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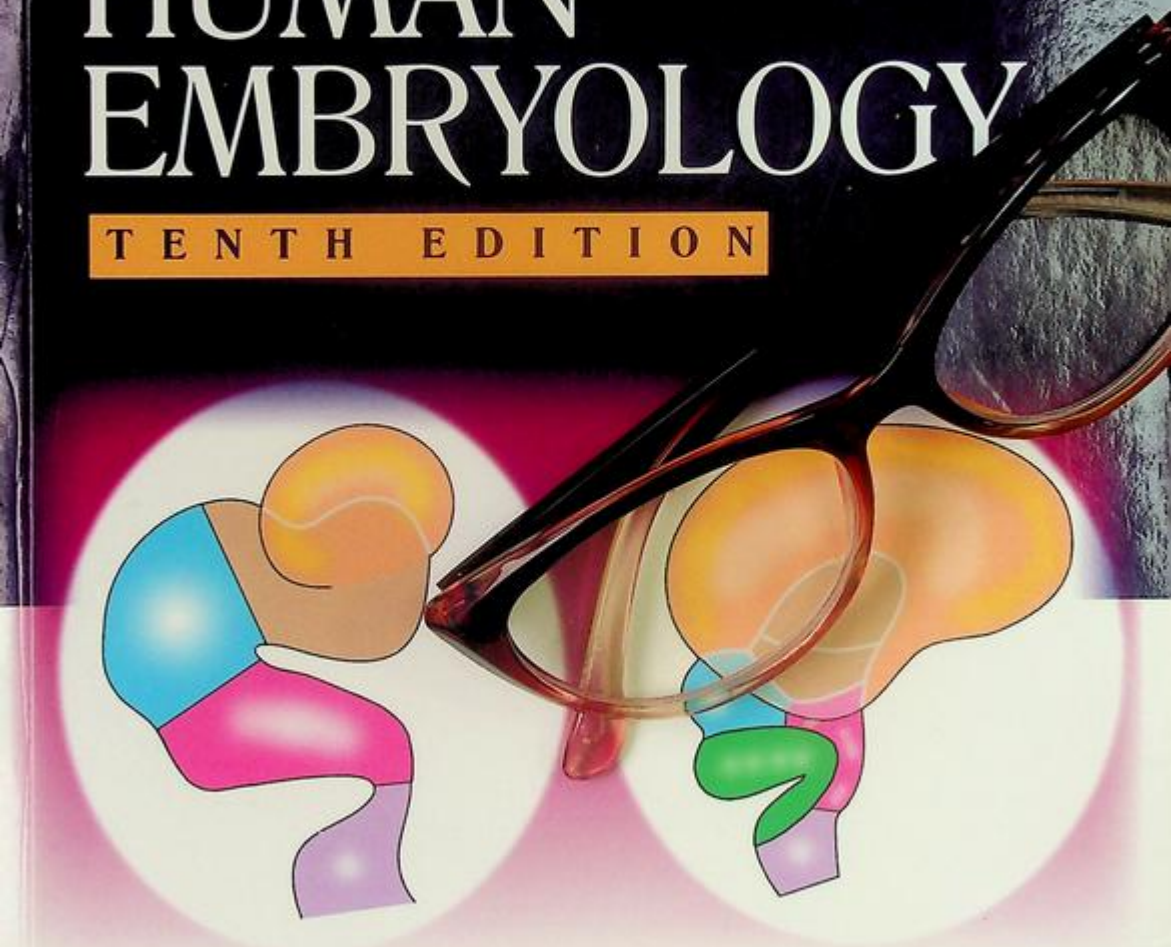

Inderbir Singh

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Preface to the Tenth Edition

The publication of the tenth edition of this book takes place at a historic juncture.

The book, first published in 1976, went through nine editions under the patronage of "MACMILLAN" (under different names). For reasons best known to them this publisher decided to stop publication of the book in 2013. I am grateful to them for giving this book the status of a classic of medical publishing in India.

Through an agreement between Macmillan Publishers India Ltd and Jaypee Brothers, Medical Publishers Pvt. Ltd, the book has been taken over by the latter. That is how it happens that the tenth edition of the book appears under the banner of JAYPEE BROTHERS, Medical Publishers Pvt. Ltd.

The change of publisher does not mean any dilution of the standards either of content or of production values. I am sure that the enthusiasm and drive of the new publisher will carry the book to much greater heights than before, and that the book will remain a household word for generations to come.

Because of my long association with Mr. J.P. Vij (Group Chairman), I have full confidence in him. Mr. Ankit Vij (Managing Director) brings fresh ideas and a great deal of vigour and enthusiasm to the venture. I am grateful to them for all their help and support. I am much obliged to Dr Sakshi Arora (Chief Development Editor) for highly meticulous editing of the text and for improving the book in various other ways.

Dr. G.P. Pal has been associated with the book for a few editions till the ninth. He has made useful contributions and brought new vigour to the book and I thank him.

I am grateful to the very large body of teachers and students who have given me invaluable moral support and encouragement. This book could not have been what it is without their blessings.

I must end this preface on a personal note. I will soon enter my eighty fifth year and I certainly do not hope to produce another edition of any book. My overall experience of many years of book writing has been one of great satisfaction and happiness. The happiness has come from the respect, bordering on devotion, that students have showered on me. I look on them as a very big family of children and grand children. My blessings to each one of them.

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INDERBIR SINGH

Preface to the First Edition

This book on human embryology has been written keeping in mind the requirements of undergraduate medical students. The subject of embryology has traditionally been studied from imported textbooks of anatomy or of embryology. Experience has shown that the treatment of the subject in most of these books is way above the head of the average medical student in India. The difficulty has increased from year to year as there has been, and continues to be, progressive deterioration in the standards of the teaching of English in our schools and colleges. The combination of unfamiliar sophistications of language and of an involved technical subject, has very often left the student bewildered.

In this book care has been taken to ensure that the text provides all the information necessary for an intelligent understanding of the essential features of the development of various organs and tissues of the human body. At the same time, several innovations have been used to make the subject easy to understand.

Firstly, the language has been kept simple. Care has been taken not to compress too many facts into an involved sentence. New words are clearly explained.

Secondly, simultaneous references to the development of more than one structure have been avoided as far as possible. While this has necessitated some repetition, it is hoped that this has removed one of the greatest factors leading to confusion in the study of this subject.

Thirdly, almost every step in development has been shown in a simple, easy to understand, illustration. To avoid confusion, only structures relevant to the discussion are shown. As far as possible, the drawings have been oriented as in adult anatomy to facilitate comprehension.

Fourthly, the chapters have been arranged so that all structures referred to at a particular stage have already been adequately introduced.

In an effort of this kind it is inevitable that some errors of omission, and of commission, are liable to creep in. To obviate as many of these as possible a number of eminent anatomists were requested to read through the text. Their suggestions have greatly added to the accuracy and usefulness of this book. Nevertheless, scope for further improvement remains, and the author would welcome suggestions to this end both from teachers and from students.

Rohtak
January 1976

INDERBIR SINGH

Contents

Chapter 1

Some Preliminary Considerations

HIGHLIGHTS

- Embryology is the study of the development of an individual before birth.
- During the first two months we call the developing individual an ***embryo***. After that we call it a ***fetus***.
- The ***testis*** is the male sex organ or male gonad. The ***ovary*** is the female sex organ or gonad. They produce ***gametes***.
- Male gametes produced by the testis are called ***spermatozoa***. The process is called ***spermatogenesis***.
- Female gametes produced by the ovary are called ***ova***. The process is called ***oogenesis***. Spermatogenesis and oogenesis are together called ***gametogenesis***.
- ***Fertilization*** takes place when one spermatozoon enters an ovum. The fused ovum and sperm form the ***zygote***.
- Characters of parents are transmitted to offspring through codes borne on strands of DNA. ***Genes*** are made of such strands of DNA. They are located on ***chromosomes***.
- A typical cell contains 46 chromosomes (= ***diploid number***).
- A gamete contains 23 chromosomes (= ***haploid number***).
- The diploid number of chromosomes is restored as a result of fertilization.
- Multiplication of cells takes place by cell division. The usual method of cell division, seen in most tissues, is called ***mitosis.*** Daughter cells resulting from a mitotic division are similar to the parent cell, and have the same number of chromosomes (46).
- A special kind of cell division takes place in the testis and ovary for formation of gametes. It is called ***meiosis***. The gametes resulting from meiosis have the haploid number of chromosomes (23). The various gametes formed do not have the same genetic content.

WHAT IS EMBRYOLOGY?

Every individual spends the first nine months (266 days or 38 weeks to be exact) of its life within the womb (uterus) of its mother. During this period, it develops from a small one-celled structure to an organism having billions of cells. Numerous tissues and organs are formed and come to function in perfect harmony. The most spectacular of these changes occur in the first two months; the unborn baby acquires its main organs and just begins to be recognizable as human. During these two months, we call the developing individual an ***embryo***. From the third month until birth we call it a ***fetus***.

Embryology is the study of the formation and development of the embryo (or fetus) from the moment of its inception up to the time when it is born as an infant.

Human development is a continuous process that does not stop at birth. It continues after birth for increase in the size of the body, eruption of teeth, etc. Development before birth is called ***prenatal development***, and that after birth is called ***postnatal development.*** In this book, we will study prenatal development only.

Why a Medical Student Should Study Embryology

- This subject tells us how a single cell (the fertilized ovum) develops into a newborn, containing numerous tissues and organs.
- This knowledge helps us to understand many complicated facts of adult anatomy.
- Embryology helps us understand why some children are born with organs that are abnormal. Appreciation of the factors responsible for maldevelopment assists us in preventing, or treating, such abnormalities.
- Cells forming tissues in the embryo are called ***stem cells***. These cells are capable of treating certain diseases in postnatal life.

GONADS AND GAMETES

The cells that carry out the special function of reproduction are called ***gametes***. The development of a new individual begins at the movement when one male ***gamete*** (***sperm*** or ***spermatozoon***) meets and fuses with one female gamete (***ovum*** or ***oocyte***). The process of fusion of male and female gametes is called ***fertilization.*** The fused ovum and spermatozoon form the ***zygote***. The zygote later develops into an embryo and then into a fetus.

The male sex cells (spermatozoa) are produced in the male ***gonads*** (testes) while the female sex cells (ova) are produced in female gonads (ovaries). The formation of spermatozoa in testis is called ***spermatogenesis***, while the formation of ova in the ovary is called ***oogenesis***. The two are collectively referred to as ***gametogenesis***.

To understand the structure of the gametes and to study how they are formed, it is necessary to first review some facts regarding chromosomes and cell division.

SOME FACTS ABOUT CHROMOSOMES

Haploid and Diploid Chromosomes

The number of chromosomes in each cell is fixed for a given species and in human beings, it is forty-six. This is referred to as the ***diploid*** (or double) number. However, in spermatozoa and ova, the number of chromosomes is only half the diploid number, i.e., twenty-three. This is called the ***haploid*** (or half) number. After fertilization, the resulting zygote has 23 chromosomes from the sperm (or father), and 23 from the ovum (or mother). The diploid number is thus restored.

Autosomes and Sex Chromosomes

The forty-six chromosomes in each cell can be divided into forty-four ***autosomes*** and two ***sex chromosomes***. The sex chromosomes may be of two kinds, X or Y. In a man, there are forty-four autosomes, one X-chromosome and one Y-chromosome; while in a woman, there are forty-four autosomes and two X-chromosomes in each cell (Fig. 1.1). When we study the forty-four autosomes, we find that they really consist of twenty-two pairs, the two chromosomes forming a pair being exactly alike (***homologous chromosomes***). In a woman, the two X-chromosomes form another such pair; in a man this pair is represented by one X- and one Y-chromosome. One chromosome of each pair is derived from the mother and the other from the father.

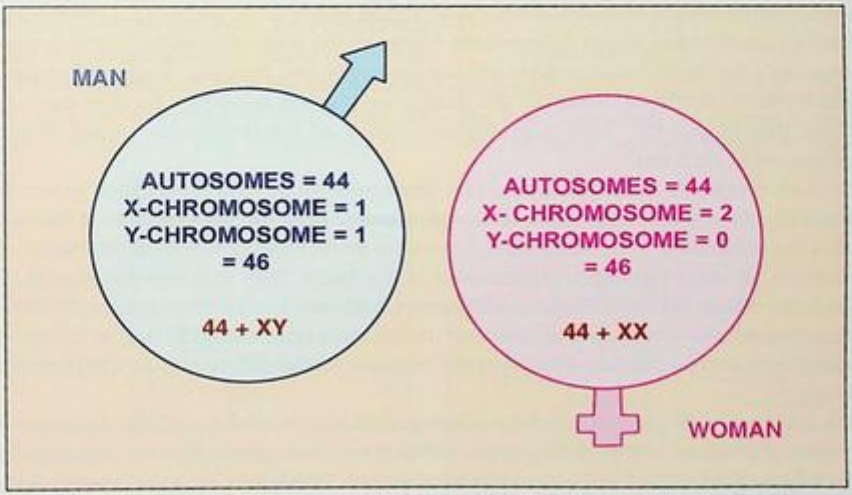

Fig. 1.1: Number of chromosomes in the somatic cells of a man and of a woman.

Chromosome Structure

In a resting cell, chromosomes are not visible under a light microscope, as their chromatin material is highly dispersed. However, during cell division, the chromatin network in the nucleus becomes condensed into a number of chromosomes. The appearance of a typical chromosome is illustrated in Fig. 1.2. It is made up of two rod shaped structures or ***chromatids*** placed more or less parallel to each other. The chromatids are united to each other at a light staining area called the ***centromere*** (or ***kinetochore***). Each chromatid has two arms, one on either side of the centromere. Individual chromosomes differ from one another in total length, in the relative length of the two arms and in various other characteristics; these differences enable us to identify each chromosome individually. Classification of chromosomes in this way is called ***karyotyping***. Karyotyping makes it possible for us to detect abnormalities in chromosome number or in individual chromosomes.

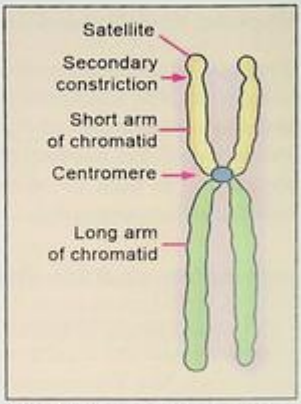

Fig. 1.2: Diagram to show the parts of a typical chromosome.

Significance of Chromosomes

The entire human body develops from the fertilized ovum. It is, therefore, obvious that the fertilized ovum contains all the information necessary for formation of the numerous tissues and organs of the body, and for their orderly assembly and function. Each cell of the body inherits from the fertilized ovum, all the directions that are necessary for it to carry out its functions throughout life. This tremendous volume of information is stored within the chromosomes of each cell.

Each chromosome bears on itself a very large number of structures called ***genes***. Genes are made up of a nucleic acid called ***deoxyribonucleic acid*** (or ***DNA***) and all information is stored in the molecules of this substance. Genes are involved in synthesis of proteins.

Proteins are most important constituents of our body. They make up the greater part of each cell and of intercellular substances. Enzymes, hormones and antibodies are also proteins. The nature and functions of a cell depend on the proteins synthesized by it. It is, therefore, not surprising that one cell differs from another because of the differences in the proteins that constitute it.

We now know that genes control the development and functioning of cells, by determining what types of proteins will be synthesized within them. Thus genes play an important role in the development of tissues and organs of an individual. Traits (characters) of an individual are determined by genes carried on his (or her) chromosomes. As we have seen half of these are inherited from the father and half from mother.

We have seen above that chromosomes are made up predominantly of a nucleic acid called ***deoxyribonucleic acid*** (or ***DNA***), and all information is stored in molecules of this substance.

When the need arises, this information is used to direct the activities of the cell by synthesizing appropriate proteins. To understand how this becomes possible, we must consider the structure of DNA in some detail.

