact organization, become polymorphous, and shift their position to surround the notochord.

Table Number of Somites Correlated to Approximate Age in Days

Approximate Age (days)	No. of Somites
1-4	20
4-7	21
7-10	22
10-13	23
13-17	24
17-20	25
20-23	26
23-26	27
26-29	28
34-35	30

These cells are collectively known as the **sclerotome.** They will surround the spinal cord and notochord to form the *vertebral column.*

Cells at the dorsolateral portion of the somite also migrate as precursors of the limb and body wall musculature. These cells migrate down the ventral side of the remaining dorsal epithelium of the somite, proliferate, and form a new layer, the **myotome**.

The remaining dorsal epithelium forms the **dermatome**.

Each segmentally arranged *myotome* contributes to **muscles** of the, while *dermatomes* disperse to form the **dermis** and subcutaneous tissue of the skin.

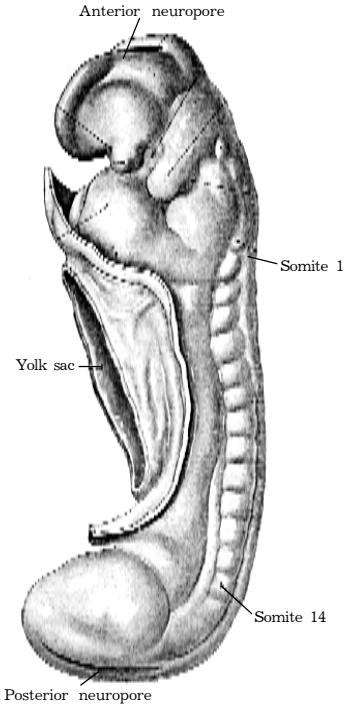


Fig. 40. **The left lateral aspect (B) of a reconstruction of human embryo at about the 23 and 25th day.**

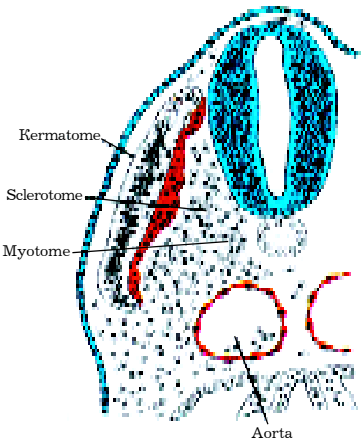


Fig. 41. **Cells of the ventral and medial walls of the somite lose their epithelial arrangement and migrate in the direction of the notochord.** These cells collectively constitute the sclerotome. Cells at the dorsolateral portion of the somite migrate as precursors to limb and body wall musculature. Korsomedial cells migrate beneath the remaining dorsal epithelium of the somite to form the myotome.

Each myotome and dermatome retains its innervation from its segment of origin, no matter where the cells migrate.

Each somite forms:

1) its own **sclerotome** (the cartilage and bone component),

2) its own **myotome** (providing the segmental muscle component), and

3) its own **dermatome,** the segmental skin component.

Each myotome and dermatome also has its own segmental nerve component.

Paraxial mesoderm differentiates into the:

- sclerotome
- myotome
- dermatome

Sometomeres 1-7 do not form somites but contribute mesoderm to the **pharyngeal arches**.

Intermediate mesoderm

Intermediate mesoderm connects the paraxial mesoderm and lateral mesoderm.

It forms a longitudinal elevation along the dorsal body wall known as the **urogenital ridge.**

In cervical and upper thoracic regions, it forms segmental cell clusters (future **nephrotomes),** whereas more caudally, it forms an unsegmented mass of tissue, the **nephrogenic cord**, which gives rise to future kidneys and gonads.

Lateral plate

The **lateral mesoderm** divides into two layers:

1) the **somatic** (or parietal) and

2) splanchnic (or visceral**)** mesoderm layers.

1). The **somatic** or **parietal mesoderm** layer, which continuous with the extraembryonic mesoderm covering the *amnion.*

The parietal layer together with overlying ectoderm will form the *lateral* and *ventral body wall.*

The parietal mesoderm surrounding the intraembryonic cavity will form the thin mesothelium, which will line the *peritoneal,*

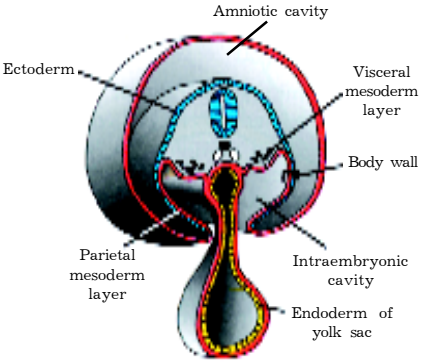


Fig. 42. Transverse section through a 21-day showing parietal and visceral mesoderm layers. The intraembryonic cavities communicate with the extraembryonic cavity (chorionic cavity).

pleural and pericardial cavities and secrete *serous fluid.*

2). The **splanchnic** or **visceral mesoderm** layer, which continuous with extraembryonic mesoderm covering the *yolk sac.*

The visceral mesoderm will form a thin mesothelium or *serous membrane* around each organ of thoracic cavity (lungs, heart) and peritoneal cavity.

The visceral mesoderm and embryonic endoderm will form the *wall of the gut.*

Together, these two layers line a newly formed cavity, the **intraembryonic coelom**, which is continuous with the *extraembryonic cavity* on each side of the embryo.

Kuring the second month, the *intraembryonic coelom* is divided into three body cavities:

- *pericardial cavity*
- *pleural cavity*
- *peritoneal cavity*

From somite region the lateral plate of each side extends *cranially* within the margins of the embryonic disk and fuses in the midline cranial to the **prochordal plate**, which with the overlying ectoderm forms the **buccopharyngeal membrane**.

The lateral plate mesoderm splits to form the intraembryonic coelom. That part of the mesoderm, of bilateral origin, origin to the prochordal plate is called the **cardiogenic mesoderm** since the heart later develops in this region.

Kefferentiationofthe entoderm

The endoderm covers the ventral surface of the embryo and forms the roof of the yolk sac.

With the development and growth of the brain, the embryonic disk begins to bulge into embryonic cavity and to fold craniocaudally (longitudinal folding).

Folding occurs in both the *median* and *horizontal planes*. This folding is most pronounced in the regions of the head and tail, where the **head fold** and **tail fold** are formed.

Kuring longitudinal folding cranial (or anterior) portion of the endoderm of the yolk sac is incorporated into the embryo as the **foregut**.

The foregut lies between the brain and heart and the oropharyngeal membrane separates the foregut from the **stomodeum**.

At the cranial end, the foregut is bounded by ectodermal-endodermal membrane called **the buccopharyngeal membrane**.

The **buccopharyngeal membrane** lies in the depths of an ectodermal depression – the stomatodeum, or primitive mouth. In late somite period this membrane breaks down, thereby establishing continuity between stomatodeum and foregut.

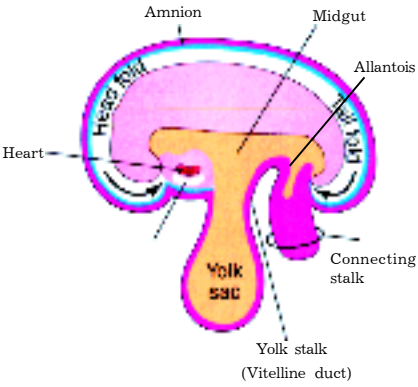


Fig. 43. **Schematic diagram of sagittal section of embryo illustrating the embryonic folding (*the head and tail folds*).**

In the *tail region the endoderm* of the yolk is incorporated and forms **hindgut**.

The *terminal part of the hindgut* soon dilates to form the **cloacal membrane**. The membrane itself then lies in a shadow depression called *exteral cloaca*.

In later development the **cloaca** becomes divided by the

urorectal septum into ventral *urogenital sinus* and a dorsal *rectum*, the cloacal membrane is also divided into ventral *urogenital membrane* and a dorsal *anal membrane*. Later, these membranes break down to give continuity between the cloacal derivatives and the exterior.

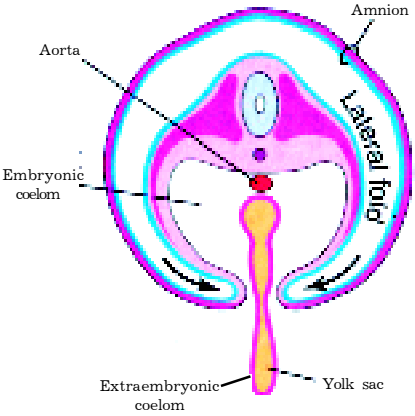


Fig. 44. **Drawings illustrating lateral embryonic folding (about 26 days).** ***After lateral folding the connection between the midgut and yolk sac is reduced. (Transverse section).***

The part between foregut and hindgut is the **midgut**, which communicates with the yolk sac by the broad stalk, the **vitelline duct**. Only much later, when the vitelline duct is obliterated, does the midgut lose its connection with yolk cavity and obtain its free position in the abdominal cavity.

Folding of the sides of the embryo produces right and left **lateral folds**, which roll the edges of the embryonic disk ventrally and forming a cylindrical embryo.

Derivations of the ectoderm

I. SURFACE ECTODERM

give rise to:

a) Epidermis and its appendages (*hair, and nails, subcutaneous glands and mammary glands*).

b) Adenohypophysis (anterior part of pituitary gland).

c) Enamel of teeth.

d) Lens of eye.

e) Internal ear.

II. NEURAL CRESTS

give rise to:

a) Pseudounipolar ganglion cells of the spinal ganglia (dorsal root ganglia).

b) Multipolar ganglion cells of autonomic ganglia.

c) The nervous cells of *cranial ganglia* V,VII, IX and X also partly derived from neural crests cells.

d) Neuralemmal *Schwann cells* in peripheral nervous system.

e) Meningeal coverings of the brain and spinal cord (the pia mater and arachnoid mater).

f) Chromaffin cells of *suprarenal medulla.*

g) Pigment cells.

h) Parafollicular cells (calcitonin-producing C cells) of thyroid glands.

III. NEURAL TUBE

give rise to:

a) The wall of the neural tube thickens to form the ***brain*** and the ***spinal cord***.

b) The neural canal of the neural tube is converted into the *ventricular system* of the brain and the *central canal* of the spinal cord.

Derivations of the mesoderm

I. PARAXIAL MESODERM

give rise to:

a) Sclerotome gives rise to *skeleton* (vertebral column) except cranium.

b) .**Myotome** gives rise to *striated skeletal muscle* (trunk, limbs), *muscles of head.*

c) Dermatome give rise to *dermis* and *subcutaneous tissue of the skin.*

II. INTERMEDIARE MESODERM

give rise to:

a) Urinary system (pronephros, mesonephros, metanephros,) including ducts.

b) Gonads and *accessory glands.*

III. LATERAL PLATE of MESKERM
give rise to:
a) Serous membranes of pleura, pericardium, and peritoneum.
b) Suprarenal gland cortex.
c) Germinal epithelium of gonads.
d) Myocardium, endocardium of heart.
e) Connective tissue and muscle of viscera.
IV. HEAK MESKERM
give rise to:
a) Cranium.
b) Kentin.
c) Connective tissue of head.

Kerivations of the entoderm

I. ENKKERM of the GUT
give rise to:
a) Epithelium lining gastrointestinal tract (*stomach, small intestine*, most part of *large intestine* except caudal portion of rectum).
b) The parenchyma of *liver* and *pancreas*.
c) Epilelium lining respiratory tract (*pharynx, trachea, bronchi, lungs*).
d) The parenchyma of the *thyroid gland, parathyroid gland.*
e) The reticular stroma of *thymus*.
f) The epithelium lining of the *urinary bladder* and *urethra.*
g) The epithelium lining of the *tympanic cavity* and *auditory tube.*

Fetalmembranes

Fetal membranes are **provisory organs of embryo and fetus,** which provide the normal human development during prenatal period.

Fetal membranes are developed *from the fertilized egg,* yet not forming part of the embryonic body.

Mainfunctions:

–Fetal membranes are of functional importance during embryonic life, being concerned with the supply or *storage of nutriment, respiratory exchange, excretion* and *mechanical protection* of the embryo.

– Fetal membranes are also known to *transmit antibodies* from mother to young, thus providing for passive immunity of the newborn.

– They *produce hormones*, which resemble those of the ovary and adenohypophysis, and are an essential part of the endocrine system during pregnancy.

– They are largely shed or absorbed at hatching or birth.

Types of Fetal membranes:

1. yolk sac;
2. amnion;
3. allantois;
4. chorion;
5. placenta;
6. umbilical cord.

The first phase of gastrulation (delamination) begins at 7th – 7,5 day of development and proceed at the same time with the implantation.

At once fetal membranes form (*yolk sac, amnion and chorion*), which provide entrance of nutrients and further development of embryo.

The formations of these fetal membranes take place about during **second week**.

First of all amnion and yolk sac develop.

Amnion

Formation

* The **amnioticcavity** appears in 7,5 day human embryo.

The *cleft* (small flattened space) appears in the embryoblast between the epiblastic cells and trophoblast. This new forming cleft-cavity is the primordium of the *amniotic cavity*.

Soon amniogenic (amnion-forming) cells – *amnioblasts* - separate from the epiblast and line the amnion, which encloses the amniotic cavity.

* The **epiblast** forms the *floor* of the amniotic cavity and is continuous peripherally with the amnion.

The **extraembryonic mesoderm** surrounds the amnion, yolk sac and lines the inner aspect of cytotrophoblast.

The *extraembryonic* ***somatic*** *mesoderm* surrounds the amnion and lines inner aspect cytotrophoblast.

The *extraembryonic* ***visceral*** (or splanchnic) *mesoderm* surrounds the yolk sac.

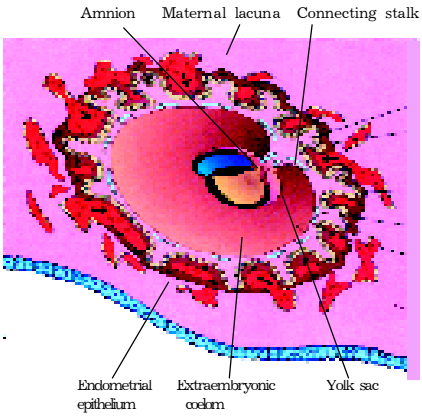


Fig.45. **Sagitalsectionofan implantedembryo(about16days): extraembryonicsomaticmesoderm coverstheamnionandlines cytotrophoblast.**

As changes occur, the extraembryonic mesoderm forms a large isolated cavity, the ***extraembryonic coelom.***

The extraembryonic coelom is fluid-filled cavity surrounds the amnion and yolk sac, except where they are attached to the cytotrophoblast by the **connectingstalk**.

· In the *first half of pregnancy* the **epithelial cells**, which originate from *amnioblasts*, are flattened and contain abundant glycogen.

· In *latter stages* they become *cuboidal* and

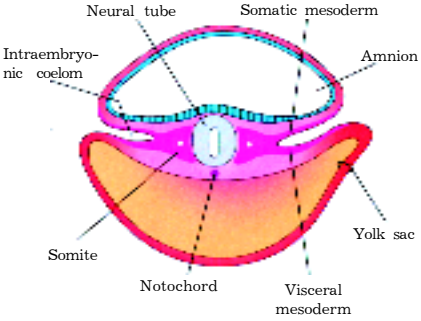


Fig. 46. **Drawings illustrating development of amnion, yolk sac and connecting stalk (transverse section through the embryo).**

columnar, the glycogen diminishes in amount, and lipid droplets appear in the cytoplasm. Irregular microvilli appear in their free surface.

· On the outside the amnion is covered by *extraembryonic somatic mesoderm*, which differentiates into the thin layer of **connective tissue.**

· The amnion forms a fluid-filled **amniotic sac** that surrounds the developing embryo and fetus (see fig. 43).

· The amniotic sac gradually *expands the extraembryonic coelom* and progressively ensheaths the connecting stalk, yolk sac, allantois.

· This expansion continues until the *coelom is obliterated* entirely, except for a small portion, which is included within the proximal part of the **umbilical cord**.

The region contained within and ensheathed by the tubular portion of the amnion is now called the **umbilical cord**.

Further growth of the amnion brings its external surface into intimate contact with the inner aspect of the *chorion*.

The ***extraembryonic coelom*** is thus gradually obliterated except for a cleft at the placental end of the umbilical cord and the space, containing the **vitelline duct** and vessels.

Because the amnion is attached to the margins of the embryonic disk, its junction with the embryo is located on the ventral surface after embryonic folding.

At the *end of the third month*, the amnion enlarges and comes in contact with the inner aspect of the chorion.

As the **amnion enlarges**, it gradually *obliterates the chorionic cavity* (extraembryonic coelom) and forms the epithelial covering of the umbilical cord.

Main steps of the obliteration of extraembryonic coelom

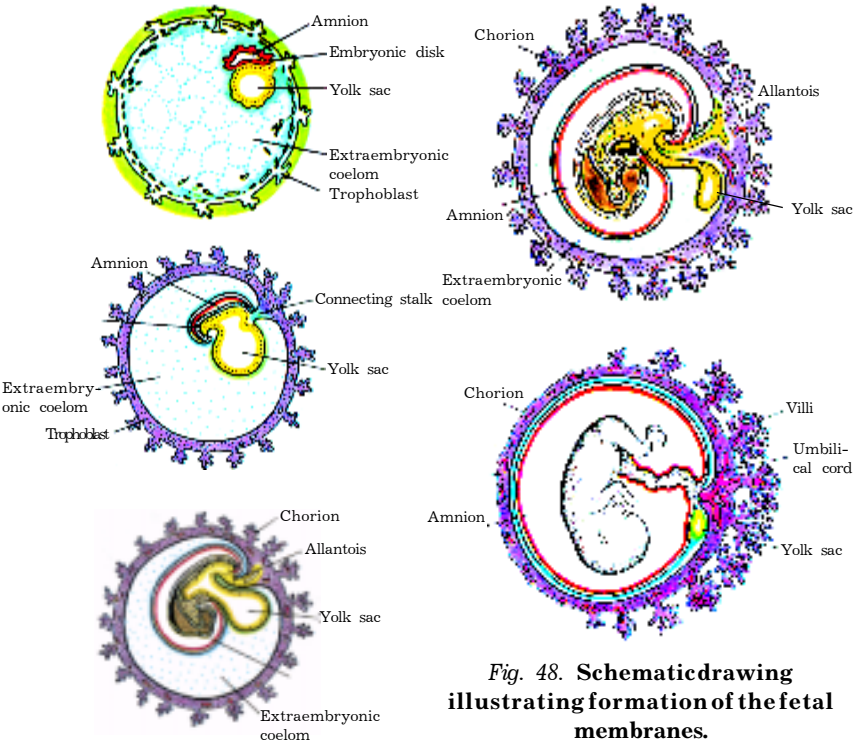


Fig. 48. **Schematic drawing illustrating formation of the fetal membranes.**

Amniotic fluid (orliquor amnii)

Amniotic fluid occupies the amniotic cavity and increases in amount.

The **volume of amniotic fluid** normally increases slowly, reaching

§ about 30 ml at 10 weeks,

§ about 350 ml at 20 weeks

§ 700 -to 1000 ml by 37-40 weeks (at the end of pregnancy).

Composition of amniotic fluid

Amniotic fluid is basically water (about 99%) that **contains**:

- *organic substances*
- inorganic substances
- *desquamated fetal epithelial cells*

Half *organic substances* are **proteins**. The other half consists of *carbohydrates, lipids, enzymes, hormones, pigments,* and *fetal urine*.

As pregnancy advances, the composition of the amniotic fluid changes as fetal excreta (*meconium* and *urine*) are added.

Production of amniotic fluid

Most amniotic fluid is derived **from maternal tissue**:

1) by dialysis (diffusion) maternal blood in the *decidua parietalis* through the *amniochorionic membrane ;*

2) by diffusion through the *chorionic plate* from maternal blood *in the intervillous spaces* of the placenta;

Amniotic fluid is derived **from the fetus**:

1) by dialysis of fetal blood through blood vessels in the *umbilical cord;*

2) by diffusion through the *skin* of the fetus before keratinization of the skin;

3) Fluid is also secreted by the fetal ***respiratory tract*** and enters the amniotic cavity. The *daily rate* of contribution of fluid to the amniotic cavity from the respiratory tract is **300** to **400 ml.**

4) Beginning in the eleventh week, the fetus contributes to the amniotic fluid by ***excreting urine*** into the amniotic cavity. By late pregnancy about a **500 ml** of urine is added daily.

Resorption of amniotic fluid

Amniotic fluid is constantly resorbed during pregnancy by several possible routes.