Basic Structure of DNA

DNA in a chromosome is in the form of very fine fibres. Each fibre consists of two strands that are twisted spirally to form what is called a ***double helix***. The two strands are linked to each other at regular intervals.

Each strand of the DNA fibre consists of a chain of ***nucleotides***. Each nucleotide consists of a sugar, deoxyribose, a molecule of phosphate and a base (Fig. 1.3). The phosphate of one nucleotide is linked to the sugar of the next nucleotide (Fig. 1.4). The base that is attached to the sugar molecule may be ***adenine, guanine, cytosine*** or ***thymine***. The two strands of a DNA fibre are joined together by the linkage of a base on one strand with a base on the opposite strand (Fig. 1.5).

This linkage is peculiar in that adenine on one strand is always linked to thymine on the other strand, while cytosine is always linked to guanine. Thus, the two strands are complementary and the arrangement of bases on one strand can be predicted from the other.

The order in which these four bases are arranged along the length of a strand of DNA determines the nature of the protein that can be synthesized under its influence. Every protein is made up of a series of amino acids; the nature of the protein depending upon the amino acids present, and the sequence in which they are arranged. Amino acids may be obtained from

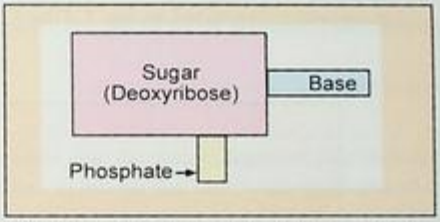

Fig. 1.3: Composition of a nucleotide. The base may be adenine, cytosine, guanine or thymine.

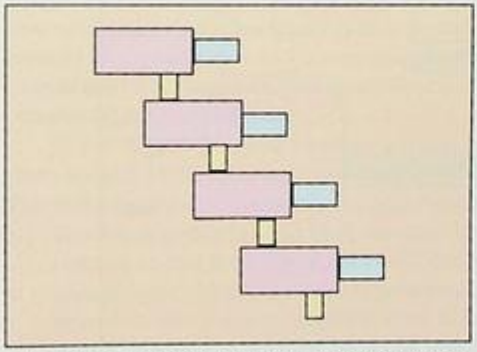

Fig. 1.4: Linkage of nucleotides to form one strand of a DNA molecule.

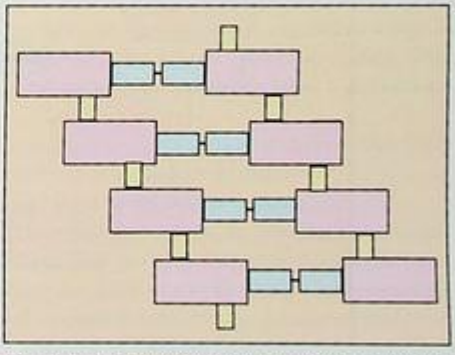

Fig. 1.5: Linkage of two chains of nucleotides to form part of a DNA molecule.

food or may be synthesized within the cell. Under the influence of DNA, these amino acids are linked together in a particular sequence to form proteins.

Further Details of DNA Structure

In the preceding paragraphs the structure of DNA has been described in the simplest possible terms. We will now consider some details.

- The structure of the sugar deoxyribose is shown in Fig. 1.6. Note that there are five carbon atoms and also note how they are numbered.
- Next observe, in Fig. 1.7, that C-3 of one sugar molecule is linked to C-5 of the next molecule through a phosphate linkage (P). It follows that each strand of DNA has a 5' end and a 3' end.
- Next observe that although the two chains forming DNA are similar, they are arranged in opposite directions. In Fig. 1.7 the 5' end of

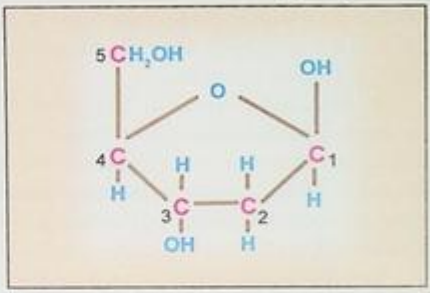

Fig. 1.6: Diagram to show the structure of deoxyribose. Note the numbering of carbon atoms.

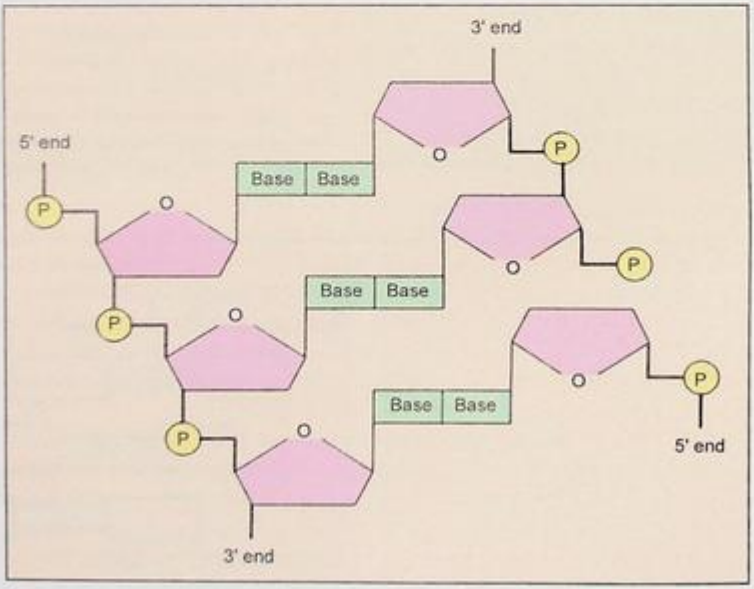

Fig. 1.7: Diagram to show how nucleotides are linked to form a chain of DNA. The asymmetric placing of bonds gives a helical shape to the chain.

the left chain, and the 3' end of the right chain lie at the upper end of the figure. The two chains of nucleotides are, therefore, said to be ***antiparallel***.

- The C-1 carbon of deoxyribose gives attachment to a base. This base is attached to a base of the opposite chain as already described.
- The reason why adenine on one strand is always linked to thymine on the other strand is that the structure of these two molecules is complementary and hydrogen bonds are easily formed between them. The same is true for cytosine and guanine.

Ribonucleic Acid (RNA)

In addition to DNA, cells contain another important nucleic acid called ***ribonucleic acid*** or ***RNA***. The structure of a molecule of RNA corresponds fairly closely to that of one strand of a DNA molecule, with the following important differences.

- RNA contains the sugar ribose instead of deoxyribose.
- Instead of the base thymine, it contains uracil.

RNA is present both in the nucleus and in the cytoplasm of a cell. It is present in three main forms, namely ***messenger RNA*** (***mRNA***), ***transfer RNA*** (***tRNA***) and ***ribosomal RNA***. Messenger RNA acts as an intermediary between the DNA of the chromosome and the amino acids present in the cytoplasm and plays a vital role in the synthesis of proteins from amino acids.

Synthesis of Protein

We have seen that a protein is made up of amino acids that are linked together in a definite sequence. This sequence is determined by the order in which the bases are arranged in a strand of DNA. Each amino acid is represented in the DNA molecule by a sequence of three bases (***triplet code***). It has been mentioned earlier that there are four bases in all in DNA, namely adenine, cytosine, thymine and guanine. These are like letters in a word. They can be arranged in various combinations so that as many as sixty four code 'words' can be formed from these four bases. There are only about twenty amino acids that have to be coded for so that each amino acid has more than one code. The code for a complete polypeptide chain is formed when the codes for its constituent amino acids are arranged in proper sequence. That part of the DNA molecule that bears the code for a complete polypeptide chain constitutes a ***structural gene*** or ***cistron***.

At this stage, it must be emphasized that a chromosome is very long and thread-like. Only short lengths of the fibre are involved in protein synthesis at a particular time.

The main steps in the synthesis of a protein may now be summarized as follows.

- The two strands of a DNA fibre separate from each other (over the area bearing a particular cistron) so that the ends of the bases that were linked to the opposite strand are now free.
- A molecule of messenger RNA is synthesized using one DNA strand as a guide (or ***template***), in such a way that one guanine base is formed opposite each cytosine base of the DNA strand, cytosine is formed opposite guanine, adenine is formed opposite thymine, and uracil is formed opposite adenine. In this way, the code for the sequence in which amino

acids are to be linked is passed on from DNA of the chromosome to messenger RNA. This process is called ***transcription***. That part of the messenger RNA strand that bears the code for one amino acid is called a ***codon***.

- This molecule of messenger RNA now separates from the DNA strand and moves from the nucleus to the cytoplasm (passing through a nuclear pore).
- In the cytoplasm, the messenger RNA becomes attached to a ribosome.
- As mentioned earlier, the cytoplasm also contains another form of RNA called transfer RNA. In fact, there are about twenty different types of transfer RNA each corresponding to one amino acid. On one side, transfer RNA becomes attached to an amino acid. On the other side, it bears a code of three bases (***anticodon***) that are complementary to the bases coding for its amino acid on messenger RNA. Under the influence of the ribosome several units of transfer RNA, along with their amino acids, become arranged along side the strand of messenger RNA in the sequence determined by the code on messenger RNA. This process is called ***translation***.
- The amino acids now become linked to each other to form a polypeptide chain. From the above, it will be clear that the amino acids are linked up exactly in the order in which their codes are arranged on messenger RNA, which in turn, is based on the code on the DNA molecule (but also see below). Chains of amino acids formed in this way constitute polypeptide chains. Proteins are formed by union of polypeptide chains.

The flow of information from DNA to RNA and finally to protein has been described as the "central dogma of molecular biology".

Duplication of Chromosomes

One of the most remarkable properties of chromosomes is that they are able to duplicate themselves. From the foregoing discussion on the structure of chromosomes it is clear that duplication of chromosomes, involves the duplication (or replication) of DNA. This takes place as follows (Fig. 1.8):

- The two strands of the DNA molecule to be duplicated unwind and separate from each other so that their bases are 'free'.
- A new strand is now synthesized opposite each original strand of DNA in such a way that adenine is formed opposite thymine, guanine is formed opposite cytosine, and vice versa.

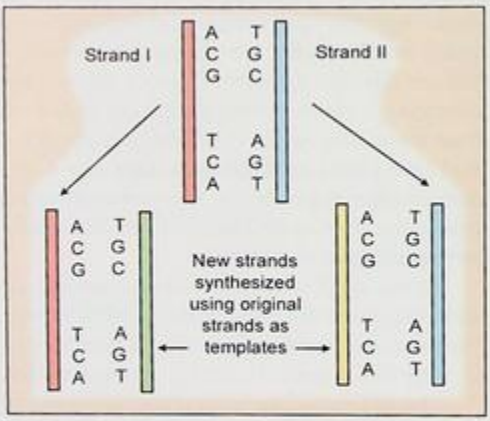

Fig. 1.8: Scheme to show how a DNA molecule is duplicated.

This new strand becomes linked to the original strand of DNA to form a new molecule. As the same process has taken place in relation to each of the two original strands, we now

have two complete molecules of DNA. It will be noted that each molecule has one strand that belonged to the original molecule and one strand that is new. It will also be noted that the two molecules formed are identical to the original molecule.

Structure of Fully Formed Chromosomes

Each chromosome consists of two parallel rod-like elements that are called ***chromatids*** (Fig. 1.9). The two chromatids are joined to each other at a narrow area that is light staining and is called the ***centromere*** (or ***kinetochore***). In this region, the chromatin of each chromatid is most highly coiled and, therefore, appears to be thinnest. The chromatids appear to the 'constricted' here and this region is called the ***primary constriction***. Typically, the centromere is not midway between the two ends of the chromatids, but somewhat towards one end. As a result, each chromatid can be said to have a ***long arm*** and a ***short arm***. Such chromosomes are described as being ***submetacentric*** (when the two arms are only slightly different in length); or as ***acrocentric*** (when the difference is marked) (Fig. 1.10).

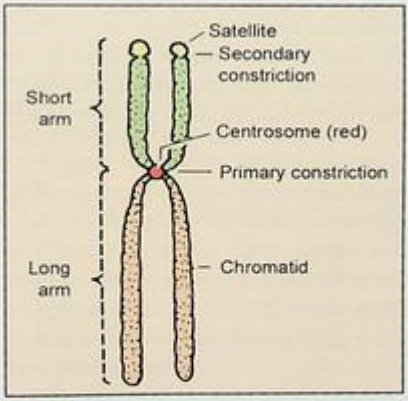

Fig. 1.9: Diagram to show the terms applied to some parts of a typical chromosome. Note that this chromosome is submetacentric.

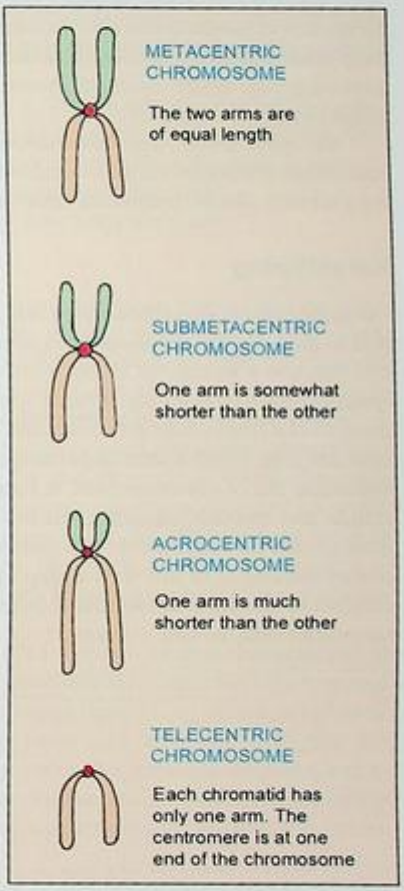

Fig. 1.10: Nomenclature used for different types of chromosomes, based on differences in lengths of the two arms of each chromatid.

In some chromosomes, the two arms are of equal length: such chromosomes are described as ***metacentric***. Finally, in some chromosomes the centromere may lie at one end: such a chromosome is described as ***telocentric***.

Differences in the total length of chromosomes, and in the position of the centromere are important factors in distinguishing individual chromosomes from each other. Additional help in identification is obtained by the presence in some chromosomes of ***secondary constrictions***. Such constrictions lie near one end of the chromatid. The part of the chromatid 'distal' to the constriction may appear to be a rounded body almost separate from the rest of the chromatid: such regions are called ***satellite bodies***. (Secondary constrictions are concerned with the formation of nucleoli and are, therefore, called ***nucleolar organizing centres***). Considerable help in identification of individual chromosomes is also obtained by the use of special staining procedures by which each chromatid can be seen to consist of a number of dark and light staining transverse bands.

We have noted that chromosomes are distinguishable only during mitosis. In the interphase (between successive mitoses) the chromosomes elongate and assume the form of long threads. These threads are called ***chromonemata*** (Singular = ***chromonema***).

Karyotyping

Using the criteria described above, it is now possible to identify each chromosome individually and to map out the chromosomes of an individual. This procedure is called karyotyping. For this purpose a sample of blood from the individual is put into a suitable medium in which lymphocytes can multiply. After a few hours, a drug (colchicin, colcemide) that arrests cell division at a stage when chromosomes are most distinct, is added to the medium. The dividing cells are then treated with hypotonic saline so that they swell up. This facilitates the proper spreading out of chromosomes. A suspension containing the dividing cells is spread out on a slide and suitably stained. Cells in which the chromosomes are well spread out (without overlap) are photographed. The photographs are cut out and the chromosomes arranged in proper sequence. In this way, a map of chromosomes is obtained, and abnormalities in their number or form can be identified. In many cases, specific chromosomal abnormalities can be correlated with specific diseases.

CELL DIVISION

Multiplication of cells takes place by division of pre-existing cells. Such multiplication constitutes an essential feature of embryonic development. Cell multiplication is equally necessary after the birth of the individual for growth and for replacement of dead cells. We have seen that chromosomes within the nuclei of cells carry genetic information that controls the development and functioning of various cells and tissues; and, therefore, of the body as a whole. When a cell divides, it is essential that the entire genetic information within it be passed on to both the daughter cells resulting from the division. In other words, the daughter cells must have chromosomes identical in number (and in genetic content) to those in the mother cell. This type of cell division is called ***mitosis***.