1. Fetus swallows amniotic fluid and absorbs by the fetus ***digestive*** and ***respiratory tracts.***

§ Kuring the final stages of pregnancy, the fetus swallows **up to 400 ml** of amniotic fluid **per day.**

§ Amniotic fluid is absorbed into the fetal bloodstream through the *wall of gastrointestinal tract.*

§ The fluid passes into the fetal blood and *enter the maternal blood* in the intervillous spaces of the placenta.

§ Excess water in the fetal blood is excreted by the **fetal kidney** and returned to the amniotic sac through the fetal urinary tract.

2. There is ***rapid exchange*** between the amniotic fluid and maternal and fetal circulations probably by way of the placenta and fetal kidney.

The water content of amniotic fluid changes every **3 hours**.

Functions

Amniotic fluid plays a major role in fetal growth and development.

1) Amniotic fluid provides a *buoyant medium* which *supports the delicate tissues* of the embryo.

2) Amniotic cavity containing fluid allows the *free movement of the fetus.*

3) Amniotic fluid (**A.f.**) absorbs mechanical pressures, thereby *protecting* the embryo from most *external trauma.*

4) Absorption the amniotic fluid with swallowing permits normal fetal *lung development.*

5) A.f. *prevents adherence* of the amnion to the embryo and fetus.

6) A.f. acts as a *barrier to infection* and contains antibodies.

7) A.f. assists in *regulation of fetal body temperature.*

8) A.f. provides *homeostasis* of fluid and electrolytes.

CLINICAL CONSIDERATIONS

Oligohydramnios is low volume of amniotic fluid. It results in most cases of diminished placental blood flow when there is renal agenesis (*failure of kidney formation*). The absence of fetal urine contribution to the amniotic fluid is main cause of oligohydramnios.

Obstructive uropathy (urinary tract obstruction) results in similar decrease of fluid.

Compression of the umbilical cord is also a potential complication.

Polihydramnios is high volume of amniotic fluid in excess of 2000 ml.

It results when the fetus does not swallow the usual amount of amniotic fluid (*esophageal atresia*).

It may be associated with severe anomalies of CNS (*anencephaly*).

Amniocentesis –is the aspiration of fluid from amniotic sac.

Amniocentesis is performed between weeks 12 and 14 after fertilization. It has a 0,5% risk of miscarriage.

Amniocentesis is used to perform the following studies:

1. Alfa-fetoprotein assay.

High level of б-fetoprotein (AFP) in the amniotic fluid usually indicates the presence of a neural tube defect (*spina bifida, anencephaly, meroanencephaly*).

Low levels of AFP indicate chromosomal aberrations such as *trisomy 21.*

2. Spectrophotometry is used to diagnose *hemolytic disease.*

3. Sex chromosomatin studies are used to diagnose sex-linked diseases (*X-linked muscular dystrophy, hemophilia*).

4. DNA analysis are used to identify defective chromosomes early in pregnancy (*cystic fibrosis, hematologic diseases, neurologic disease, phenylketonuria*).

5. Enzyme analysis are used to identify steroid sulfatase deficiency, disorders of connective tissue (*hypophosphatasia), lysosomal storage diseases.*

Yolksac

Formation

The end of the second week of development is characterized by the appearance of extraembryonic mesoderm, which is a fine, loose connective tissue.

Extraembryonic splanchnic (splanchnopleuric) mesoderm forms the wall of the **primary yolk sac**.

The **extraembryonic coelom** appears between extraembryonic splanchnic mesoderm, which forms the wall of the primary yolk sac, and the extraembryonic somatic (somatopleuric) mesoderm, which lines the inner aspect of cytotrophoblast. In the same time the primary yolk sac decreases in size.

Some cells of hypoblast migrate along the inner surface of primary yolk sac and a smaller **secondary yolk sac** forms.

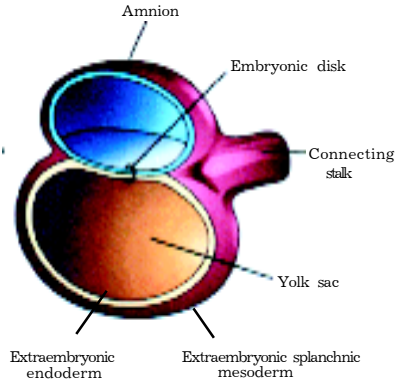


Fig. 49. **Schematic drawing illustrating formation of amnion and yolk sac. The wall of the yolk sac is composed of two layers:** 1 – internal endodermal layer originating from hypoblast; 2 – external mesodermal layer originating from epiblast.

The **secondary yolk sac** is covered on its outer aspect by the *extraembryonic splanchnic mesoderm* and on its inner aspect by the *extraembryonic endoderm*.

Kuring the *fourth week* the **folding endoderm** of the *dorsal wall* of the yolk sac is incorporated into the embryo and gives rise to the *primordial gut* (foregut, midgut, and hindgut).

The yolk sac remains attached to the midgut by a narrow **yolk stalk**.

The communication between the gut and yolk sac (7th week) is reduced to a relatively slender duct called the yolk stalk.

As the amniotic cavity expands and obliterates most of the extraembryonic coelom, the amnion forms the epithelial covering of umbilical cord.

The yolk stalk compressed into the umbilical cord.

The remainder of the yolk sac extends out of the embryo ventrally and is pushed against the connecting stalk by the amnion.

The yolk sac then is gradually obliterated (look schema "*Main steps of the obliteration of extraembryonic coelom*").

By **10 week** the yolk sac shrunk to pear-shaped remnant about **5 mm** in diameter.

By **20 week** the yolk sac is very small and is usually no visible.

Functions

1. The human yolk sac contains **no yolk**. It may have a role in the selective transfer of nutrients to the embryo at early stage of human development.

The yolk sac has a role in the **transfer of nutrients** to the embryo during the *second and third weeks,* when the uteroplacental circulation is being established.

The trophoblast absorbs nutritive fluid from the lacunae networks, which is transferred to the embryo.

2. The yolk sac mesoderm gives rise to the **angioblastic tissue**. It is first formed in the deepest layer of mesoderm early in third week.

· Tissue spaces form the angioblastic tissue and the cells, which line these spaces, take on the characters of typical flattened endothelial cells of capillaries.

· The **capillaries** of yolk sac fuse with each other and give raise the **vitelline veins** that grow toward the embryo.

· The **portal vein** develops from an anastomotic network formed by the vitelline veins around the duodenum.

· The localized groups of mesodermal cells project into the interior of developing capillary plexuses and become cut off to form **blood islets**.

· These cells soon differentiating into the *first generation of stem blood cells* that give rise to *primary* erythrocytes and then – to *secondary* **erythrocytes**.

The yolk sac is the first **source of blood** cells that enter the embryonic circulation via vitelline veins.

The yolk sac is important as a **source of blood** until the fetal liver replaces this function in about the 6th week of the development.

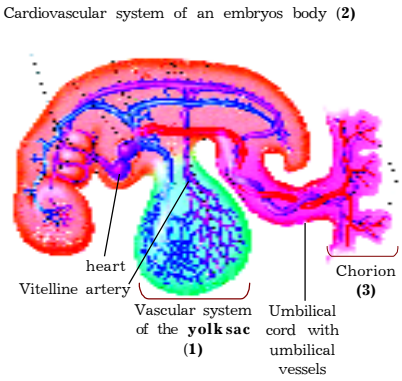


Fig. 50. **Kiagramoftheprimordial cardiovascularsysteminanembryo ofabout21days.**

Vascular system contains:

(1) – vascular system of the yolk sac,
(2) - cardiovascular system of an embryos body,
(3) – vascular system of the chorion.

• The umbilical vein carries oxygenated blood and nutrients from the chorion.

3. The **primordialgermcells (gonadoblasts)** appear in the endoderm layer of the yolk sac wall in the *third week* of the development.

The newly forming primordial germ cells subsequently *migrate* to the developing *sex gonads* along the wall of the yolk sac toward the wall of the hindgut.

The gonadoblasts embedding the developing sex gonad differentiate into the **spermatogonia** in males and **oogonia** in females.

• Vessels of the yolk sac form a *vascular plexus* that is connected to the heart tubes by vitelline veins.

Allantois

Formation and functions

In the 3d week of the development (on about day 16) *diverticulum from the caudal wall of the yolk sac* appears and extends into the connecting stalk. This diverticulum is called **allantois**.

The *diverticulum* arises early as a solid outgrowth. It soon becomes *canalized*.

The allantoises wall is composed of two germ layers:

1 – internal *endodermal layer*;

2 – external layer of *extraembryonic splanchnic mesoderm*.

The allantois grows for a variable distance into the connecting stalk mesoderm but does not reach to the chorion (see fig. 44).

The blood vessels develops within the extraembryonic mesoderm of allantois. The vascular plexus in the wall of allantois fuse and give rise to **umbilicalarteries** and **veins**.

Blood formation occurs in its wall during the third to fifth weeks.

The umbilical vessels connect the **circulatory system** of the *embryo and chorion.*

The paired umbilical arteries pass through the *connecting stalk* (later the *umbilical cord*) and become continuous with vessels in the chorion.

The **umbilical arteries** carry *poorly oxygenated blood* from embryo to the placenta.

Proximal part of the umbilical arteries becomes the ***internal iliac arteries and superior vesical arteries*** after the birth.

The **umbilical veins** carry *well-oxygenated blood* from the placenta to the embryo.

The right umbilical vein disappears during the seventh week of the development.

The **distal portion of the umbilical vessels** connect with the *chorionic vessels*, which differentiate at the same time in the chorionic mesoderm and form arterio-capillary-venous system of the chorionic villi.

Kistal parts of umbilical vessels obliterate after birth and become the ***median umbilical ligaments***.

· *Folding* of the caudal ending of the embryo results partially incorporation of allantois into the embryo. After the folding the allantois is partially incorporated into the body of the embryo, where it forms the **cloaca**.

· The intraembryonic part of the allantois runs from the umbilical cord to the *urinary bladder*, with which it is continuous.

· The allantois soon constricts and becomes a thick fibrous cord, the **urachus**. It extends from the apex of the urinary bladder to the umbilical cord.

· Kuring the second month, the extraembryonic part of the allantois degenerates.

· After the birth the urachus becomes a fibrous cord, the **median umbilical ligament.**

Umbilicalcord

By the **19th or 20th day** chorionic cavity becomes larger and the embryo is attached to trophoblast shell by a narrow **connectingstalk.**

This stalk is composed of **extraembryonic mesoderm** continuous with that lining the inner surface of the trophoblast and is attached to the embryo at its caudal end (fig. 45).

As a result of the folding of the embryo a patent opening called the **primitiveumbilicalring** exists on the ventral surface of the developing embryo.