A different kind of cell division called ***meiosis*** occurs during the formation of the gametes. This consists of two successive divisions called the ***first*** and ***second meiotic divisions***. The cells resulting from these divisions (i.e., gametes) differ from other cells of the body in that—

- The number of chromosomes is reduced to half the normal number, and
- The genetic information in the various gametes produced is not identical.

MITOSIS

Many cells of the body have a limited span of functional activity, at the end of which they undergo division into two daughter cells. The daughter cells in turn have their own span of activity, followed by another division. The period during which the cell is actively dividing is the phase of mitosis. The period between two successive divisions is called the ***interphase***.

Mitosis is conventionally divided into a number of stages called ***prophase, metaphase, anaphase*** and ***telophase***. The sequence of events of the mitotic cycle is best understood starting with a cell in telophase. At this stage each chromosome consists of a single chromatid (Fig. 1.11G). With the progress of telophase, the chromatin of the chromosome uncoils and elongates and the chromosome can no longer be identified as such. However, it is believed to retain its identity during the interphase (which follows telophase). This is shown diagrammatically in Fig. 1.11A.

During a specific period of the interphase, the DNA content of the chromosome is duplicated so that another chromatid identical to the original one is formed; the chromosome is now made up of two chromatids (Fig. 1.11B). When mitosis begins (i.e., during prophase), the chromatin of the chromosome becomes gradually more and more coiled so that the chromosome becomes recognizable as a thread-like structure that gradually acquires a rod-like appearance (Fig. 1.11C). Towards the end of prophase, the two chromatids constituting the chromosome become distinct (Fig. 1.11D) and the chromosome now has the typical structure illustrated in Fig. 1.2.

While these changes are occurring in chromosomes, a number of other events are also taking place. The two centrioles separate and move to opposite poles of the cell. They produce a number of microtubules that pass from one centriole to the other and form a ***spindle***. Meanwhile the nuclear membrane breaks down and nucleoli disappear (Fig. 1.11D). With the

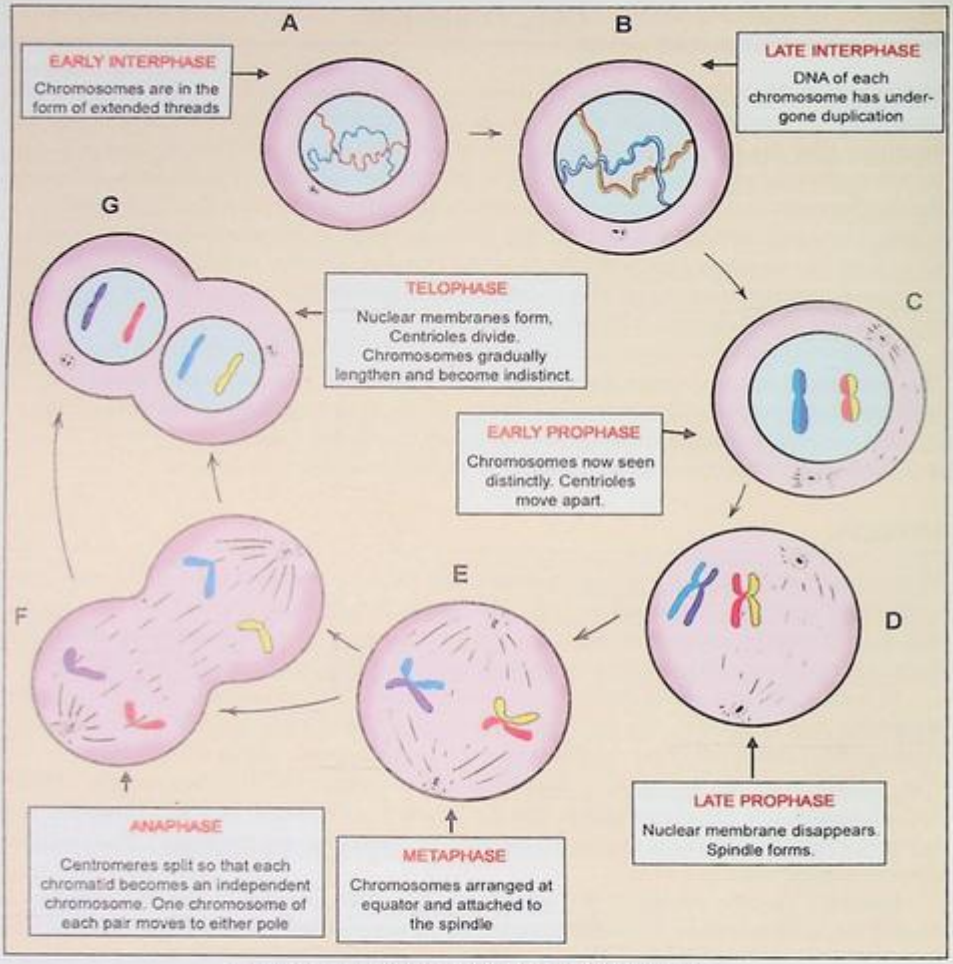

Fig. 1.11: Scheme to show the main steps of mitosis.

formation of the spindle, chromosomes move to a position midway between the two centrioles (i.e., at the equator of the cell) where each chromosome becomes attached to microtubules of the spindle by its centromere. This stage is referred to as ***metaphase*** (Fig. 1.11E).

In the ***anaphase***, the centromere of each chromosome splits longitudinally into two so that the chromatids now become independent chromosomes. At this stage, the cell can be said to contain forty-six pairs of chromosomes. One chromosome of each such pair now moves along the spindle to either pole of the cell (Fig. 1.11F).

This is followed by ***telophase*** in which the two daughter nuclei are formed by appearance of nuclear membranes. Chromosomes gradually elongate and become indistinct. Nucleoli reappear. The centriole is duplicated at this stage or in early interphase (Fig. 1.11G).

The division of the nucleus is accompanied by the division of the cytoplasm. In this process, the organelles are presumably duplicated and each daughter cell comes to have a full complement of them.

MEIOSIS

As already stated, meiosis consists of two successive divisions called the first and second meiotic divisions. During the interphase preceding the first division, duplication of the DNA content of chromosomes takes place as in mitosis. As a result, another chromatid identical to the original one is formed. Thus, each chromosome is now made up of two chromatids.

First Meiotic Division

The ***prophase*** of the first meiotic division is prolonged and is usually divided into a number of stages as follows:

- **Leptotene:**
  The chromosomes become visible (as in mitosis). Although each chromosome consists of two chromatids, these cannot be distinguished at this stage (Fig. 1.12A).
- **Zygotene:**
  We have seen that the forty-six chromosomes in each cell consist of twenty-three pairs (the X and Y chromosomes of a male being taken as a pair). The two chromosomes

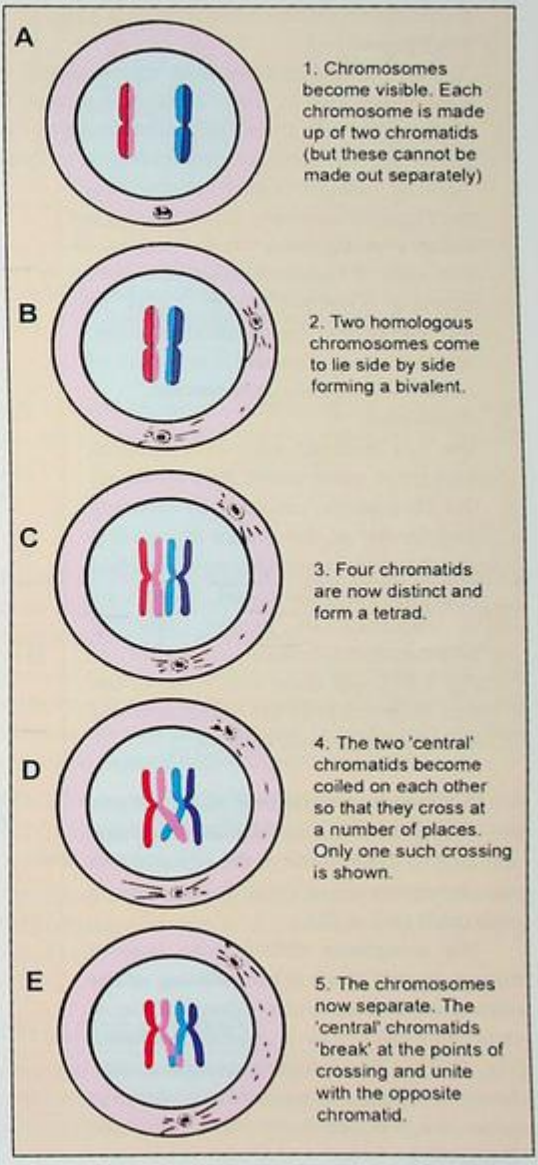

Fig. 1.12: Stages in the prophase of the first meiotic division.

of each pair come to lie parallel to each other, and are closely apposed. This ***pairing*** of chromosomes is also referred to as ***synapsis*** or conjugation. The two chromosomes together constitute a ***bivalent*** (Fig. 1.12B).

- **Pachytene:**
  The two chromatids of each chromosome become distinct. The bivalent now has four chromatids in it and is called a ***tetrad***. There are two central and two peripheral chromatids, one from each chromosome (Fig. 1.12C). An important event now takes place. The two central chromatids (one belonging to each chromosome of the bivalent) become coiled over each other so that they cross at a number of points. This is called ***crossing over***.
  For sake of simplicity only one such crossing is shown in Fig. 1.12D. At the site where the chromatids cross, they become adherent: the points of adherence are called ***chiasmata***.
- **Diplotene:**
  The two chromosomes of a bivalent now try to move apart. As they do so, the chromatids involved in crossing over 'break' at the points of crossing and the 'loose' pieces become attached to the opposite chromatid. This results in exchange of genetic material between these chromatids. A study of Fig. 1.12E will show that each of the four chromatids of the tetrad now has a distinctive genetic content.

The ***metaphase*** follows. As in mitosis the forty-six chromosomes become attached to the spindle at the equator, the two chromosomes of a pair being close to each other (Fig. 1.13A).

The ***anaphase*** differs from that in mitosis in that ***there is no splitting of the centromeres***. One entire chromosome of each pair moves to each pole of the spindle (Fig. 1.13B). The resulting daughter cells, therefore, have twenty-three chromosomes, each made up of two chromatids (Fig. 1.13C).

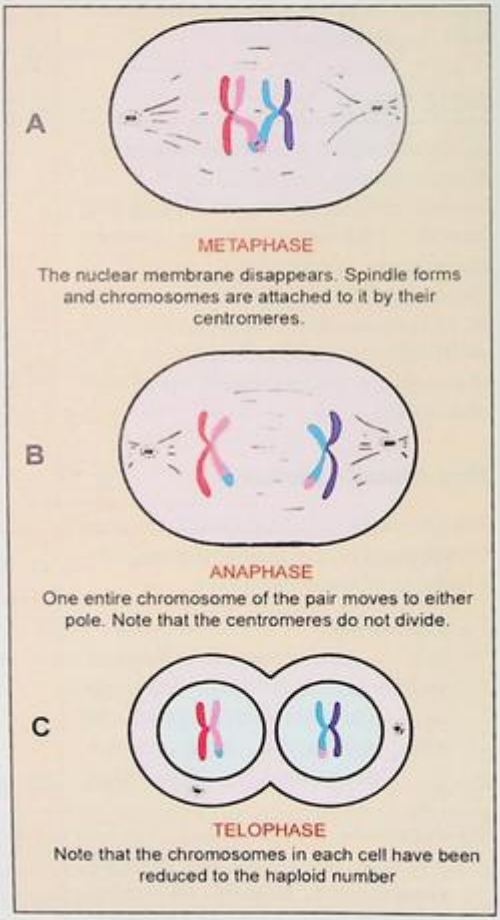

Fig. 1.13: Metaphase (A), anaphase (B), and telophase (C) of the first meiotic division.

The anaphase is followed by the ***telophase*** in which two daughter nuclei are formed. The division of the nucleus is followed by division of the cytoplasm.

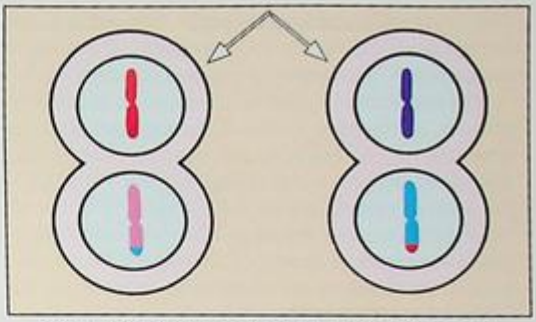

Fig. 1.14: Daughter cells resulting from the second meiotic division. These are not alike because of the crossing-over during the first meiotic division.

Second Meiotic Division

The first meiotic division is followed by a short ***interphase***. This differs from the usual interphase in that ***there is no duplication of DNA***. Such duplication is unnecessary as chromosomes of cells resulting from the first division already possess two chromatids each (Fig. 1.13C).

The second meiotic division is similar to mitosis. However, because of the crossing over that has occurred during the first division, the daughter cells are not identical in genetic content (Fig. 1.14).

Significance of Meiosis

- In this kind of cell division, there is reduction of the number of chromosomes from diploid to haploid. At the time of fertilization, the diploid number (46) is restored. This provides consistency of chromosome number from generation to generation.
- As stated earlier, the forty-six chromosomes of a cell consist of twenty-three pairs, one chromosome of each pair being derived from the mother and one from the father. During the first meiotic division, the chromosomes derived from the father and those derived from the mother are distributed between the daughter cells entirely at random.
- This, along with the phenomenon of crossing over, results in thorough shuffling of the genetic material so that the cells produced as a result of various meiotic divisions (i.e., ova or spermatozoa) all have a distinctive genetic content.
- A third step in this process of genetic shuffling takes place at fertilization when there is a combination of randomly selected spermatozoa and ova. It is, therefore, not surprising that no two persons (except identical twins) are alike.

A NOTE ON CHRONOLOGY OF EMBRYOLOGICAL EVENTS

In an earlier section, it has been emphasized that one of the main objectives of the study of embryology, by medical students, is to understand the causation of congenital anomalies. In this connection, it has been observed that if a growing embryo is exposed to certain agents (chemical or physical), abnormalities in development can result. Such agents are called ***teratogens***.

The list of known teratogens keeps increasing. It has also been observed that some particular organs are most sensitive to teratogens when they are passing through critical phases in their development. This period of greatest susceptibility to teratogens differs from organ to organ.

The importance of having a knowledge of the timing of embryological events, thus, becomes obvious. In the early stages of development, the age of an embryo is reckoned in days. Later, when events are less dramatic, age can be expressed in weeks or months. However, the exact age of an embryo is not always known. An estimate can be made by observing the size of the embryo (expressed as C.R. length), or some other feature like the number of somites. In most textbooks of embryology, there are numerous references to the timing of embryonic events (most commonly in terms of C.R. length). The disadvantage of doing so is that it adds yet one more complication to the understanding of an already intricate subject. Because of this reason references to the timetable of development have been kept to the minimum in the main text of this book. However, a timetable of events is added at the end of chapters wherever relevant.

Chapter 2

Spermatogenesis and Oogenesis

HIGHLIGHTS

- A ***spermatozoon*** has a head, a neck, a middle piece and a principal piece or tail (Fig. 2.1).
- ***Stages of spermatogenesis*** are summarized in Fig. 2.5.
- Spermatozoa are derived from rounded ***spermatids***. The process of conversion of a spermatid to a spermatozoon is called ***spermiogenesis*** (Fig. 2.6).
- ***Stages of oogenesis*** are summarized in Fig. 2.8.
- An ***ovarian follicle*** is a rounded structure that contains a developing ovum surrounded by follicular cells. The follicle has a cavity filled with fluid (Fig. 2.12).
- Ovarian follicles have a cellular covering called the ***theca interna.*** The cells of the theca interna produce oestrogens (Fig. 2.13).
- The follicle gradually increases in size and finally bursts and expels the ovum. This process of shedding of the ovum is called ***ovulation***.
- The ***corpus luteum*** is formed by enlargement and transformation of follicular cells, after-shedding of the ovum (Fig. 2.16). The corpus luteum secretes progesterone, which is essential for maintenance of pregnancy.

In this chapter, we shall first study the structure of a mature spermatozoon (male sex cell) before considering its formation in the testis.

STRUCTURE OF A MATURE SPERMATOZOON

A spermatozoon is a highly specialized, free swimming, actively motile cell. The spermatozoon has a ***head***, a ***neck***, a ***middle piece*** and a ***principal piece*** or ***tail*** (Fig. 2.1). An ***axial filament*** passes through the middle piece and extends into the tail. The spermatozoon measures about 60 μm in length.

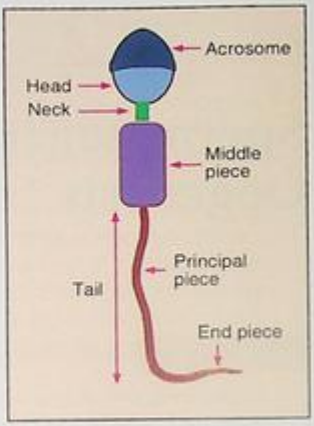

Fig. 2.1: Parts of a spermatozoon.

The Head

The head of the human spermatozoon is piriform in shape and measures 4 μm in length. It is derived from the nucleus, which consists of 23 highly condensed chromosomes. The head is covered by a cap-like structure called the ***acrosome*** (also called the ***acrosomic cap*** or ***galea capitis***). The acrosome contains enzymes that help in penetration of the spermatozoon into the ovum during fertilization (see Chapter 4).

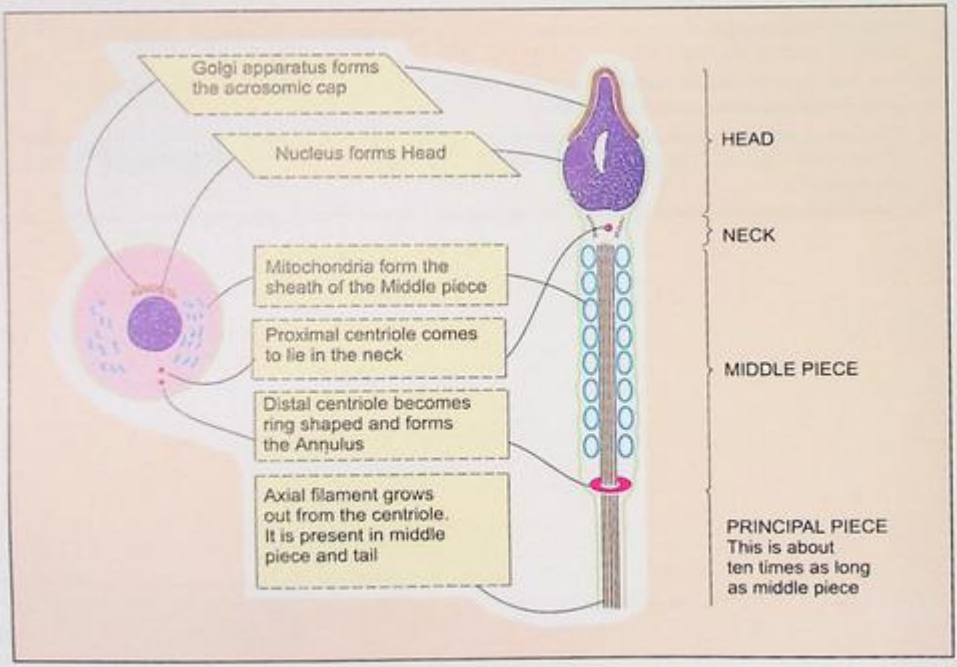

Fig. 2.2: Parts of a spermatozoon and their derivation. According to some authorities, the distal centriole forms the basal body, not the annulus.

The Neck

The neck is narrow: it contains a funnel-shaped ***basal body*** and a spherical ***centriole***. The basal body is also called the ***connecting piece*** because it helps to establish an intimate union between the head and the remainder of the spermatozoon.

The Axial Filament

The axial filament begins just behind the centriole. It passes through the middle piece and most of the tail. At the point where the middle piece joins the tail, the axial filament passes through a ring-like structure called the ***annulus***. The part of the axial filament, which lies in the middle piece, is surrounded by a ***spiral sheath*** made up of mitochondria.

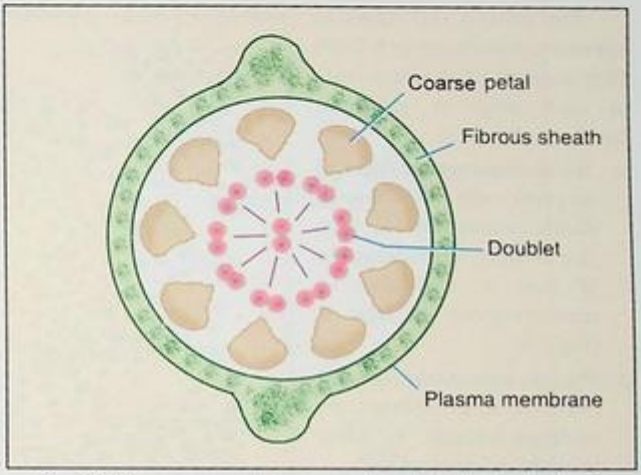

Fig. 2.3: Transverse section across the principal piece (tail) of a spermatozoon to show the arrangement of fibrils.

The axial filament is really composed of several fibrils arranged as illustrated in Fig. 2.3. There is a pair of central fibrils, surrounded by nine pairs (doublets) arranged in a circle around the central pair. The whole system of fibrils is kept in position by a series of coverings. Immediately outside the fibrils, there is a fibrous sheath. In the region of the middle piece, the fibrous sheath is surrounded by spirally arranged mitochondria. Finally, the entire spermatozoon is enclosed in a plasma membrane.

Further Details

- The chromatin in the head of the spermatozoon is extremely condensed. This makes the head highly resistant to various physical stresses. The chemical basis for condensation is the replacement of histones by protamines.
- The basal body is made up of nine segmented rod-like structures. On its proximal side (i.e. towards the head of the spermatozoon), the basal body has a convex ***articular surface*** which fits into a depression (***implantation fossa***) in the head.
- In addition to the doublets, the axial filament contains nine coarser petal-shaped fibrils, one such fibril lying just outside each doublet.

SPERMATOGENESIS

In the male, the formation of gametes (spermatozoa) takes place only during the reproductive period, which begins at the age of puberty (12 to 16 years) and continues even into old age. Spermatozoa are formed in the wall of the seminiferous tubules of the testes. If we look at one of these tubules under a microscope, we find that there are many cells of different sizes and shapes (Fig. 2.4). Most of these represent stages in the formation of spermatozoa, but some (called ***Sertoli cells***) have only a supporting function.

The various cell-stages in spermatogenesis are as follows (the number of chromosomes at each stage is given in brackets) (Fig. 2.5):

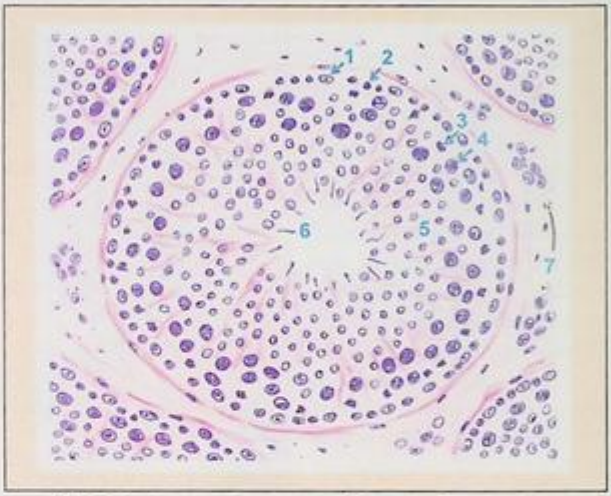

Fig. 2.4: Microscopic structure of a seminiferous tubule.

- The ***spermatogonia (type A)*** or ***germ cells*** (44 + X + Y) divide mitotically, to give rise to more spermatogonia of type A, and also to spermatogonia of type B (Fig. 2.5).
- The ***spermatogonia (type B)*** (44 + X + Y) enlarge, or undergo mitosis, to form primary spermatocytes.
- The ***primary spermatocytes*** (44 + X + Y) now divide so that each of them forms two secondary spermatocytes. This is the first meiotic division: it reduces the number of chromosomes to half.
- Each ***secondary spermatocyte*** has 22 + **X** or 22 + **Y** chromosomes. It divides to form two spermatids. This is the second meiotic division and this time there is no reduction in chromosome number.
- Each ***spermatid*** (22 + **X** or 22 + **Y**) gradually changes its shape to become a spermatozoon. This process of transformation of a circular spermatid to a spermatozoon is called ***spermiogenesis***.

Spermiogenesis

The process by which a spermatid becomes a spermatozoon is called ***spermiogenesis*** (or ***spermateleosis***) (Figs. 2.2, 2.6). The spermatid is a more or less circular cell containing a nucleus, Golgi apparatus, centriole and mitochondria. All these components take part in forming the spermatozoon. The nucleus forms the head. The Golgi apparatus is transformed into the acrosomic cap.

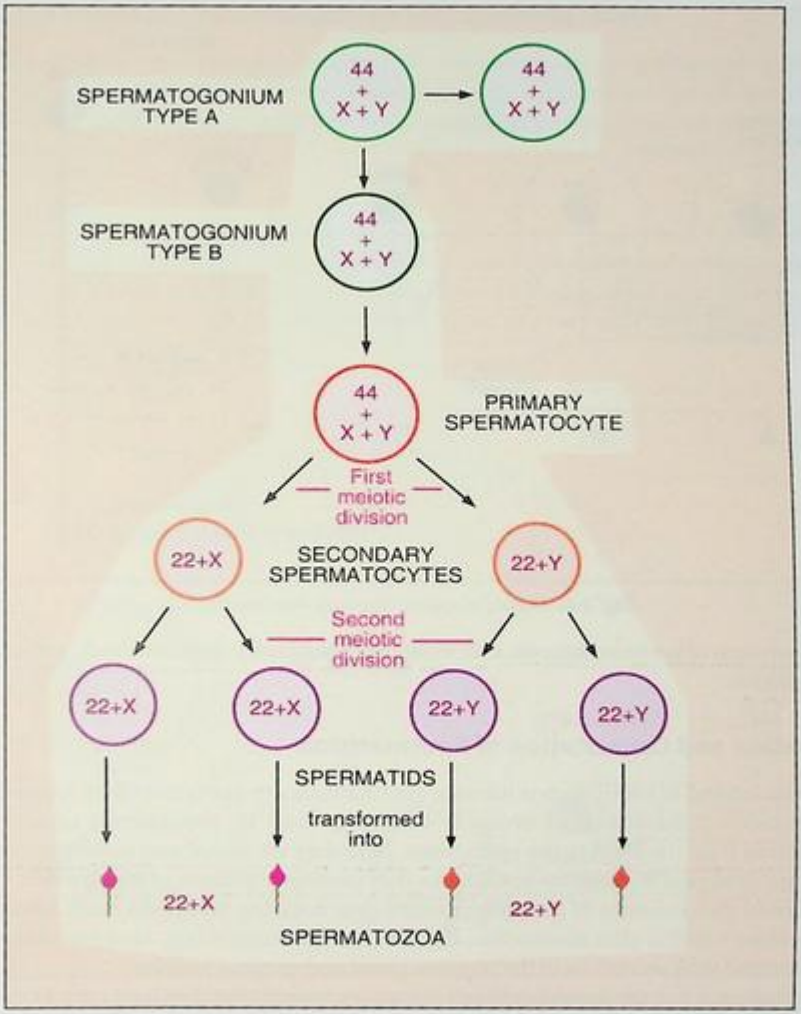

Fig. 2.5: Stages in spermatogenesis. Note the number of chromosomes at each stage.

The centriole divides into two parts that are at first close together: the axial filament appears to grow out of them. One centriole becomes spherical and comes to lie in the neck. According to some workers, the other centriole forms the basal body, but according to some others it forms the annulus. The part of the axial filament between the neck and the annulus, becomes surrounded by mitochondria, and together with them forms the middle piece. The remaining part of the axial filament elongates to form the principal piece or tail. Most of the cytoplasm of the spermatid is shed, but the cell membrane persists as a covering for the spermatozoon.

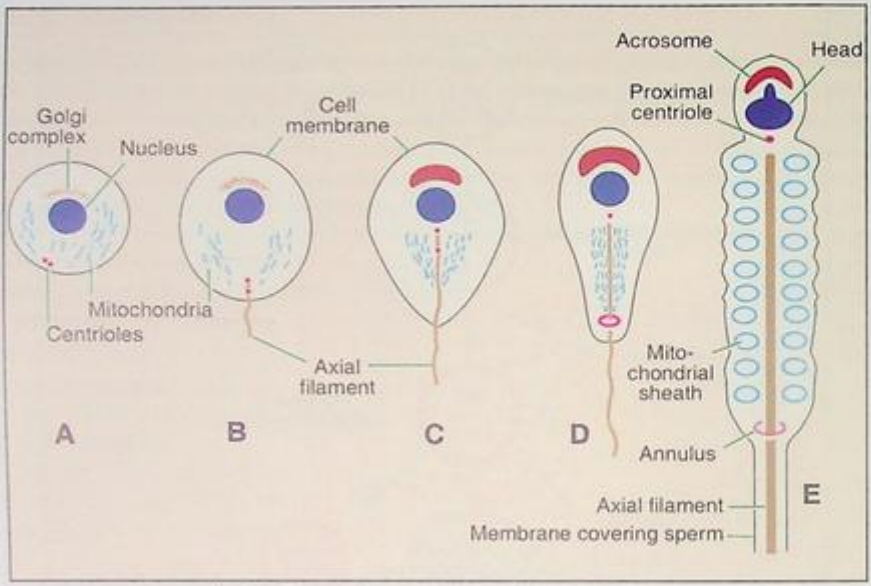

Fig. 2.6: Stages in spermiogenesis. Also see Fig. 2.2.

The process of spermatogenesis, including spermiogenesis, requires about two months for its completion.

Maturation and Capacitation of Spermatozoa

When first formed in seminiferous tubules, spermatozoa are immature. They are non-motile and incapable of fertilizing an ovum. A current of fluid in seminiferous tubules carries spermatozoa from the testis to the epididymis. Here they are stored and undergo maturation. As spermatozoa pass through the epididymis they undergo a process of ***maturation***. Changes take place in glycoproteins of the plasma membrane covering the sperm head. Spermatozoa acquire some motility after maturation, but become fully motile only after ejaculation when they get mixed with secretions of the prostate gland and seminal vesicles.

Spermatozoa acquire the ability to fertilize an ovum only after they have been in the female genital tract for some time. This final step in their maturation is called ***capacitation***. In the process of capacitation, the glycoprotein coat and seminal proteins lying over the surface of the spermatozoon are altered. Spermatozoa usually undergo capacitation in the uterus or uterine tube, under the influence of substances secreted by the female genital tract. When a spermatozoon comes in contact with the zona pellucida, changes take place in the membranes over the acrosome and enable release of lysosomal enzymes. This is called the ***acrosome reaction***. Some enzymes help in digesting the zona pellucida and in penetration of the spermatozoa through it. Changes in the properties of the zona pellucida constitute the **zona *reaction***.