At about the middle of the **secondmonth** the three following structures pass through the *primitive umbilical ring*:

1) connecting stalk;
2) yolk stalk (vitelline duct), containing vitelline vessels;
3) allantois (fig. 48, 51).

Kuring further development the primitive umbilical ring constricts.

The amniotic cavity enlarges and comes in contact with chorion, thereby obliterating the chorionic cavity.

As the amnion expands, it pushes the vitelline duct, connecting stalk, and allantois together to form the **primitive umbilical cord** (fig. 48, 60, 64).

The **primitive umbilical cord** contains:

1) the yolk sac and its stalk;
2) the umbilical vessels;
3) remnant of the allantois.

The allantois is not functional in humans and degenerates to form the **median umbilical ligament** in the adult.

When in addition the allantois, the yolk sac stalk and the vitelline vessels are obliterated, all that remains in the cord are the umbilical vessels surrounded by **jelly of Wharton**.

Jelly of Wharton has a *mesenchymal* origination, is rich in mucopolysaccharides and functions as a *protective layer for the umbilical blood vessels.*

The **definitive umbilical cord** contains:

1) the umbilical vessels (**right and left umbilical arteries, left umbilical vein);**

2) and mucus connective tissue **(Wharton's jelly).**

At birth umbilical cord is about **2 cm** in diameter and **50 to 60 cm long.**

The *attachment* of the umbilical cord to the placenta is usually **near the center** of the fetal surface of the fetal placenta.

CLINICAL CONSIDERATIONS

1. An extremely *long umbilical cord* may encircle the neck of the fetus.

2. A *short umbilical cord* may cause difficulties during delivery by pulling the placenta from its attachment in the uterus.

3. *Presence of one umbilical artery within the cord* is an abnormal condition that generally indicates the presence of cardiovascular anomalies. (Normally two umbilical arteries are present.)

Placenta types

Placenta types in eutherian mammals is classified of according to the intimacy of the union between the *fetal* and *maternal tissues*.

or in other words, according to the *structure* of the membrane *separating the maternal and fetal blood* in the functional parts of the placenta.

The name of the placenta is formed by a combination of the names of the maternal and fetal tissues, which are in contact.

Placenta types:

1 – epitheliochorial placenta;

2 – syndesmochorial placenta;

3 – endotheliochorial placenta;

4 – hemochorial placenta.

If the epithelium of the uterus persists and the trophoblast of the chorion merely lies in contact with it, the placenta is spoken of as *epitheliochorial*. This type of placenta has **horse, pig, cattle**.

If the epithelium disappears and chorion lies in contact with the connective tissue of the uterus, the placenta is called *syndesmochorial*. This type of placenta has **cow, deer, giraffe**.

If the uterine epithelium and connective tissue of the uterus disappear and the chorion comes into contact with the endothelium of the maternal vessels, as in the **dog, cat**, it is an *endotheliochorial* placenta.

In many mammals (**Primates** including **man**, Tarsiidae, Sirenia, Rodentia) the invasive activity of the placental trophoblast is greater, so that eventually even the endothelium of the maternal blood vessels is destroyed and placenta is called *hemochorial*.

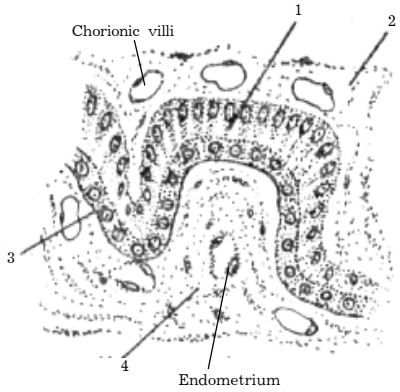


Fig 52. **Schema of epiteliochorial placenta.**

Kesignation:

1 — trophoblast; 2 — chorionic connective tissue containing blood vessels; 3 — endometrium epithelium; 4 — connective tissue of endometrium with maternal blood vessels.

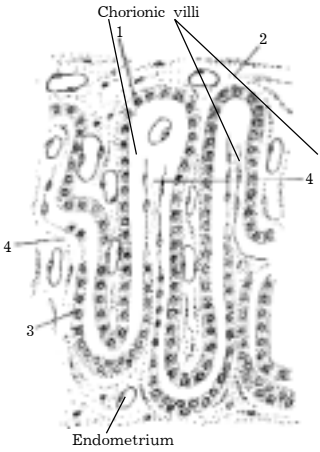


Fig 53. **Schema of syndesmochorial placenta.**

Kesignation:

1 — trophoblast; 2 — chorionic connective tissue containing blood vessels; 3 — endometrium epithelium; 4 — connective tissue of endometrium with maternal blood vessels.

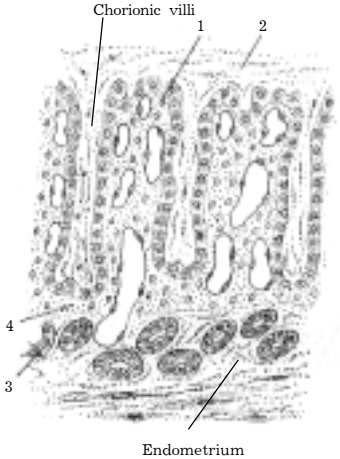


Fig 54. **Schema of endotheliochorial placenta.**

Resignation:

1 — trophoblast; 2 — chorionic connective tissue containing blood vessels; 3 — endometrium epithelium; 4 — connective tissue of endometrium with maternal blood vessels.

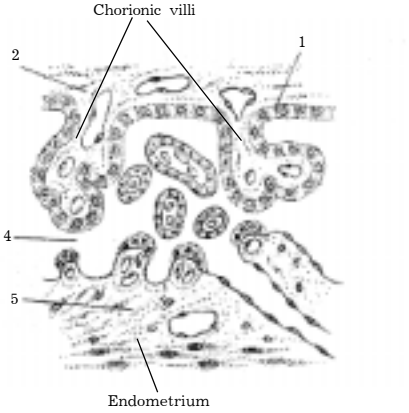


Fig 55. **Schema of hemochorial placenta.**

Resignation:

1 — trophoblast; 2 — chorionic connective tissue containing blood vessels; 3 — endometrium epithelium; 4 — connective tissue of endometrium with maternal blood vessels; 5 – lacunae.

Types of implantation

Fig. 56. **Kiffuse placenta of the pig.**

Fig. 57. **Cotyledonic placenta of ruminants (calf).**

Placenta formation occurs in the same time with the implantation.

Three main ***types of implantation*** are recognized among the mammals:

1) centraltype in which the blastocyst remains in the uterine cavity (rabbit, carnivores);

2) eccentrical type, in which the blastocyst comes to lie in the uterine crypt or resses;

3) interstitial type, in which the blastocyst come to lie entirely within the substance of the endometrium (man).

Humanplacenta

Chorion.Chorionicvilli.

The development of chorionic villi consists of two periods:

1. The period of *primary, secondary, and tertiary villi* formation. This period is continuous from 9th day until 50th day of gestation.

2. Period of *cotyledons* formation. This period is continuous from 50th day to 90 day of gestation.

The **trophoblast** becomes differentiated in the early blastocyst stage. The trophoblast layer represents the precursor of the fetal components of the placenta.

As the trophoblast erodes the uterine epithelium and penetrates the underlying endometrial stroma, it differentiates into two distinct layers:

1 – cytotrophoblast – inner cellular layer;

2 - syncytiotrophoblast – outer syncytial layer.

These layers become progressively more extensively folded and are called **primarychorionicvilli.**

· The finger-like primary villi are surrounded on the outside by a *syncytiotrophoblast.*

· The inner cellular layer, with distinct cell boundaries, is called the *cytotrophoblast*, and it is this layer that forms the outer syncytial layer.

This differentiation occurs some 9-11 day following ovulation. The period from 9th to the 12th day is one of the intensive growth and differentiation of the chorion. Kuring this time the villi are established.

The *primary* ***villous stems*** increase in length and their cytotrophoblasic cores extend distally to the region of attachment of the syncytium to the endometrium.

Primary chorionic villi begin to *branch* shortly after they appear at the end of the second week.

Early in the third week, about day 16, **extraembryonic somaticmesoderm** grows into the primary villi, forming a central core of mesenchymal tissue (of loose connective tissue).

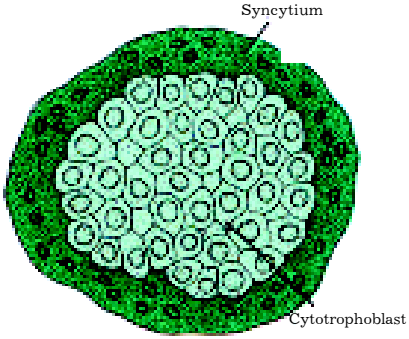


Fig. 58. **Schematic diagram of the transverse section of primary chorionic villus, showing a core of cytotrophoblastic cells covered by a layer of syncytium.**

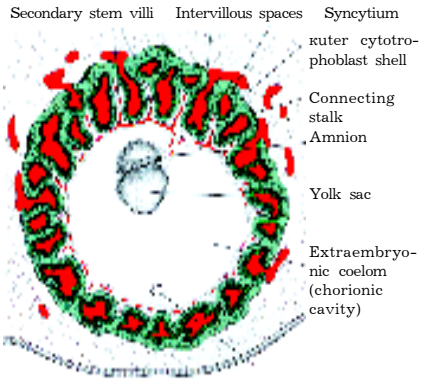


Fig. 59. **Diagram showing an embryo early at the end of the third week. The secondary villi give the trophoblast a characteristic radial appearance. The intervillous spaces are found throughout the trophoblast and are lined with syncytium. The embryo is suspended in the extraembryonic coelom by means of the connecting stalk.**

These villi are called **secondary chorionic villi** and cover the entire surface of the chorionic sac.

When the cytotrophoblast becomes lined with mesoderm the two layers together constitute **chorion**.

The peripheral part of the syncytium absorbs the destroying maternal tissues, extravasated blood and continues to invade the adjacent endometrium.

At the end of the third week the **blood vessels** develop in the cores of many *secondary chorionic villi*. Some mesenchymal cells in the villi differentiate into capillaries and blood cells.