Difference between Spermatogenesis and Spermiogenesis

Spermatogenesis is the complete process of formation of a spermatozoon from a spermatogonium. It includes the first and second meiotic division and spermiogenesis. On the other hand, spermiogenesis is the process of transformation of a rounded spermatid into a spermatozoon.

OOGENESIS

The female gonad is the ovary. It has an outer part called the cortex and an inner part, the medulla (Fig. 2.7.). The cortex contains many large round cells called oogonia. All the oogonia to be used throughout the life of a woman are produced at a very early stage (possibly before birth) and do not multiply thereafter.

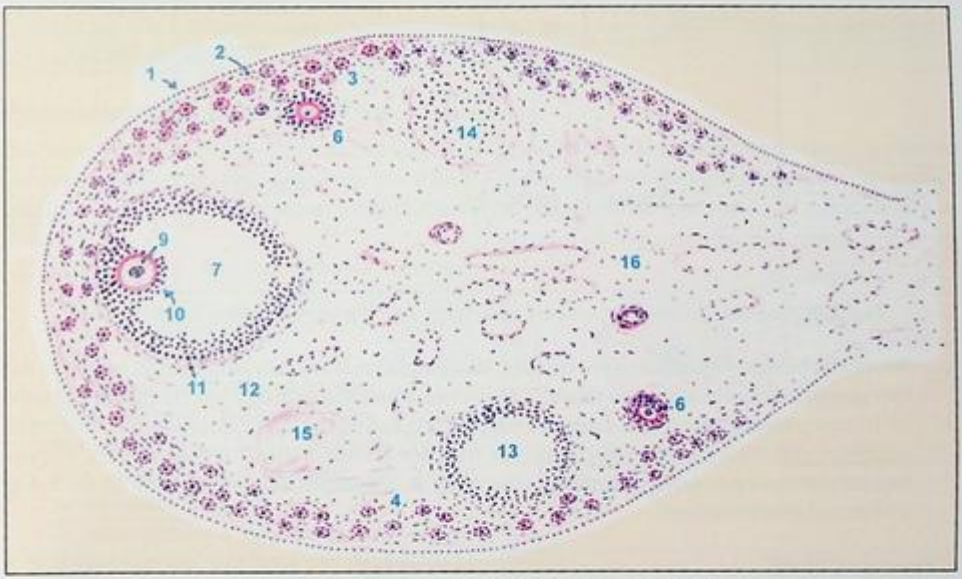

Fig. 2.7: Panoramic view of the structure of an ovary.

Ova are derived from oogonia as shown in Fig. 2.8. Note how similar the process is to spermatogenesis. However, there are important differences as well.

Differences between Spermatogenesis and Oogenesis

- Observe that whereas one primary spermatocyte gives rise to four spermatozoa, one primary oocyte forms only one ovum.

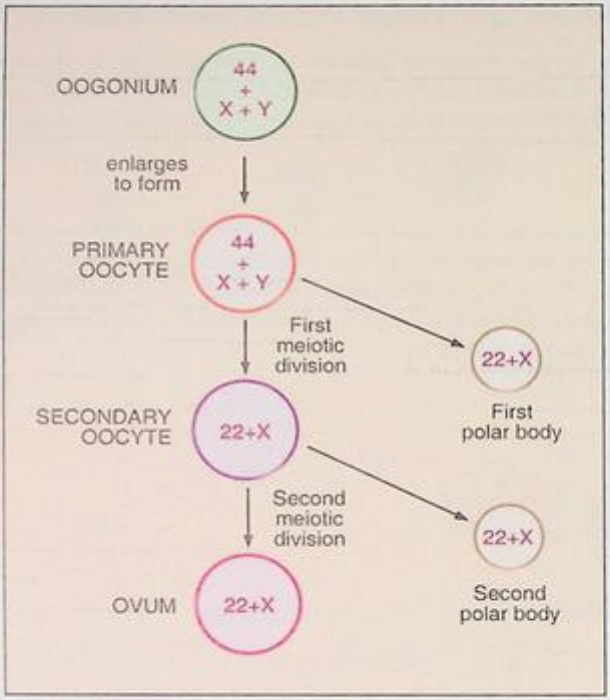

Fig. 2.8: Stages in oogenesis. Compare each stage with the corresponding one in Fig. 2.5.

- When the primary spermatocyte divides, its cytoplasm is equally distributed between the two secondary spermatocytes formed. However, when the primary oocyte divides, almost all its cytoplasm goes to the daughter cell, which forms the secondary oocyte. The other daughter cell (first polar body), receives half the chromosomes of the primary oocyte, but almost no cytoplasm. The first polar body is, therefore, formed merely to get rid of unwanted chromosomes.

Further Details

- In the late fetal period primary oogonia enlarge to form ***primary oocytes***.
- At the time of birth all primary oocytes are in the prophase of first meiotic division. Their number is about 40,000.
- The primary oocytes remain in prophase and do not complete their first meiotic division until they begin to mature and are ready to ovulate.
- The reproductive period of a female is between 12 to 50 years of age. With each menstrual cycle, a few primary oocytes (about 5 to 30) begin to mature and complete the first meiotic division shortly before ovulation.

- The first meiotic division of a primary oocyte produces two unequal daughter cells. Each daughter cell has the haploid number of chromosomes (23). The large cell, which receives most of the cytoplasm, is called the ***secondary oocyte,*** and the smaller cell is known as the first polar body.
- The secondary oocyte immediately enters the second meiotic cell division. Ovulation takes place while the oocyte is in metaphase. The secondary oocyte remains arrested in metaphase till fertilization occurs.
- The second meiotic division is completed only if fertilization occurs. This division results in two unequal daughter cells. The smaller daughter cell is called the ***second polar body***. The first polar body may also divide during the second meiotic division.
- If fertilization does not occur, the secondary oocyte fails to complete the second meiotic division and degenerates about 24 hours after ovulation.
- In each menstrual cycle, 5 to 30 primary oocytes start maturing, but only one of them reaches maturity and is ovulated. The remaining degenerate.
- During the entire reproductive life of a female, only around 400 ova are discharged (out of 40,000 primary oocytes available).

Formation of Ovarian Follicles

We have seen that ova develop from oogonia present in the cortex of the ovary. The oogonia are surrounded by other cells that form the stroma. These stromal cells form ***ovarian*** or ***Graafian follicles*** that surround ova and protect them. The stages in the formation of a follicle are as follows:

- Some cells of the stroma become flattened and surround an oocyte (Fig. 2.9). These flattened cells ultimately form the ovarian follicle and are, therefore, called follicular cells.
- The flattened follicular cells become columnar (Fig. 2.10). Follicles up to this stage of development are called ***primordial follicles.***
- A homogeneous membrane, the ***zona pellucida***, appears between the follicular cells and the oocyte (Fig. 2.10).
- The follicular cells proliferate to form several layers. These constitute the ***membrana granulosa*** (Fig. 2.11). The cells may now be called ***granulosa cells.***
- A cavity (or ***antrum***) appears within the membrana granulosa. With its appearance, a follicle is formed (follicle = small sac) (Fig. 2.12).

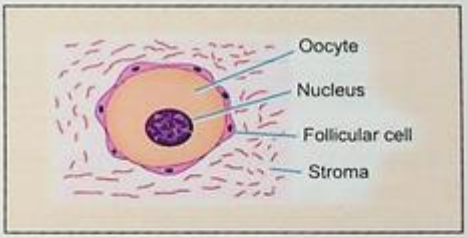

Fig. 2.9: Early stages in the formation of ovarian follicles.

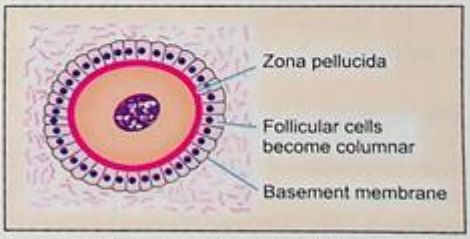

Fig. 2.10: Early stages in the formation of ovarian follicles.

- The cavity of the follicle rapidly increases in size. As a result, the wall of the follicle (formed by the granulosa cells) becomes relatively thin. The oocyte now lies eccentrically in the follicle, surrounded by some granulosa cells that are given the name ***cumulus oophoricus*** (or ***cumulus ovaricus***). The cells that attach it to the wall of the follicle are given the name ***discus proligerus*** (Fig. 2.13).
- As the follicle expands, the stromal cells surrounding the membrana granulosa become condensed to form a covering called the theca interna (theca = cover). The cells of the theca interna later secrete a hormone called oestrogen; and they are then called the cells of the ***thecal gland*** (Fig. 2.13).
- Outside the theca interna some fibrous tissue becomes condensed to form another covering for the follicle called the ***theca externa*** (Fig. 2.13). The ovarian follicle is now fully formed.

Ovulation

The shedding of the ovum from the ovary is called ovulation. The ovarian follicle is at first very small compared to the thickness of the cortex of the ovary (Fig. 2.14A).

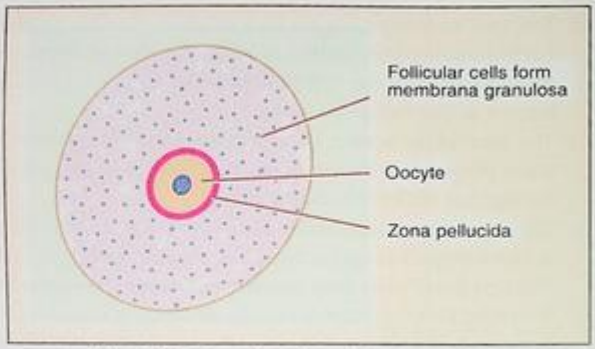

Fig. 2.11: Formation of membrana granulosa.

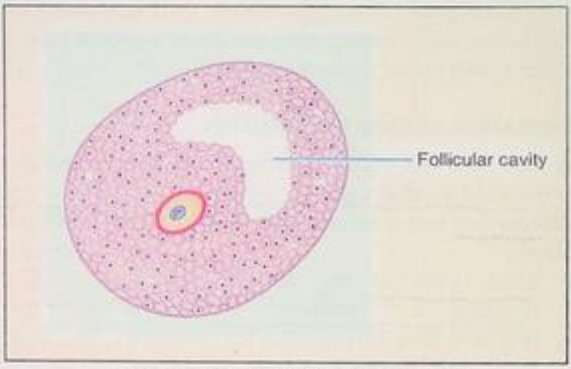

Fig. 2.12: Formation of follicular cavity.

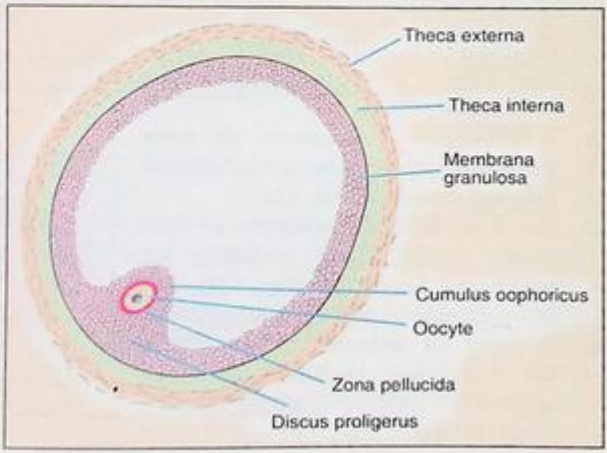

Fig. 2.13: Fully formed ovarian follicle.

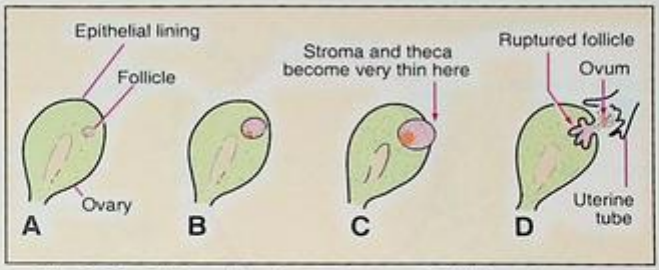

Fig. 2.14: Relationship of a growing ovarian follicle to the ovary.

As it enlarges, it becomes so big that it not only reaches the surface of the ovary, but also forms a bulging in this situation. Ultimately, the follicle ruptures and the ovum is shed from the ovary (Fig. 2.14D).

Just before ovulation the follicle may have a diameter of 15 mm. The stroma and theca on this side of the follicle become very thin. An avascular area (***stigma***) appears over the most convex point of the follicle. At the same time, the cells of the cumulus oophoricus become loosened by accumulation of intercellular fluid between them.

The following factors may lead to ovulation:

- Ovulation occurs due to high concentration of LH (Luteinizing Hormones) in blood just before ovulation (see Chapter 3).
- A high concentration of LH leads to increase activity of the enzyme ***collagenease,*** which in turn digests the collagen fibres surrounding the follicle.
- Increase in concentration of ***prostaglandins*** causes contraction of smooth muscle in the wall of the ovary.
- The increased pressure of fluid in the follicular cavity is also a significant factor for ovulation to occur.
- However, the enzymatic digestion of the follicular wall seems to be the main factor responsible for ovulation.

Structure of the Ovum

The ovum that is shed from the ovary is not fully mature. It is really a secondary oocyte that is undergoing division to shed off the second polar body (Fig. 2.8).

At this stage, the ovum has the appearance illustrated in Fig. 2.15. Note that it is surrounded by the zona pellucida. Some cells of the corona radiata can be seen sticking to the outside of the zona pellucida. No nucleus is seen, as the nuclear membrane has dissolved for the second meiotic division. A spindle is, however, present. Between the cell membrane (or ***vitelline membrane***) and the zona pellucida, a distinct ***perivitelline space*** is seen. The first polar body lies in this space. Note that the ovum is a very large cell and measures more than 100 μm in diameter. In contrast, most other cells of the body measure less than 10 μm. (One μm is one thousandth of a millimetre).

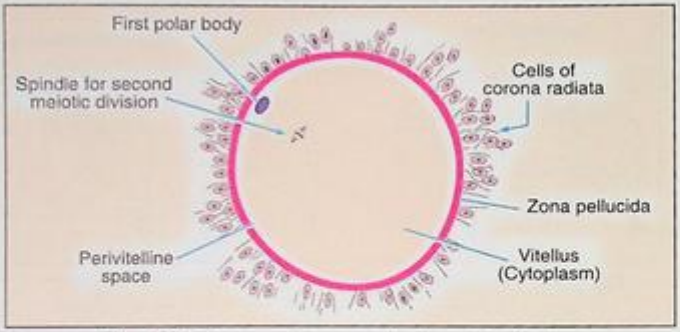

Fig. 2.15: Structure of ovum at the time of ovulation.

Fate of the Ovum

Let us see what happens to the ovum that is shed from the ovary. You already know that the ovary is closely embraced by the fimbriated end of the uterine tube. Therefore, the ovum is easily carried into the tube partly by the follicular fluid discharged from the follicle and partly by the activity of ciliated cells lining the tube. The ovum slowly travels through the tube towards the uterus, taking three to four days to do so. If sexual intercourse takes place at about this time, the spermatozoa deposited in the vagina swim into the uterus and into the uterine tube. One of these spermatozoa may fertilize the ovum. If this happens, the fertilized ovum begins to develop into an embryo. It travels to the uterus and gets implanted in its wall. On the other hand, if the ovum (secondary oocyte) is not fertilized it dies in 12 to 24 hours. It passes through the uterus into the vagina and is discharged.

Corpus Luteum

The corpus luteum is an important structure. It mainly secretes a hormone progesterone, but secretes some oestrogen also. The corpus luteum is derived from the ovarian follicle, after the latter has ruptured to shed the ovum, as follows (Fig. 2.16):

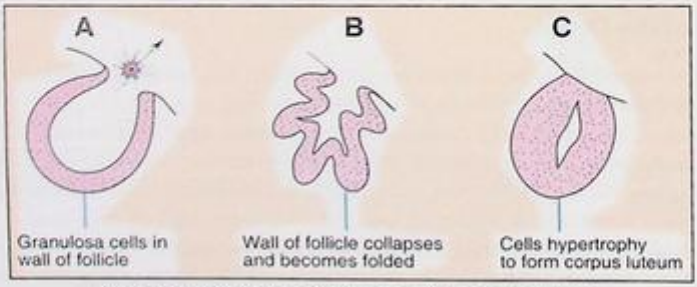

Fig. 2.16: Stages in the formation of the corpus luteum.