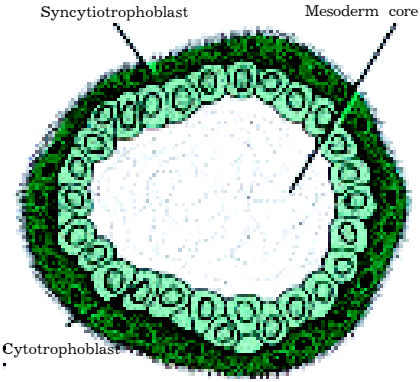


Fig. 60. **Schematic diagram of the transverse section of secondary chorionic villus with a core of mesoderm covered by single layer of cytotrophoblactic cells, which in turn is covered by syncytium.**

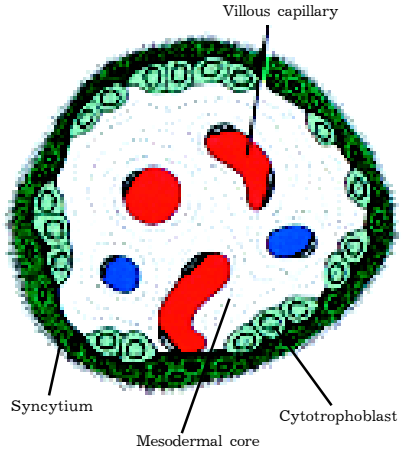
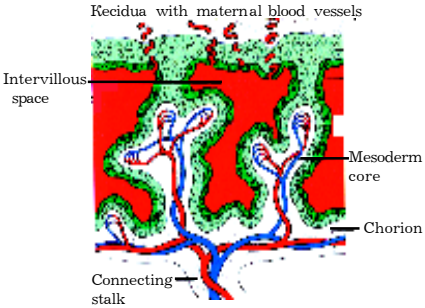


Fig. 61. **Shematic diagram of the transverse section of tertiary chorionic villus. The mesoderm contains a number of blood capillaries.**



1 – syncytium;
2 – syncytium covering the tertiary villi.

Fig. 62. **Schematic diagram of chorionic villi at the end of the third week of development. The capillaries in the villi are in contact with the vessels in the connecting stalk, which in turn are connected to the intra-embryonic vessels.**

When the **blood vessels** are visible in chorionic villi they are called **tertiary chorionic villi**.

The *capillaries in the chorionic villi* fuse to form arteriocapillary **networks**, which soon become connected with the blood vessels of embryo through vessels that differentiate in the mesoderm of the connecting stalk and allantois.

Thus the **arteriocapillary network** of villous stems, chorionic plate and connecting stalk give rise to the *extraembryonic vascular system.*

Blood begins to circulate through the primitive cardiovascular system and the villi **about 21 days**.

The *intervillous spaces* provide the site:

– exchange of nutrients,

– metabolic products and intermediates, and wastes between the maternal and fetal circulatory systems.

Summary

1). Primary villi contain two components:

i. a central cytotrophoblastic core;

ii. syncytiotrophoblast (syncytium) covers the cytotrophoblast, resting on it;

2). Secondary villi contain three components:

i. the central core is composed of extraembryonic somatic mesoderm (nonvascular mesoderm);

ii. the cytotrophoblast surrounds the mesodermal core;

iii. syncytiotrophoblast (syncytium) covers the outer surface of the villi;

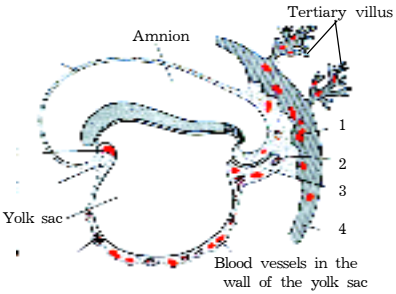


Fig. 63. **Shematic diagram of blood vessel formation in the chorion (with the formation of tertiary villi), the connecting stalk, and the wall of the yolk sac in a presomite embryo of approximately 19 days (modified from Keibel and Elze).**

Resignation:

1 – blood vessels in the chorionic plate; 2 – allantois; 3 – connecting stalk; 4 – chorionic plate.

3). Tertiary villi are composed of:

i. the central core is composed of vascular mesoderm (contains blood vessels;

ii. the cytotrophoblast surrounds the mesodermal core;

iii. the surface of the villi is formed by the syncytium.

Decidua

Decidua (L. *deciduus*, a falling off) refers to the *gravid endometrium* — the functional layer of the endometrium in a pregnant woman.

The term *decidua* is appropriate because this part of the endometrium separates ("falls away") from the remainder of the uterus after *parturition* (childbirth).

The *lytic activity* of the syncytiotrophoblast causes the **rupture** of maternal arterial and venous blood vessels in the edematous stroma of endometrium, especially at the implantation site.

The *endometrium* at the time of implantation is approximately **5-6 mm thick**. Its **glands** are actively secreting a mixture of mucopolysaccharides, glycogen, and lipids.

The **endometriumstroma** is edematous. The stroma cells are becoming transformed into **decidual cells**. These cells have polygonal shape and accumulate glycogen and lipid material.

The full significance of **decidualcells** is not understood, but it has also been suggested that they protect the maternal tissue against uncontrolled invasion by the syncytiotrophoblast, and that they may be involved in hormone production.

These changes of endometrium together constitute the so-called **decidualreaction**, which is at first confined to the area immediately adjacent to the implanting embryo but soon throughout the whole endometrium.

The uterine mucosa is highly modified in pregnancy, and is called the **decidua**.

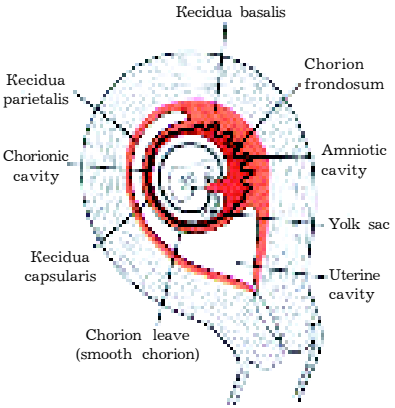


Fig. 64. **Relationoffetalmembranes to wall of the uterus. (end of the second month). The yolk sac in the chorionic cavity is between the amnion and chorion. At the smooth chorionvillihavedisappeared.**

After implantation of the blastocyst and **until the 4th month** of gestation three topographical **parts of the decidua** can be recognized:

– **decidua basalis** that is at the base of the placenta;

– **decidua capsularis** encapsulates the superficial chorionic sac;

– **deciduaparietalis** lines the rest of the uterus.

The **deciduabasalis** give rise to the ***maternal portion of the placenta.***

The maternal portion of the placenta develops from endometrium (maternal tissues).

KECIKUAL CELLS

The decidual cells are large polygonal-shaped cells that accumulate glycogen and lipid inclusions in lightly staining acidophilic cytoplasm.

Some of decidual cells are macrophages and have bone marrow origination. This group of decidual cells takes part in immune reactions.

After implantation decidual cells similar to connective tissue fibroblasts, but than ones increase in their size and store inclusions. The number of decidual cells gradually increases until 4-6 week of gestation.

Fig. 65. **A photograph of a section through a portion of the uterus to show the placenta and chorionic sac containing a 36 mm embryo. The basal plate separating the chorionic villi and the intervillous space from the decidua basalis appears as a thin band across the greater part of the attachment area. The decidua basalis is still distinct. The upper part of the decidua capsularis, together with the abembryonic portion of the chorion, is markedly attenuated. (Hamilton and Boyd by the courtesy of J. *Anat., Lond.*).**

Morphologically decidual cells are classified into the:

1) Large decidual cells;

2) Small decidual cells.

Functionally decidual cells are classified into the:

1) Macrophages.

2) Endocrine cells.

3) NK-cells (natural killer cells).

Main functions of decidual cells:

– protect the maternal tissue **against uncontrolled invasion** by the syncytiotrophoblast;

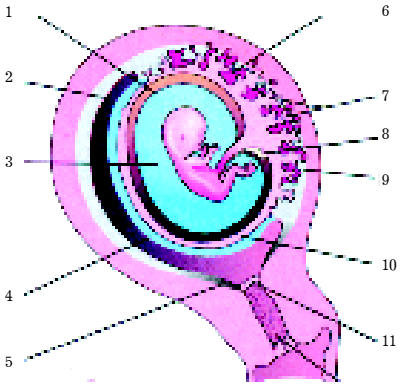
– take part in **fibrinoid formation;**

– **hormone production** (prostaglandins, progesterone-like hormone, cytokines);

– provide **immunosuppressive effect** against the maternal immune cells.

Further development of the chorionic villi and decidua

Through the *first 8 week* villi are found round the whole periphery of the chorionic sac and cover the entire chorionic surface. They are not uniformly developed round the conceptus.



Kesignation: 1 – amnion; 2 – uterine cavity; 3 – amniotic sac; 4 – decidua capsularis; 5 – decidua parietalis; 6 – intervillous space; 7 – villous chorion; 8 - yolk sac; 9 – decidua basalis; 10 – smooth chorion; 11 – internal os of uterus.

Fig. 66. **Fusiong of the amnion with inner surface of the chorion. The chorionic villi persist only where the chorion is associated with the deciduabasalis.**

The villi on the side of the chorion toward the decidua basalis *enlarge* and become branched, while those on the side toward the decidua capsularis *rapidly degenerate* between the 3rd and 4th month.

As fetus and the chorionic sac grow, the chorion expends and, with it now very thin covering of decidua capsularis, projects into the uterine cavity.

The *villi* associated with the *decidua capsularis* soon degenerate, producing a relatively avascular area, the **smoothchorion.**

The *villi* associated with *decidua parietalis* rapidly increase in number and enlarge. This part of the chorionic sac is called the **villous chorion** or **chorion frondosum**. The layer of the chorion, from which the villi are projected, is called the **chorionic plate**.

The ***chorion frondosum*** give rise to ***fetal portion of the placenta.***

The **fetalportion** of the placenta develops *from fetal tissues*.

So thus the placenta is a **fetomaternalorgan,**which contains**:**

– **maternal portion** of the placenta.

– **fetal portion** of the placenta.

The fetal portion of the placenta (**villouschorion**) is attached to the maternal portion of the placenta (**decidua basalis**) by the **syncytiotrophoblastic shell** — the external layer of trophoblastic cells on the maternal surface of the placenta.

The **chorionicvilli** attach firmly to the decidua basalis through the syncytotropho-blastic shell and anchor the **chorionic sac** to the decidua basalis.

Villi that attach to the maternal tissues through the cytotrophoblastic shell are **stem villi** (*anchoring villi*).

The villi that grow from the sides of the stem villi are **branch villi** (*terminal villi*).

At is through the walls of the **branch villi** that the main exchange of material between the blood of the mother and the embryo takes place.

The **branchvilli** are bathed in continually changing maternal blood in the intervillous space.

The **decidua capsularis** disappears by degeneration. The smooth chorion intimately related to the decidua parietalis.

· At **4,5 months** the **smoothchorion** consists of several layers of cytotrophoblastic cells only.

The surface *epithelium of the decidua parietalis* soon disappears and its stroma is intimately fused with cytotrophoblast of the smooth chorion.

· By the **fifth month**, the two layers fuse and the uterine lumen is obliterated.

· At this time the amnion is also fuses with the inside of the chorion.

The increased **thickness of the placenta** is due to growth in size and length of the villi of the chorion frondosum, and is not caused by further penetration into maternal tissues.

Until the end of the fourth month the normal placenta grows both in *thickness* and *circumference*.

After this period there is no increase in thickness but the placenta continues to *grow circumferentially* until near the end of pregnancy.

As the placenta continues to mature during the 4-5 months the number of **stem villi** increases. The villous trees grow into the intervillous blood lakes.

The **intervillous space,** containing maternal blood, gradually becomes subdivided by the formation of **septa**, which project

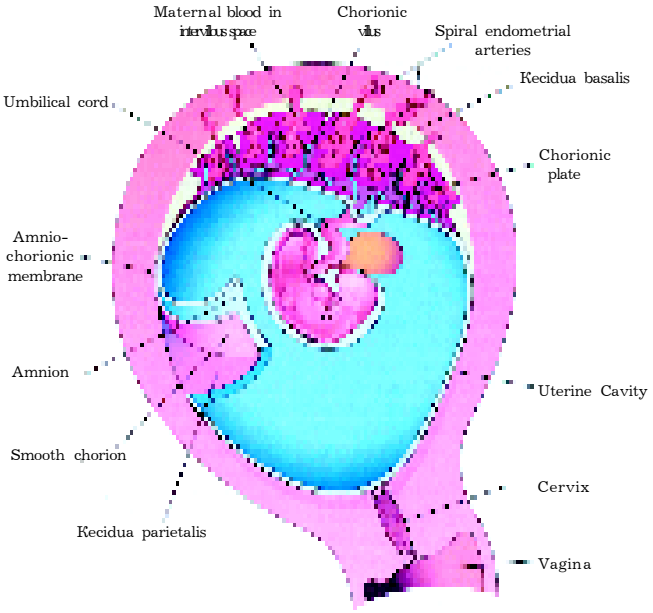


Fig. 67. **Fusion of smooth chorion the decidua parietalis.**

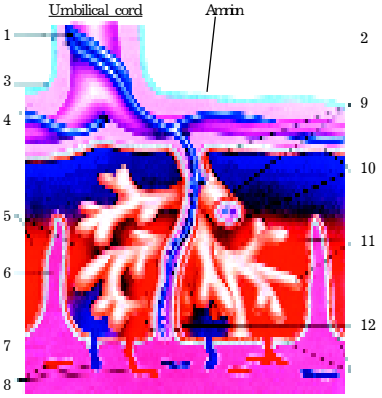


Fig. 68. **Schema of human placenta.** 1 – umbilical arteries; 2 – umbilical vein; 3 – amnion; 4 – chorion; 5 – cotyledons; 6 – septa; 7 – decidua basalis; 8 – maternal blood vessels; 9 – syncytium; 10 – cytotrophoblast; 11 – branch villi; 12 – stem villus.

from the basal plate of decidua basalis into the intervillous space.

The **septa** do not reach the chorionic plate. These septa have a core of maternal tissue.

The fetal portion of the placenta thus incompletely is divided into **cotyledons**. As the septa do not reach the chorionic plate there are *communications* between the intervillous spaces.

The fetal blood circulation is at all times separated from maternal circulation. Hence the human placenta is of the **hemochorial type.**

Cytotrophoblast and syncytiotrophoblastchanges

By the end of the second month ***cytotrophoblast*** becomes disappear. Kisappearance of the cytotrophoblastic cells progress from the smaller to larger villi.

From third month cytotrophoblast almost all disappears on the surface of the villi. The single cytotrophoblastic cells remain at the base of the stem villi until the end of the pregnancy.

The syncytiotrophoblast (***syncytium***) gradually replaces cytotrophoblast on the surface of the villi.

The syncytium is relatively thick during the first four months of gestation but gradually becomes thinner as pregnancy advances until it forms a thin membrane in the later months.

Electronmicrographs of syncytium show that its free surface has many microvilli – over 1 billion/cmI at term – that increase the surface area for exchange between the maternal and fetal blood.

Frequently the syncytium becomes very thin, and large pieces containing several nuclei may break off and drop into the intervillous blood lakes.

These pieces, known as **syncytialknots**, enter the maternal circulation and usually degenerate without causing any symptoms. Some knots lodge in capillaries of the maternal lung where they are rapidly destroy by local enzyme action.

Fibrinoid

From the second part of the gestation syncytium disappear over some areas of the villi. In the same time these areas are covered by ***fibrinoid.***

The **fibrinoid** *consists* of fibrin and other unidentified substances that stain intensely with eosin.

The *thickness* of the fibrinoid is about **0,1-2 mkm.**

It contains sulfated proteoglycans that have negative charge and push off maternal lymphocytes. So thus fibrinoid has immunomasking effect and prevents development of immune response into the paternal antigens, which present in fetal genome.

Some authors suppose that fibrinoid is destroying material of syncytium and decidual cells. It main function is to prevent the invasion of syncytium into the maternal organism.

Fulltermplacenta

The human placenta is classified as:

· **hemochorial** because of the nature of the placental membrane;

· **deciduate** because maternal decidua is shed at birth along with the fetal placenta;

· **villous** because of its villi

· **discoidal** because of its circular shape.

The fully developed placenta covers **15 to 30%** of the decidua and weighs about one-sixth that of the fetus.

At the full term the human placenta has the shape of a **flattened cake** (*plakuos=placenta=cake).*

It has a **diameter of 15-16 cm** (6-7 inches) and a thickness is about 3 cm.

Its weight is about **500-600 grams**. Kuring the second half of pregnancy placenta increases in weight much less rapidly than the fetus.

The **placenta** is a **fetomaternal organ,** which contains**:**

a. maternal portion

b. fetal portion

Fetalportionoftheplacenta

The fetal portion of the human placenta at full term contains:

– *about 15-20 large* cotyledons,

– about 40-50 *small* cotyledons,

– until 150 *rudimental* cotyledons.

Each **cotyledon** (*placental lobes*) consists of two or more main **stem villi** and many **branch villi** that are incompletelly separated by matenal septa.

The **sterm villi (**synonym – **anchoring villi)** give rise to numerous highly branched **terminal villi** (syn.: **branch** or **free villi**). The chorionic villi originate from the chorionic plate.

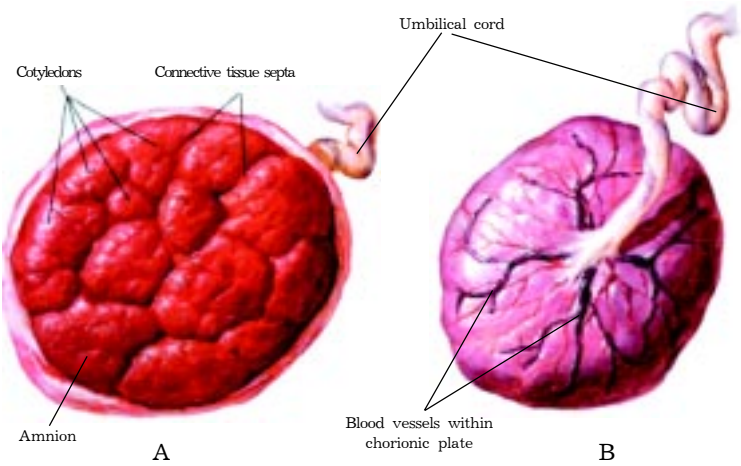


Fig. 69. **Photographoffullterm placenta: maternal aspect (A) and fetal aspect (B).**

The ***core of the villi*** is constituted by stroma of the connective tissue that contains:

1. fibroblasts, most of which convert into fibrocytes toward the end of pregnancy;

2. large phagocytic cells termed **Hofbauer cells** which are more numerous in early stage of gestation;

3. ground substance (intercellular matrix) contains:

a) mostly fine *reticular fibers* and only after third month of gestation small number of *collagen fibers* appears; These fibers are thicker and form bundles in the stem villi.

b) high level of *hyaluronic acid* and *chondroitin sulfate*, which increase viscosity of the ground substance;

c) From 7-8 week of the development content of hyaluronidase gradually increases. This enzyme depolymerizes hyaluronic acid and thus decreases viscosity of the stoma and provides metabolic exchanges with maternal blood.

4. the **blood vessels** that are branches of umbilical vessels and form extensive arterio-capillary-venous networks within the chorionic villi stroma.

As the **capillaries** in the stroma increase in size their walls eventually come into intimate relation with the syncytium.

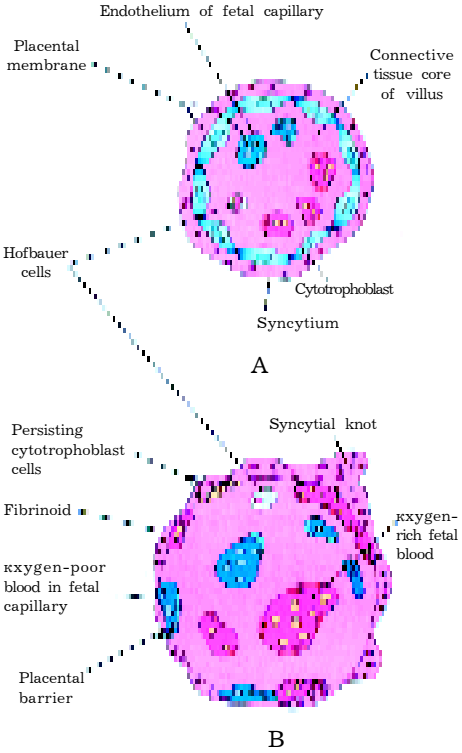


Fig. 70. **Shematic diagram of sections through a branch villus at 10 weeks (A) and full term (B). The placental barrier separates the maternal blood in the maternal lacunae from the fetal blood in the capillaries in the villi. At full term placental barrier becomes very thin. Hofbauer cells are phagocytic cells.**

The capillaries approach the surface of the villi but are always separated from the basement membrane of the trophoblast by some delicate connective tissue.

· **Basament membrane** separates connective tissue core and persisting cytotrophoblast cells that remain near the base of the stem villi

· Thin layer of **syncytium** covers the villi.