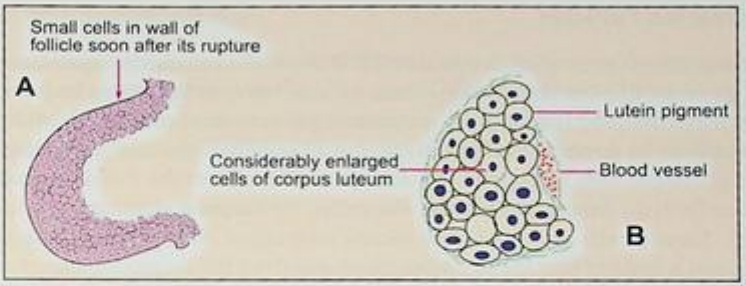

Fig. 2.17: Transformation of follicular cells (A), to luteal cells (B).

- When the follicle ruptures, its wall collapses and becomes folded.
- At this stage, the follicular cells are small and rounded (Fig. 2.17A). They now rapidly enlarge. As they increase in size, their walls press against those of neighbouring cells so that the cells acquire a polyhedral shape (Fig. 2.17B). Their cytoplasm becomes filled with a yellow pigment called ***lutein***. They are now called ***luteal cells***. The presence of this yellow pigment gives the structure a yellow colour and that is why it is called the corpus luteum (= yellow body). Some cells of the theca interna also enlarge and contribute to the corpus luteum.
- We have seen that the corpus luteum secretes progesterone. This secretion has to be poured into the blood like secretions of endocrine glands. All endocrine glands are richly supplied with blood vessels for this purpose. The ovarian follicle itself has no blood vessels, but the surrounding theca interna is full of them. When the corpus luteum is forming, blood vessels form the theca interna invade it and provide it with a rich supply of blood.

  The subsequent fate of the corpus luteum depends on whether the ovum is fertilized or not.
- If the ovum is not fertilized, the corpus luteum persists for about 14 days. During this period it secretes progesterone. It remains relatively small and is called the ***corpus luteum of menstruation***. At the end of its functional life, it degenerates and forms a mass of fibrous tissue called the ***corpus albicans*** (= white body) (Fig. 2.18).
- If the ovum is fertilized and pregnancy results, the corpus luteum persists for three to four months. This is larger than the corpus luteum of menstruation, and is called the ***corpus luteum of pregnancy***.

The corpus luteum of pregnancy may occupy one-third to half the total volume of the ovary. The progesterone secreted by it is essential for the maintenance of pregnancy in the first few months. After the fourth month, the corpus luteum is no longer needed, as the placenta begins to secrete progesterone. Degeneration of the corpus luteum in the early months of pregnancy is prevented by chorionic gonadotropin (hCG) secreted by the trophoblast cells of the developing embryo.

The series of changes that begin with the formation of an ovarian follicle and end with the degeneration of the corpus luteum constitute what is called an ***ovarian cycle***. An ovarian cycle has an average duration of 28 days, with ovulation occurring at mid-cycle i.e., on the 14th day.

Fate of Ovarian Follicles

We have seen that in each ovarian cycle, one follicle reaches maturity, sheds an ovum, and becomes a corpus luteum. At the same time, several other follicles also begin to develop, but do not reach maturity (Fig. 2.18). It is interesting to note that, contrary to what one might expect, these follicles do not persist into the next ovarian cycle, but undergo degeneration. The ovum and granulosa cells of each follicle disappear. The cells of the theca interna, however, proliferate to form the ***interstitial glands***, also called the ***corpora atretica*** (singular = ***corpus atreticum***). These glands are believed to secrete oestrogens. After a period of activity, each gland becomes a mass of scar tissue indistinguishable from the corpus albicans formed from the corpus luteum.

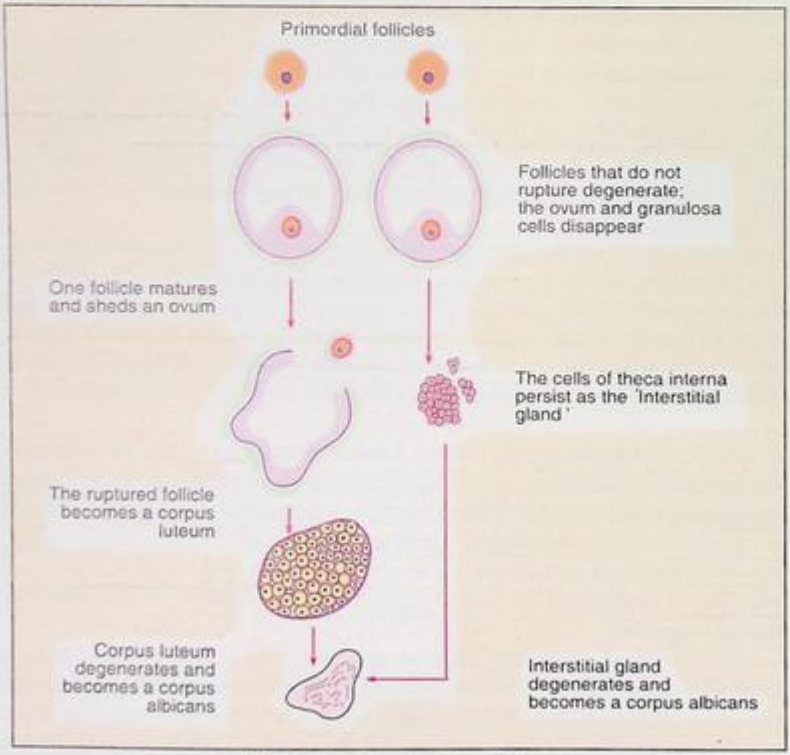

Fig. 2.18: Fate of ovarian follicles.

Ovarian Cycle and Hormones

The changes taking place during the ovarian cycle are greatly influenced by certain hormones produced by the hypophysis cerebri (see Chapter 3). The hormones produced by the theca interna and by the corpus luteum in turn influence other parts of the female reproductive system (notably the uterus), resulting in a cycle of changes referred to as the ***uterine*** or ***menstrual cycle***.

Reproductive Period

In an individual, the formation of gametes takes place only during the reproductive period which begins at the age of puberty (10 to 14 years). In women it ends between the ages of 45 and 50 years, but in men it may continue till the age of 60 years or more.

Viability of Gametes

An ovum usually degenerates 24 hours after ovulation. However, at the most it may survive for two days. Similarly, sperms usually degenerate 48 hours after ejaculation, but may survive up to four days in female genital tract.

Table 2.1: Differences between Male and Female Gametes

Male Gamete (sperm)	Female Gamete (ovum)
Sperm is small but long (about 60 µm in length and about 2 µm in width).	Ovum is a massive cell about 120 µm in diameter.
It is highly motile.	It is immotile.
There is very little cytoplasm. This gives it high motility.	The oocyte contains a large amount of cytoplasm.
Shape is adapted for motility.	Shape adapted to provide ample storage of nutrition for the embryo formed after fertilization.
Spermatozoa are of two chromosomal types (22+X) and (22+Y).	All ova have (22+X) chromosomes.

Clinical Correlation

Abnormalities in Formation of Gametes

Abnormalities of Form

Spermatozoa may be too large (giant) or too small (dwarf). The head, body or tail may be duplicated. The ovum may have an unusually large nucleus or two nuclei. Two oocytes may be seen in one follicle.

Chromosomal Abnormalities

The gametes may be abnormal in chromosomal content as follows:

- During the first meiotic division, the two chromosomes of a pair, instead of separating at anaphase, may both go to the same pole. (This is called ***non-disjunction***.) The resulting gamete then has 24 chromosomes instead of the normal 23 (Fig. 2.19). Non-disjunction can also take place in the second meiotic division (Fig. 2.20).
- At fertilization by this gamete, the zygote will, therefore, have 47 chromosomes; there being three identical chromosomes instead of one of the normal pairs. This is called ***trisomy***. Depending upon the particular chromosomes involved, various abnormalities are produced.
- Trisomy of chromosome 21 results in a condition called ***mongolism*** or ***Down's syndrome.*** In this condition the child has a broad face, obliquely placed palpebral fissures, epicanthus, a furrowed lower lip, and broad hands with a single transverse crease. Usually, the patients are mentally retarded and have anomalies of the heart.
- The presence of an extra **X** or **Y** chromosome can give rise to various syndromes associated with abnormal genital development, mental retardation and abnormal growth. Some of these are: **XXX** (abnormal female); **XXY** (***Klinefelter's syndrome***: abnormal male); **XYY** (abnormal male). In Klinefelter's syndrome, the subject is a male (because of the presence of a **Y** chromosome). However, the testes are poorly developed leading to sterility and gynaecomastia.
- Patients with **XXX** chromosomes show two masses of sex chromatin in their cells and are sometimes referred to as 'super females'. However, there is nothing 'super' about them. In fact, their bodies show poor sexual development (i.e. they are infantile), and menstruation is scanty. Mental retardation is usual.
- When both chromosomes of a pair go to one gamete (as described above), the other gamete resulting from the division has only 22 chromosomes (instead of the normal 23); and at fertilization, the zygote has only 45 chromosomes. Hence one pair is represented by a single chromosome. This is called ***monosomy*** (Fig. 2.19).
- The best known example of this is a female with only one **X** chromosome (***Turner's syndrome***). In this syndrome, the subject is always female (because of absence of a **Y** chromosome). There is agenesis of ovaries. Associated deformities include mental retardation, skeletal abnormalities, and folds of skin on the sides of the neck (webbed neck).
- Such anomalies may affect more than one pair of chromosomes. Alternatively, one pair may be represented by more than three chromosomes. When this happens with the sex chromosomes, individuals with the constitution **XXXY, XXXXY, XXYY, or XXXX** may be produced.
- Sometimes, a gamete may have the diploid number of chromosomes so that the zygote will have 46 + 23 (i.e. 69) chromosomes. This is called ***triploidy.*** Higher multiples of 23 may also be seen. Such fetuses are generally born dead.

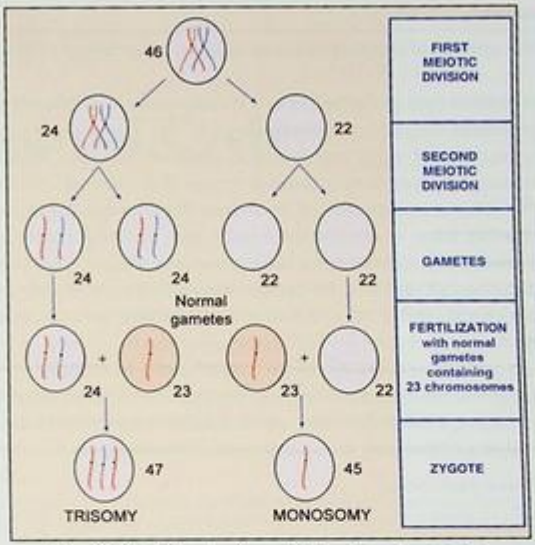

Fig. 2.19: Effects of non-disjunction during the first meiotic division.

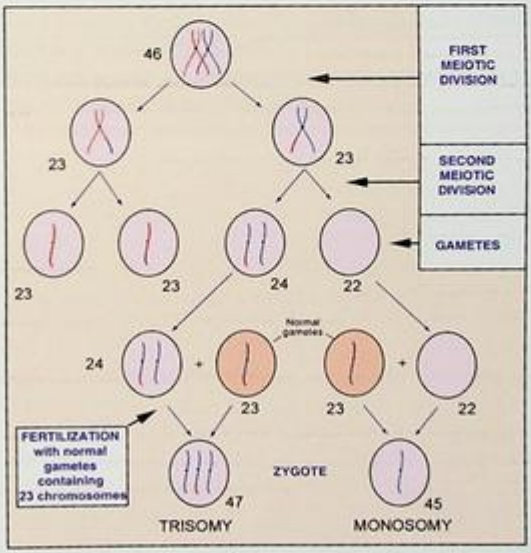

Fig. 2.20: Effects of non-disjunction during the second meiotic division.

Clinical Correlation *contd...*

- Abnormalities in the process of crossing over can result in a number of chromosomal abnormalities as follows:
  - Part of a chromosome may get attached to a chromosome of a different pair ***(translocation).***
  - Part of a chromosome may be lost ***(deletion).***
  - The two chromosomes of a pair may break at unequal distances. When each piece joins the opposite chromosome, one chromosome is longer than normal and some of the genes are ***duplicated***. The other chromosome will be shorter than normal, some genes being missing.
  - A piece separating from a chromosome may get inverted before joining the opposite chromosome ***(inversion).*** Although the same genes are present, their sequence is disturbed.
- We have seen that during cell division, the centromere splits longitudinally so that each chromatid becomes a separate chromosome. Sometimes, the centromere splits transversely producing two dissimilar chromosomes. One chromosome is made up of the short arms of both chromatids, while the other is made up of the long arms. These are called ***isochromosomes.***

  Chromosomal errors of the type described above may also occur during segmentation of the ovum. This results in a fetus having a mixture of cells with normal and abnormal chromosomes. This is called ***mosaicism***. Such individuals may also show various abnormalities.

Gene Abnormalities (Gene Mutations)

Genes are responsible for normal embryological development. A change in the structure of a gene may occur at the time of gametogenesis. This may give rise to birth defects. The change in the structure or function of a gene is called ***gene mutation.*** At present, many birth defects are known which are caused by gene mutation.

A more detailed account of abnormalities of gametes, of interest to postgraduate students, is given on the accompanying CD.

Chapter 3

The Menstrual Cycle

HIGHLIGHTS

- The term ***menstrual cycle*** is applied to cyclical changes that occur in the endometrium every month. The most obvious feature is a monthly flow of blood (***menstruation***).
- The menstrual cycle is divided into the following phases: ***postmenstrual***, ***proliferative***, ***secretory***, ***menstrual*** (Fig. 3.3).
- The menstrual cycle is also divided into the ***follicular phase*** (in which changes are produced mainly by oestrogens), and the ***luteal phase*** (in which effects of progesterone predominate). Both phases are of roughly equal duration.
- The main changes in the endometrium are (a) increase in thickness, (b) growth of uterine glands, (c) changes in epithelial cells lining the glands and (d) increase in thickness and fluid content of the endometrial stroma (Figs. 3.4, 3.5).
- Just before onset of menstruation, the blood supply to superficial parts of the endometrium is cut off (Fig. 3.6). This part is shed off and there is bleeding.
- The menstrual cycle is influenced by oestrogens, by progesterone, by the follicle stimulating hormone (FSH) and by the Luteinizing hormone (LH).

The period of a woman's life in which she can bear children is called the ***reproductive period***. The most obvious feature of this period is a monthly flow of blood from the uterus that is referred to as ***menstruation*** (or ***menses***). The onset of menstruation (***menarche***) takes place at about 12 years of age. Menstruation ceases to occur at about 45 years of age, and this is referred to as ***menopause***.

The monthly menstruation is the external manifestation of a series of cyclic changes taking place in the uterus. These changes constitute the ***menstrual cycle***. Simultaneously, cyclic changes also take place in the ovaries, and these constitute the ***ovarian cycle***. The most important event in the ovarian cycle is ovulation (Chapter 2).

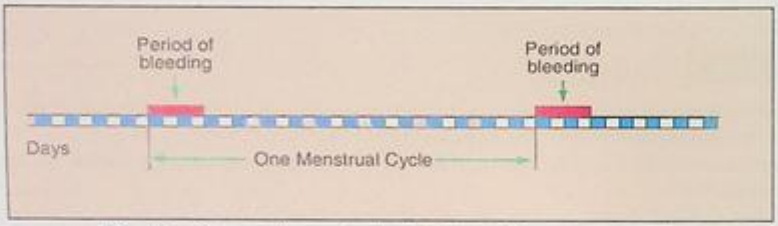

Fig. 3.1: Diagram illustrating the definition of a menstrual cycle.