· **Fibrinoid** forms the outermost layer of the villi.

The chorionic plate is covered:

1) on its fetal aspect by the **amniotic epithelium**, followed by a *connective tissue* layer carring the main branches of the umbilical vessels. The connective tissue layer is derived from fusion between the mesoderma-covered surface of the amnion and chorion and is more fibrous.

2) on its maternal aspect a diminishing layer of *cytotrophoblast* with thin layer of *syncytium.*

Fetal portion changes at the end of pregnancy

At the end of pregnancy changes of fetal placenta include:

a. an increase in *fibrous tissue* in the core of the villi;

b. thickening of *basement membranes* in fetal capillaries;

c. obliterative changes in small *capillaries* of the villi;

d. deposition of *fibrinoid* on the surface of the villi in the junctional zone and in the chorionic plate.

Maternalportionoftheplacenta

The maternal portion of the placenta is derived from the endometrium.

At full term maternal portion of the human placenta contains:

- *basal plate*
- *septa*
- *lacunae (or intervillous spaces) with maternal blood*
- *junctional zone*

By the end of the **4th month** the decidua basalis is replaced by the fetal part of the placenta. The chorionic villi invade and erode the decidua basalis, thus **intervillousspaces** develop and enlarge.

The intervillous spaces or **lacunae** are filled with maternal blood.

The deepest part of the decidua basalis, which forms the floor of the lacunae, is called the **basalplate** (or**decidualplate**). It contains opening of the destroying maternal blood vessels.

The **Rohr's stria of fibrinoid** is amorphous extracellular material. It covers the surface of basal plate, and prevents development of immune response.

Between the intervillous spaces are located projections of decidua, which are called **placentalsepta.**

The placentalsepta project toward the **chorionic plate,** but **septa** do not reach the chorionic plate. The septa incompletely divide the fetal portion of the placenta into **cotyledons**. Therefore the intervillous spaces with the maternal blood are communicated.

The **junctionalzone**is located at the periphery of the placenta, near the boundary between the villous chorion and smooth chorion. The junctional zone is the zone of strong attachment of fetal and maternal portions of the placenta. The junctional zone prevents blood outpouring from the maternal lacunae.

The fetal portion of the placenta (**chorionic villi)** attaches firmly to the maternal portion of the placenta (basalis plate) through the cytotrophoblastic shell and anchor the **chorionic sac** to the decidua basalis.

Changes at the end of pregnancy

Throughout the second half of pregnancy the basal plate is thinned and becomes progressively modified. These changes include:

i. a relative diminution of the decidual elements; The *glands* disappear after 6th month in the deeper portion of the decidua basalis.

ii. an increasing deposition of fibrinoid;

iii. admixture of fetal and maternal derivatives.

Placentalbarrier
(*placental membrane*)

The **placentalbarrier** is called also the **placentalmembrane**.

The **placentalbarrier** separates maternal and fetal blood. It contains the extrafetal tissues separating the maternal and fetal blood.

The placental barrier is composed of four layers:

1. the *endothelium* lining the fetal vessels;
2. the *connective tissue* in the *villus core*;
3. the diminished *cytotrophoblastic layer,* which lies on the *trophoblast basement membrane*;
4. the *syncytium;*
5. the *fibrinoid.*

Eventually cytotrophoblast cells disappear over large areas of the villi leaving only thin patches of syncytium. As a result, the placental barrier consists of four layers (**1, 2, 4, 5**).

As pregnancy advances, the placental barrier **becomes progressively thinner** and fetal capillaries are located near the basement membrane of syncytium. So that blood in many fetal capillaries is extremely close to the maternal blood in the maternal lacunae.

The placental barrier is not a true barrier, since many substances pass through it freely.

Substances with a molecular weight of 600 to 1000 tend to easily cross the placental barrier.

Some metabolites, hormones, drugs, and toxins, through present in the maternal blood, do not pass through the placental barrier.

* *Hormones.*

1) Most maternal hormones do not cross the placenta. The hormones that do cross, such as **thyroxine**, do so only at a slow rate.

2) Testosterone and certain synthetic progestins rapidly cross the placenta and may cause masculinization of female fetuses in some cases.

3) Even more dangerous was the use of the synthetic **estrogen** diethylstilbestrol, which easily crosses the placenta. This compound produced carcinoma of the vagina and abnormalities of the testes in individuals who were exposed to it during their intrauterine life

**Infectious Agents.*

a) Viruses. Cytomegalovirus, rubella and coxsackie viruses, and viruses associated with variola, varicella, measles, and poliomyelitis may pass through the placental membrane and cause *fetal infection.* In some cases, such as the **rubella virus,** congenital anomalies, such as cataracts, may be produced.

b) Microorganisms. Microorganisms such as *Treponema pallidum* that causes syphilis and *Tbxoplasma gondii* that produces destructive changes in the brain and eyes cross the placental membrane. *Toxoplasma gondii* infect the placenta by creating lesions and then cross the placental membrane through the defects that are created.

These organisms enter the fetal blood, often causing congenital anomalies and/or death of the embryo or fetus.

** Krugs and Krug Metabolites.*

Most drugs and drug metabolites cross the placenta by simple diffusion.

1) Some drugs cause major congenital anomalies. **Fetal drug addiction** may occur after maternal use of drugs such as **heroin** and 50 to 75% of these newborns experience withdrawal symptoms.

Because psychic dependence on these drugs is not developed during the fetal period, no liability to subsequent

narcotic addiction exists in the infant after withdrawal is complete.

2) All **sedatives** and **analgesics** affect the fetus to some degree. Krugs taken by the mother can affect the embryo/fetus directly or indirectly by interfering with maternal or placental metabolism.

The amount of drug or metabolite reaching the placenta is controlled by the maternal blood level and blood flow through the placenta.

Substances that cross the placental barrier

Beneficia substances

Harmful substances

Kesignation: *Cross at a very low rate; most fetal serum pby the fetus

+In general, most drugs and their metabolites cross the placental membrane

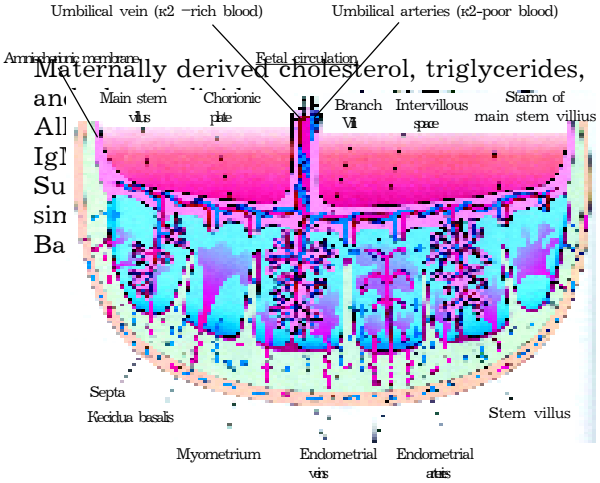
Substances that do not cross the placental barrier

Blood placental circulation

The blood placental circulation includes:

1) ***maternal placental circulation*** and

2) ***fetal placental circulation*** that are separated by **placental barrier** (or placental membrane) interposed between the fetal and maternal circulations.



Nutrients — Maternally derived cholesterol, triglycerides, an

Hormones — All

Immunoglobulins — Igl

Drugs — Su sin

Microorganisms — Ba

Fig. 71. **Schematic diagram of blood placental circulation.**

Maternalplacentalcirculation

The **maternal blood** enters the **lacunae** (intervillous spaces) through *80 to 100 spiral endometrial arteries* that pierce the basal plate of maternal portion of the placenta.

The openings of the **spiral arteries** are located at more or less regular intervals. The lumen of the spiral arteries is narrow, so *blood pressure* in the lacunae is high.

The blood flow from the spiral arteries is pulsatile and is propelled in jet-like fountains by the maternal blood pressure.

The entering blood is at a considerably **higher pressure** than that in the lacunae and spurts toward the chorionic plate forming the "roof" of the intervillous space.

As the pressure dissipates, the blood flows slowly over the branch villi. Through the placental barrier *exchanges of metabolic, waste products and gases* occur with the fetal blood as the maternal blood flows around the branch villi.

The blood eventually returns to the maternal circulation through the **endometrial veins**, which are scattered over the surface of the decidua basalis.

The maternal blood carries oxygen and nutritional substances that are nessesory for fetal growth and development.

The intervillous spaces (lacunae) of a mature placenta contain approximately **150 ml of blood**, which is replenished about *3 or 4 times per minute*. This blood moves along the chorionic villi, which have a surface area about 14 mI.

Fetal placental circulation

Poorly oxygenated fetal blood is carried to the placenta by two umbilical arteries leaves the fetus and passes through the paired **umbilical arteries** to the placenta.

As they pass into the placenta, umbilical arteries divide into several radially disposed **chorionic arteries** that branch freely in the chorionic plate before entering the chorionic villi.

The well-*oxygenated fetal blood* in the fetal capillaries passes into thin-walled veins that follow the chorionic arteries to the site of attachment of the umbilical cord.

They converge here to form the **umbilical vein**. This large vessel carries oxygen-rich blood to the fetus.

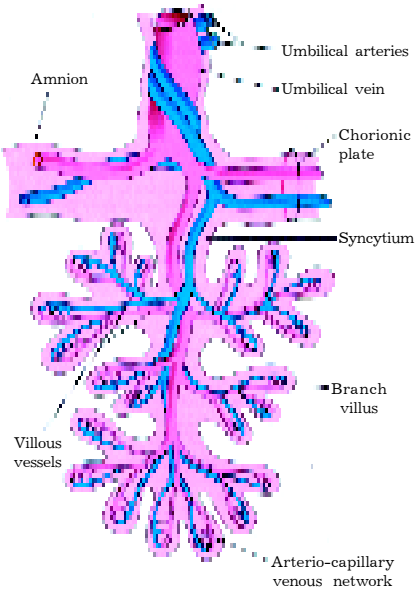


Fig. 72. **The schema of a stem chorionic villus showing its arteriocapillary-venous system. The arteries carry poorly oxygenated fetal blood and waste products from the fetus, whereas the vein carries oxygenated blood and nutrients to the fetus.**

Functions of the placents

Main functions of the placenta are:

- exchange of **nutrients** and **electrolytes;**
- exchange of **gases** (respiratory function);
- transmission of the **maternal antibodies**;
- exchange of **waste products**;
- **endocrine function** (hormone production;
- regulation of **myometrium contraction.**

The transport of different substances across the placental barrier occurs by several mechanisms:

simple diffusion
facilitated diffusion
active transport
pinocytosis

Normally, carbon dioxide, metabolic waste products, water, hormones are transferred from the fetal blood to maternal blood.

κxygen, nutrients, vitamins, some maternal antibodies, hormones, metabolites, water pass in the opposite direction.

Exchangeofnutrientsandelectrolytes

Exchange of nutrients and electrolytes is rapid and increases as pregnancy advances.

The placenta, especially during early pregnancy, **synthesizes glycogen, cholesterol,** and **fatty acids**, which serve as sources of nutrients and energy for the embryo/fetus. The fetal portion of the placenta is the site of synthesis and storage

Amino acids are actively transported and are essential for fetal growth. The concentration of most amino acids is higher in fetal plasma than ones in maternal blood.

Glucose is quickly transferred to the embryo/fetus by diffusion from maternal blood.

Vitamins cross the placental membrane and are essential for normal development. Water soluble vitamins cross the placental membrane more quickly than fat-soluble ones.

The transport of maternal **lipid substances** (cholesterol, triglycerides, phospholipids, and fatty acids) is relatively small or no.

Electrolytes are freely exchanged. **Water** is rapidly exchanged by simple diffusion.

Exchangeofgases

The respiratory function of the placenta approaches to one of adult respiratory system.

κxygen, **carbon dioxide**, and **carbon monoxide** cross the placental membrane by simple diffusion.

The **oxygen** that is joined to the hemoglobin in maternal blood crosses the placental barrier by diffusion. Than in fetal

blood oxygen binds to fetal hemoglobin and is carried to the embryo/fetus with the fetal blood (umbilical vein).

The umbilical arteries contain poorly oxygenated fetal blood with higher concentration of **carbon dioxide** than highly oxygenated maternal blood in maternal lacunae.

The **carbondioxide**crosses the placental barrier by diffusion from fetal blood to maternal blood (lacunae) and carries to maternal organism.

The exchange of oxygen and carbon dioxide *is limited* more by *blood flow* than by the efficiency of diffusion.

At full term placenta the fetus extracts **20to30mlofoxygen per minute** from maternal blood and even a short-term interruption of the oxygen supply is fatal to the fetus.

Transmissionofthematernalantibodies

Fetus immunological competence begins to develop late in the first trimester of pregnancy.

The fetus produces only small amounts of antibodies because of its immature immune system.

The passage of maternal antibodies across the placental barrier confers some degree of **passive immunity on the fetus**.

Maternal antibodies, **immunoglobu-linsG** (**IgG**) begin to be transported from the mother to fetus at approximately 14 week by pinocytosis.

Maternal antibodies provide passive immunity against a variety of infectious agents such as *diphtheria, smallpox, and measles.*

Newborns begin to produce their own IgG, but adult levels are not attained until the age of 3 years.

Transmissionofthewasteproducts

Fetal urea and uric acid pass through the placental barrier by simple diffusion.

Endocrinefunction

The syncytium is site of the placenta synthesizing of *protein* and *steroid* hormones.

The **protein** hormones are:

: human **chorionicgonadotropin** (hCG)

: human **chorionic somatomammotropin** (hCS), or human placental **lactogen** (hPL)

: human chorionic **thyrotropin** (hCT)

: human chorionic **corticotropin** (hCACTH)

The **steroid** hormones are:

: **estrogens** (predominantly estriol);

: **progesterone.**

From the 4th month placenta is the major site of synthesis of several hormones, which regulate fetal growth and development.

Human **chorionic gonadotropin** is first secreted by the syncytium during the second week. Kuring the first two months of pregnancy, the syncytium produces human **chorionic gonadotropin** (hCG), which maintains the corpus luteum. This hormone is excreted by the mother in the urine, and in the early stages of gestation, its presence is used as an **indicator of pregnancy**.

By the end of the 4th month the placenta produces **progesterone** in sufficient amounts to maintain pregnancy if the ovarian corpus luteum is removed or fails to function properly.

Progesterone can be obtained from the placenta at all stages of gestation, indicating that it is essential for the maintenance of pregnancy. The placenta forms progesterone from maternal cholesterol or pregnenolone.

The placenta produces increasing amounts of **estrogens** until just before the end of pregnancy, when a maximum level is reached. These high levels of estrogens stimulate uterine growth and development of the mammary glands.

Placental lactogen is a growth hormone-like substance that gives the fetus priority on maternal blood glucose.

Regulationofmyometriumcontraction

The *fetal hypothalamus* initiates the birth process.

Several hormones trigger the initiation of uterine contractions during the childbirth.

There are: – oxytocin
– prostaglandins
– estrogens
– cortisol

The fetal hypothalamus secretes *corticotropin-releasing hormone* (CRH), which stimulates the anterior hypophysis to produce **adrenocorticotropin**(ACTH). ACTH causes the secretion of cortisol from the suprarenal cortex. Cortisol is involved in the synthesis of **estrogens**. These steroids stimulate uterine contraction.

Peristaltic contractions of uterine smooth muscle are elicited by **oxytocin,**which is released by the posterior hypophysis. This hormone is administered clinically when it is necessary to induce labor. кxytocin also stimulates release of **prostaglandins** from the decidua that stimulates myometrial contractility.

Estrogens also increase myometrial contractile activity and stimulate the release of *oxytocin* and *prostaglandins.*

Immunologicalinterrelations:Maternal-fetal organisms

Fetal organism contains 50% of the foreign antigens for the maternal organism.

Fetal portion of the placenta contains **maternal** and **paternal antigens**, but normally rejection of fetus by the mother's immune system doesn't occur.

Protective mechanisms include:

A. Factors produced by placenta;
B. Factors produced by maternal organism;
C. Factors synthesized by embryo and fetus.

Factors produced by placenta;

Syncytium produces several factors that block immune reactions between fetal tissues of placenta and maternal tissues.

1. Fibrinoid has immunomasking effect and prevents development of immune response into the paternal antigens, which present in fetal genome.

Fibrinoid contains sulfated proteoglycans and sialomucinogens that have *negative charge* and push off maternal lymphocytes.

2. *Syncytium* synthesizes **proteins** which block maternal immune system (for example, **transferrin**).

3. *Syncytium* **looses** ability to synthesis **immunogenicantigens.** Syncytium does not contain **HLA-G** antigens. Expression of **HLA-G** is restricted to a few tissues including placental syncytium cells.

Its strategic location in the placenta is believed to provide a dual immunoprotective role:

1) evasion of T cell recognition owing to its nonpolymorphic nature, and

2) recognition by the "killer-inhibitory receptors" on NK cells, thus turning off their killer function.

4. *Syncytium* produces and maintains high concentration of **hormones** that have immunosuppressive effect (chorionic gonadotropin, progesterone, estrogen, and cortisol-binding globulin).

5. *Syncytium* synthesis **lysine** that destroys T-lymphocytes and NK-cells (natural killer cells) of maternal organism.

6. Maternal portion of the placenta contains decidual cells, some of which synthesis **proteins** with immunosuppressive effect.

Factors produced by maternal organism.

1. The endocrine system of maternal organism (suprarenal glands) produces **glucocorticoids,** which have immunosuppressive effect.

2. Through 6-72 h after fertilization maternal blood contains **factor of early pregnancy**. This earliest factor has immunosuppressive effect.

3. Maternal lymph nodes actively produce T-suppressor lymphocytes, which modulate immunosuppressive effect.

4. Immunoprotection is provided locally by certain immunosuppressor molecules, e.g., **prostaglandin** E_2, **transforming growth factor** and **interleukin** (IL-10). Kecidua-derived prostaglandins block activation of maternal T cells, as well as NK cells in situ.

Factors produced by embryo and fetus:

1. T—suppressor lymphocytes;

2. Lymphokines;

3. Alpha-fetoproteins;

4. Amniotic fluid accumulates immunosuppressive factors.

5. Zona pellucida has the same antigenic content as the maternal organism, and so thus zona pellucida prevents penetration of maternal lymphocytes toward the conceptus.

However it was shown that zona pelucida contains some antigens, which maternal organism designates as foreign antigens.

The blood of sterility women often contains antibodies to ZP.

CLINICAL CκNSIKERATIκNS

1. Abnormal placental shapes

1). **Velamentous placenta**

-is a placenta in which the umbilical vessels abnormally travel through the amniochorionic membrane before reaching the placenta proper.

If the umbilical vessels cross the internal os, a serious condition called **vasa previa** exists. In vasa previa, if one of the umbilical vessels ruptures during pregnancy, labor, or delivery, the fetus will bleed to death.

2). **Bipartite or tripartite placenta**

-is a placenta made up of two or three connected lobes.

3). **Kuplex or triplex placenta**

-is a placenta made up of two or three separate lobes.

4). **Succenturiate placenta**

—is a placenta consisting of small accessory lobes completely separate from the main placenta. -Care must be taken to assure that the accessory lobes are eliminated in the afterbirth.

5). **Membranous placenta**

-is a **thin placenta** that forms over the greater part of the uterine cavity. Care must be taken to assure that the entire placenta is eliminated during the afterbirth; may require curettage.

2. Placenta previa

-occurs when the placenta attaches in the lower part of the uterus, covering the internal os. (The placenta normally implants in the posterior superior wall of the uterus.)

Uterine vessels rupture during the later part of pregnancy as the uterus begins to gradually dilate.

The mother may bleed to death, and the fetus will also be placed in jeopardy because of the compromised blood supply.

Because the placenta blocks the cervical opening, delivery is usually accomplished by cesarean section.

Placenta previa is clinically associated with repeated episodes of **bright red vaginal bleeding.**

3. Placental abruption

-occurs when a normally implanted placenta prematurely separates from the uterus before delivery of the fetus.

Placental abruption is associated with **maternal hypertension.**

4. Erythroblastosis fetalis

-occurs when **Rh-positive fetal red blood cells** (RBCs) cross the placental membrane into the maternal circulation of an Rh-negative mother; the mother forms anti-Rh antibodies that cross the placental membrane and destroy fetal RBCs.

Destruction of fetal RBCs releases large amounts of bilirubin, leading to cerebral damage and sometimes death of the fetus.

5. Choriocarcinoma

-is a malignant tumor of the trophoblast.

Choriocarcinoma presents clinically as repeated **uterine bleeding.**

Choriocarcinoma may occur following a **normal pregnancy, abortion, or hydatidiform mole.**

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Навчальне видання

Кашуріна Н.К.
ВолковК.С.

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