To understand the menstrual cycle it is necessary to know the structure of the uterus. The wall of the uterus is made up of three layers.

1. The outermost layer or ***perimetrium*** is made up of peritoneum.
2. The main thickness of the wall is made up of smooth muscle. This is the ***myometrium***.
3. The innermost layer (corresponding to mucous membrane) is called the ***endometrium***. It is this layer which undergoes changes during the menstrual cycle.

The constituents of the endometrium are as follows (Fig. 3.2):

- The epithelium lining the surface of the endometrium.

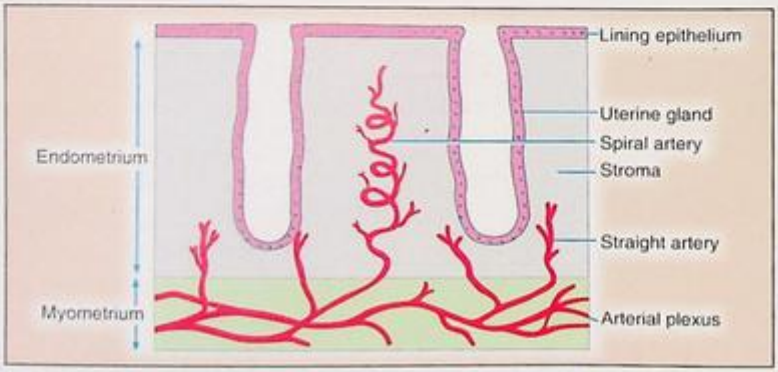

Fig. 3.2: Components of the uterine endometrium. These undergo changes during each menstrual cycle.

- The stroma fills the interval between surface epithelium and myometrium. It contains numerous simple tubular glands (uterine glands).
- The arteries that supply the endometrium tend to run vertically towards the surface. Some of these run spirally and supply the whole thickness of the endometrium, while others that remain straight are confined to the basal part.

PHASES OF THE MENSTRUAL CYCLE

The menstrual cycle is usually divided into the following phases, on the basis of changes taking place in the uterine endometrium (Fig. 3.3):

1. ***Post-menstrual***
2. ***Proliferative***
3. ***Secretory or pre-menstrual***
4. ***Menstrual***

The changes during the post-menstrual phase and during most of the proliferative phase take place under the action of oestrogens produced by the developing follicles in the ovary. Hence this period is referred to as the ***follicular phase*** of the menstrual cycle. The follicular phase constitutes the first half of the menstrual cycle. Following ovulation, the corpus luteum is formed and starts secreting progesterone. During the second half of the menstrual cycle, this hormone (along with oestrogens) produces striking changes in the endometrium. As these changes take place under the influence of the corpus luteum, this half of the menstrual cycle is called the ***luteal phase***. Just before the onset of the next bleeding, there is lowering of levels of both progesterone and oestrogens, and it is believed that this 'withdrawal' leads to the onset of menstrual bleeding.

The division of the menstrual cycle into the phases mentioned above is, however, arbitrary. The changes are really continuous and may be summarized as follows:

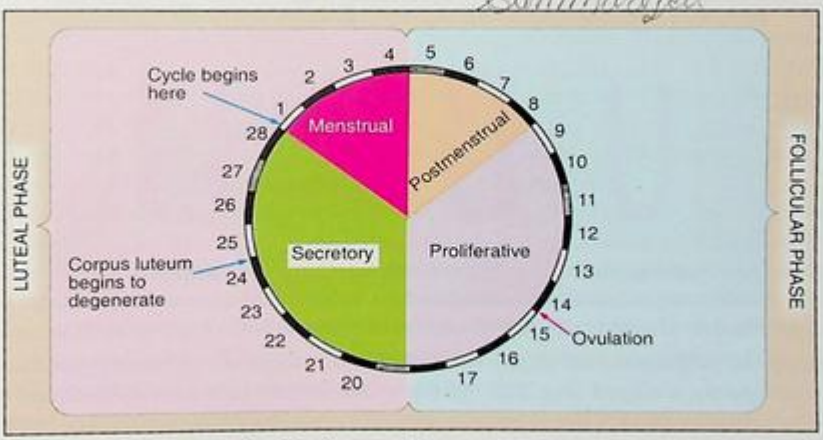

Fig. 3.3: Phases of the menstrual cycle.

- The endometrium progressively increases in thickness (Fig. 3.4). In the postmenstrual phase it is 0.5 to 1 mm thick; in the proliferative phase it is 2 to 3 mm thick; and in the secretory phase its thickness reaches 5 to 7 mm.
- The uterine glands grow in length. At first they are straight (Fig. 3.4A), but gradually become convoluted (Fig. 3.4B). Because of these convolutions, the glands acquire a 'saw-toothed' appearance when seen in longitudinal section. The glands also increase in diameter (Fig. 3.4C). The most basal parts of uterine glands, however, remain tubular and do not undergo these changes.

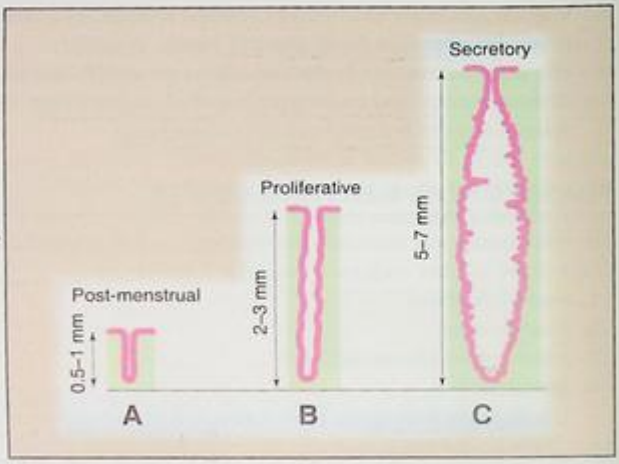

Fig. 3.4: Uterine glands at various phases of the menstrual cycle.

- The epithelium lining the glands is at first cuboidal (Fig. 3.5A). During the proliferative stage it becomes columnar (Fig. 3.5B). Glycogen accumulates in the basal portion of the epithelial cell, pushing the nucleus nearer the lumen (Fig. 3.5C). During the secretory phase the apical part of the cell is shed off as part of the secretion. The cell again becomes cubical, but the edge towards the lumen becomes irregular (Fig. 3.5D).

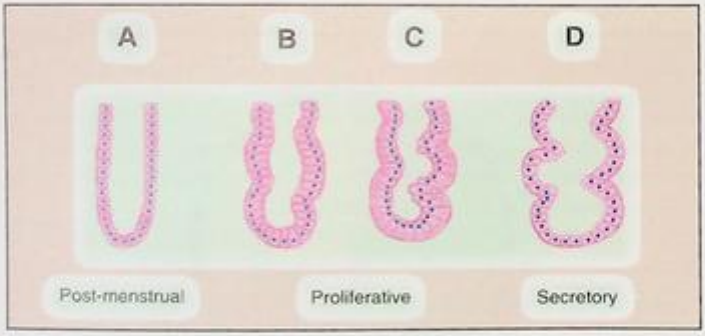

Fig. 3.5: Changes in the epithelium of uterine glands during a menstrual cycle.

- During the post-menstrual phase, the cells of the stroma are uniformly distributed and are compactly arranged (Fig. 3.2). As the endometrium increases in thickness (during the proliferative phase), the superficial part of the stroma remains compact, but the part surrounding the bodies of the uterine glands becomes spongy. The deepest part of the

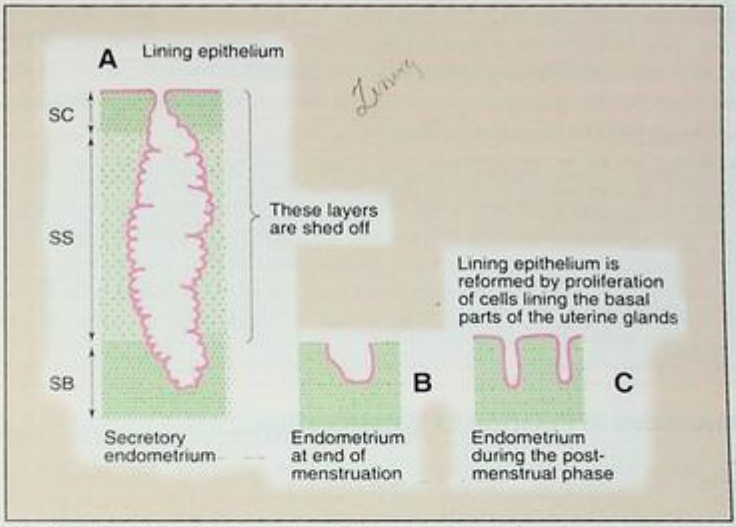

Fig. 3.6: Shedding off, and regeneration, of uterine endometrium, during a menstrual cycle. SC = stratum compactum; SS = stratum spongiosum; SB = stratum basale.

stroma also remains compact. The stroma can, therefore, be divided into the following three layers (Fig. 3.6A).

- ***Stratum compactum***
- ***Stratum spongiosum***
- ***Stratum basale***

During the secretory phase, these layers become better defined. The endometrium becomes soft and oedematous, because of the fluid secreted by the uterine glands.

- The arteries of the endometrium are small to begin with. They grow in length during the proliferative phase. During the secretory phase, the arteries supplying the superficial two-thirds of the endometrium become very tortuous, and are called spiral arteries. The arteries to the basal third of the endometrium (which does not participate in the changes associated with the menstrual cycle) remain straight and short.

Towards the end of the secretory phase the endometrium is thick, soft, and richly supplied with blood. The secretory activity of the uterine glands not only makes the endometrium soft, but also provides nutrition to the embryo. These changes are, therefore, an obvious preparation for providing a suitable environment for the fertilized ovum, when it reaches the uterus. In the absence of pregnancy, however, these measures are abortive: the superficial parts of the thickened endometrium (stratum compactum and stratum spongiosum) are shed off (Fig. 3.6B), and this is accompanied by menstrual bleeding.

Menstrual bleeding causes the endometrium to be shed off bit by bit, and the blood along with shreds of endometrium flows out through the vagina. At the end of menstruation, the

endometrium that remains is only 0.5 mm thick. It consists of the stratum basale along with the basal portions of the uterine glands (Fig. 3.6B). The epithelium of these glands rapidly proliferates and reforms the lining epithelium (Fig. 3.6C).

The endometrial changes associated with the menstrual cycle are confined to the body of the uterus. The cervical mucosa is not affected.

The mechanism for onset of menstrual bleeding is as follows. A few hours before the onset of menstrual bleeding the spiral arteries get constricted so that blood supply to superficial parts of the endometrium is cut off. This ischaemia leads to degeneration of the endometrium and also damages the walls of the blood vessels themselves. Subsequently when the arteries relax and blood again flows into the endometrium, it leaks out through the damaged blood vessels. This leaking blood is responsible for gradual shedding of endometrium.

Time of Ovulation in Relation to Menstruation

In a 28-day menstrual cycle, ovulation takes place at about the middle of the cycle (Fig. 3.3). The period between ovulation and the *next* menstrual bleeding is constant at about 14 days, but the time of ovulation does not have a constant relationship with the preceding menstruation. This is so because the length of the menstrual cycle may vary from month to month in an individual. Hence, it is difficult to predict the date of the next ovulation from the date of menstruation unless the woman has very regular menstrual periods.

There are many methods of finding out the exact time of ovulation, but the one commonly used is the temperature method. In this technique, the woman's temperature is recorded every morning. When these temperatures are plotted on a graph, we get a curve like that shown in Fig. 3.7. The temperature is low during actual menstruation. Subsequently it rises. At about the middle of the cycle, there is a sudden fall in temperature ***followed by a rise***. This rise is believed to indicate that ovulation has occurred.

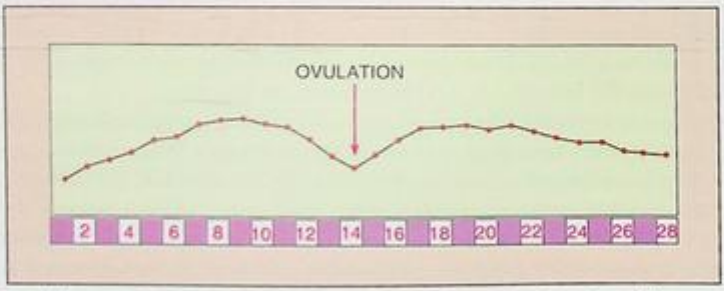

Fig. 3.7: Graph showing the morning temperature of a woman, on various days of the menstrual cycle. There is a fall in temperature at about the time of ovulation, followed by a rise.

Clinical Correlation

Importance of Determining the Time of Ovulation and "Safe Period"

A. Where pregnancy is not desired

After ovulation, the ovum is viable (i.e. it can be fertilized) for not more than two days. Spermatozoa introduced into the vagina die within four days. Therefore, fertilization can occur only if intercourse takes place during a period between four days before ovulation to two days after ovulation. The remaining days have been regarded as ***safe period*** as far as prevention of pregnancy is concerned. This forms the basis of the so-called ***rhythm-method*** of family planning.

B. Where pregnancy is desired

Knowledge regarding the time of ovulation is also of importance in cases of sterility (difficulty in having children), where the couple can be advised to have intercourse during the days most favourable for conception.

Correlation between Ovarian and Uterine Cycles

The ovarian and uterine cycles run parallel to each other. Both are of 28 days duration. The uterine cycle is dependent on ovarian cycle. The uterine endometrium shows cyclic changes, which are dependent on the hormones secreted by developing ovarian follicles and corpus luteum of the ovary.

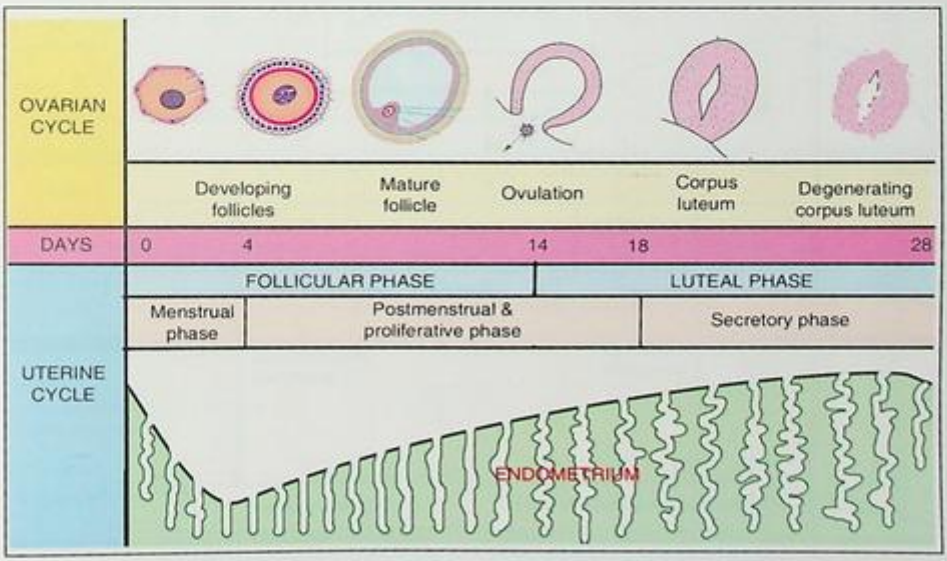

Fig. 3.8: Diagram showing correlation between ovarian and uterine cycles.

HORMONAL CONTROL OF OVARIAN AND UTERINE CYCLES

These cycles are under the control of various hormones, which can be briefly summarized as follows (Fig. 3.9):

The hypothalamus acts as a major centre for the control of reproduction. It secretes the ***gonadotropin-releasing hormones*** **(*GnRH*),** which in turn controls the secretion of ***gonadotrophic hormones*** from the anterior pituitary gland (adenohypophysis).

There are two gonadotrophic hormones. They are the ***follicle stimulating hormone (FSH)*** and the ***luteinizing hormone (LH).***

In the first half of the menstrual cycle the GnRH acts on the anterior pituitary to release FSH. The FSH acts on the ovary and stimulates the formation and maturation of ovarian follicles (Fig. 3.9).

The maturing ovarian follicles now start secreting oestrogens. The repair and proliferation of endometrium takes place under the influence of oestrogens. The endometrial stroma

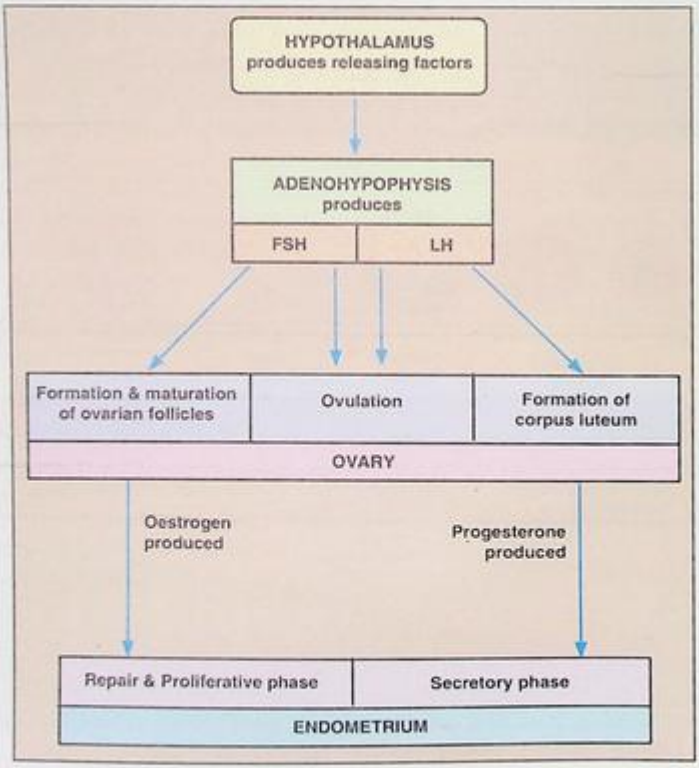

Fig. 3.9: Hormonal control of ovarian and uterine cycles.

progressively thickens, the glands in it elongate and the spiral arteries begin to grow towards the surface epithelium.

The level of oestrogen rises to a peak about two days before ovulation.

This leads to sudden increase in the level of LH secreted by the anterior pituitary (LH surge) about 24 to 36 hours before ovulation (Fig. 3.10).

The LH surge leads to ovulation; and the Graafian follicle is transformed to the corpus luteum.

The LH stimulates the secretion of progesterone by the corpus luteum. Though the secretion of progesterone predominates, some oestrogen is also produced. The combined action of oestrogen and progesterone stimulates the endometrial glands to secrete glycogen-rich mucoid material (Fig. 3.9).

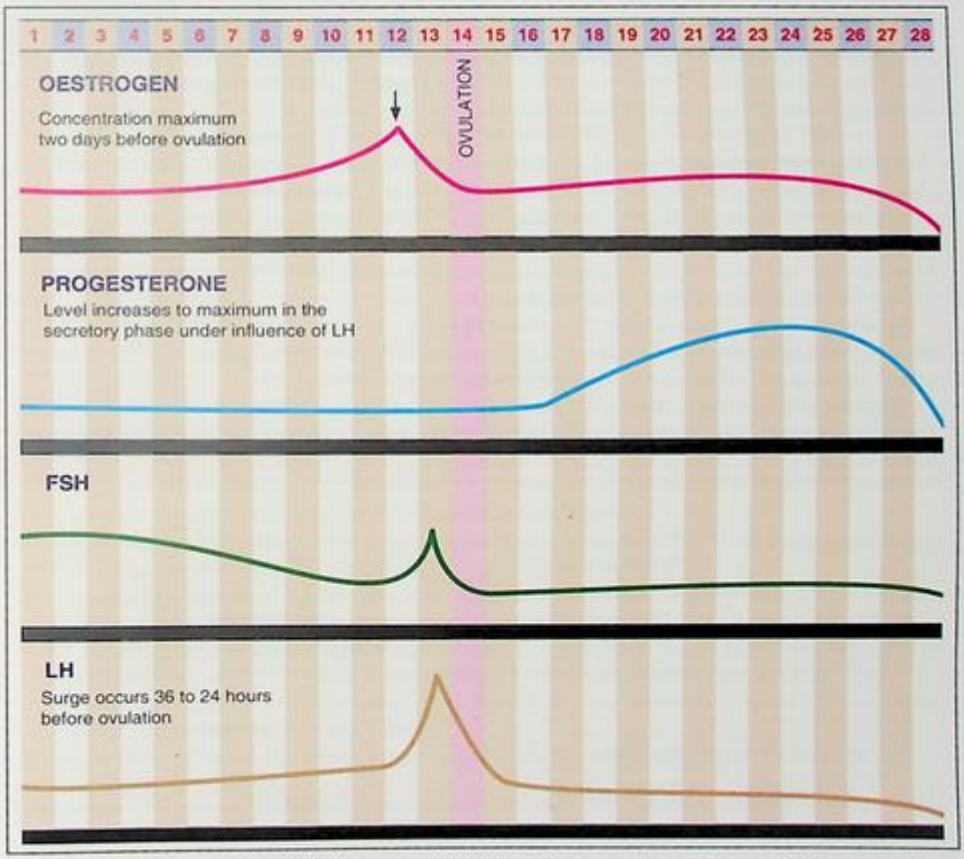

Fig. 3.10: Concentration of the hormones FSH, LH, oestrogen and progesterone during a normal menstrual cycle. Ovulation occurs because of a LH surge just before ovulation.

If fertilization does not occur, the granulosa cells produce the protein ***inhibin,*** which acts on the anterior pituitary and inhibits the secretion of gonadotrophins. This leads to regression of the corpus luteum.

Due to the regression of the corpus luteum there is a fall in the blood level of oestrogen and progesterone. The withdrawal of these hormones causes the endometrium to regress. and triggers the onset of menstruation.

If fertilization occurs, the corpus luteum does not regress. It continues to secrete progesterone and oestrogen. The secretory phase of endometrium continues and menstruation does not occur.

Clinical Correlation

Use of Hormones for Contraception

Ovulation in a woman (and by corollary, pregnancy) can be prevented by administration of contraceptive pills. The most important ingredients of such pills are progestins (in the form of synthetic compounds). Better results are obtained when a small amount of oestrogen is also given.

In the most common variety of pill (distributed by government agencies in India), the progestin is ***norethisterone acetate*** (1 mg); and the oestrogen is in the form of ***oestradiol*** (50µg). The pills are distributed in packets, each packet containing 28 pills out of which 21 pills contain these hormones, and 7 pills do not (for use in the last 7 days). The use of pills is started 5 days after onset of menstruation. They are taken continuously without any break as long as contraception is desired. Normal menstruation occurs during the 7 days in which pills without hormones are being taken. If the pills are taken regularly there is a regular menstrual cycle of 28 days duration.

Presence of progesterone in the pre-ovulatory phase prevents occurrence of ovulation. This is because the progesterone in the pill prevents the secretion of FSH and LH by the pituitary. This interferes with the maturation of follicles, and ovulation.

Stoppage of pills reduces levels of these hormones in blood. It is this withdrawal that leads to menstrual bleeding. Such pills have almost 100 per cent success in suppressing maturation of follicles and ovulation.

Chapter 4

Formation of Germ Layers

HIGHLIGHTS

- Fertilization of the ovum takes place in the ampulla of the uterine. The fertilized ovum is a large cell. It undergoes a series of divisions (clevage).
- When there are 16 cells the ovum is called a morula. It has an inner cell mass covered by an outer layer of cells, the trophoblast.
- Fluid partially separates the inner cell mass from trophoblast. The morula now becomes a blastocyst.
- The cells of the inner cell mass multipy, and are rearranged to form an ***embryonic disc*** having two layers. These layers are the ***epiblast*** and the ***hypoblast***. Later, the epiblast differentiates into three germ layers, the ***ectoderm*** (outer), the ***endoderm*** (inner), the ***mesoderm*** (middle). Cells of the hypoblast become flattened and line the yolk sac.
- A cavity appears on the ectodermal side of the disc. This is the ***amniotic cavity***. Another cavity appears on the endodermal side. This is the ***yolk sac***.
- At first the walls of the amniotic cavity and yolk sac are in contact with trophoblast. They are soon separated from the latter by ***extraembryonic mesoderm***.
- A cavity, the ***extraembryonic coelom*** appears and splits the extraembryonic mesoderm into a ***somatopleuric*** layer (in contact with trophoblast) and a ***splanchnopleuric*** layer (in contact with yolk sac).
- The trophoblast and underlying somatopleuric mesoderm form a membrane called the ***choroin***.
- The cells forming the wall of the amniotic cavity form the ***amnion***.
- The amniotic cavity is now attached to trophoblast by some mesoderm into which the extraembryonic coelom has not extended. This mesoderm forms the ***connecting stalk***.
- If we view the embryonic disc from the ectodermal side we see that near one edge it has a rounded area called the ***prochordal plate***. Here ectoderm and endoderm are not separated by mesoderm.
- An elevation, the ***primitive streak***, is also seen on the embryonic disc. A line drawn through the prochordal plate and the primitive streak divides the embryonic disc into right and left halves.
- Cells multiplying in the primitive streak move into the interval between ectoderm and endoderm and form the ***mesoderm*** (third germ layer).
- Caudal to the primitive disc we see a round area called the ***cloacal membrane***. It is made up only of ectoderm and endoderm.

cloacal

FERTILIZATION

In Chapter 2, we have seen that while the ovarian follicle is growing, the oogonium within it undergoes maturation. The oogonium enlarges to form a primary oocyte. The primary oocyte undergoes the first meiotic division to shed off the first polar body and becomes a secondary oocyte (Fig. 4.3A). At the time of ovulation, the second meiotic division is in progress and a spindle has formed for separation of the second polar body (Fig. 4.3B). At this stage, the 'ovum' enters the infundibulum of the uterine tube and passes into the ampulla (Fig. 4.1).

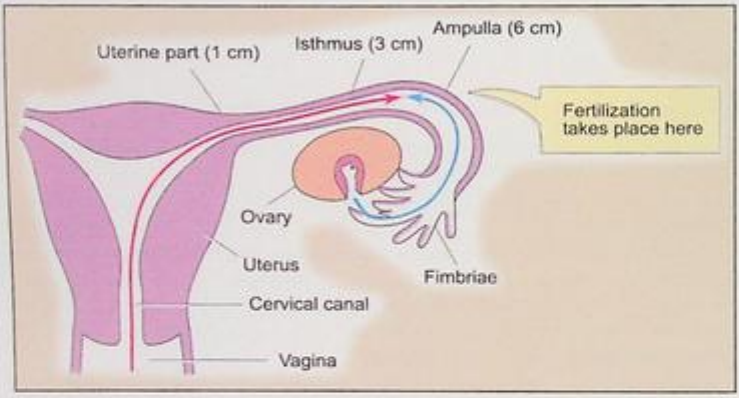

Fig. 4.1: Path taken by the sperm (red), and ovum (blue), for fertilization.

Fertilization of the ovum occurs in the ampulla of the uterine tube. Out of a few hundred capacitated sperms, which surround the ovum, only one pierces the zona pellucida and enters the ovum. As soon as the spermatozoon enters the ovum, the second meiotic division (which was so far incomplete) is completed, and the second polar body is extruded. The nucleus of the ovum becomes the ***female pronucleus***. The head of the spermatozoon (which it will be remembered is formed from the nucleus) separates from the middle piece and tail, and transforms itself into the ***male pronucleus***. Soon thereafter, the pronuclei lose their nuclear membranes. The 23 chromosomes of the female pronucleus and 23 of the male pronucleus get mixed up and form 23 pairs. These 46 chromosomes undergo changes like those in a typical mitotic division leading to the formation of an embryo having two cells (Fig. 4.4). Note that, strictly speaking, there is no one-cell stage of the embryo.

The middle piece and the tail soon separate from the head of the sperm and degenerate.

Some details on the biochemical changes occurring during fertilization are worth noting and are as follows:

- The glycoprotein of the zona pellucida is responsible for induction of the **acrosomal reaction** (Chapter 2). The release of acrosomal enzymes helps the sperm to penetrate the zona.
- When a spermatozoon comes in contact with the oocyte, plasma membranes of the two cells fuse. This, probably occurs at ***receptor sites*** that are specific for a species.

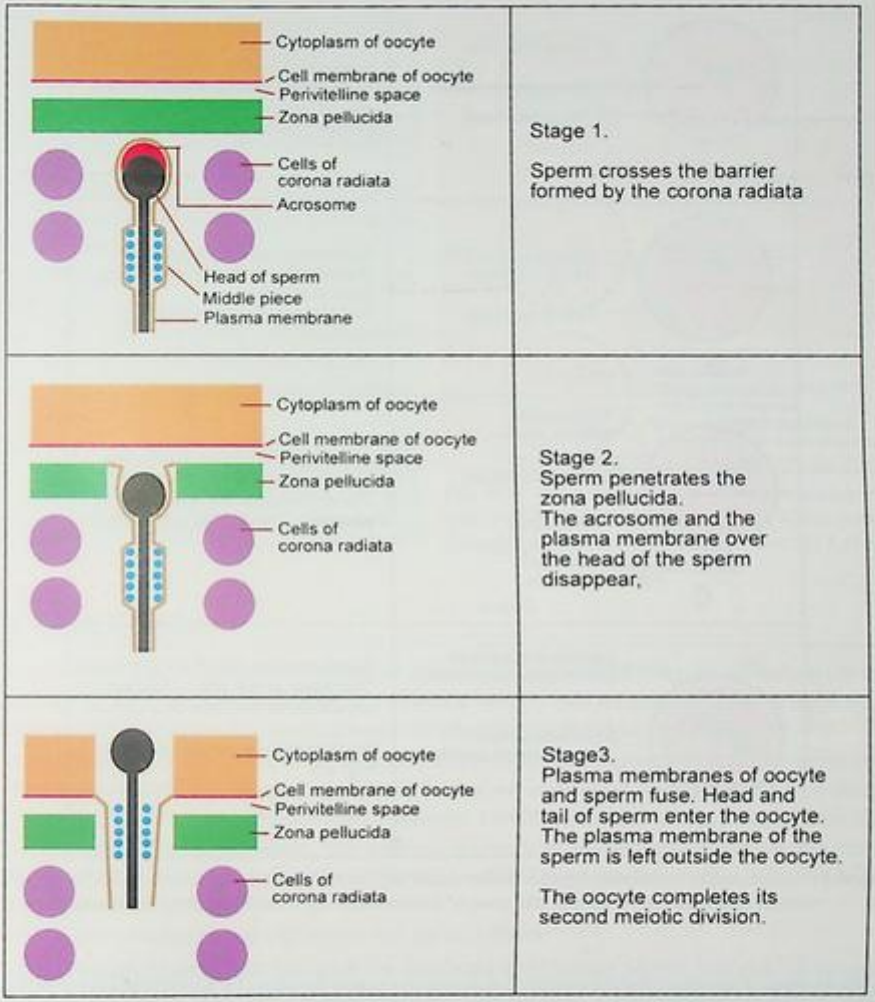

Fig. 4.2: Stages in penetration of a spermatozoon into an ovum.

Both the head and tail of the spermatozoon (excluding the plasma membrane) enter the cytoplasm of the ovum.

- Alterations taking place in the plasma membrane of the oocyte, and in the zona pellucida, ensure that no other spermatozoon can enter the oocyte.
- The zona pellucida is altered due to release of lysosomal enzymes by the plasma membrane of the oocyte. This process is called the ***zona reaction***.

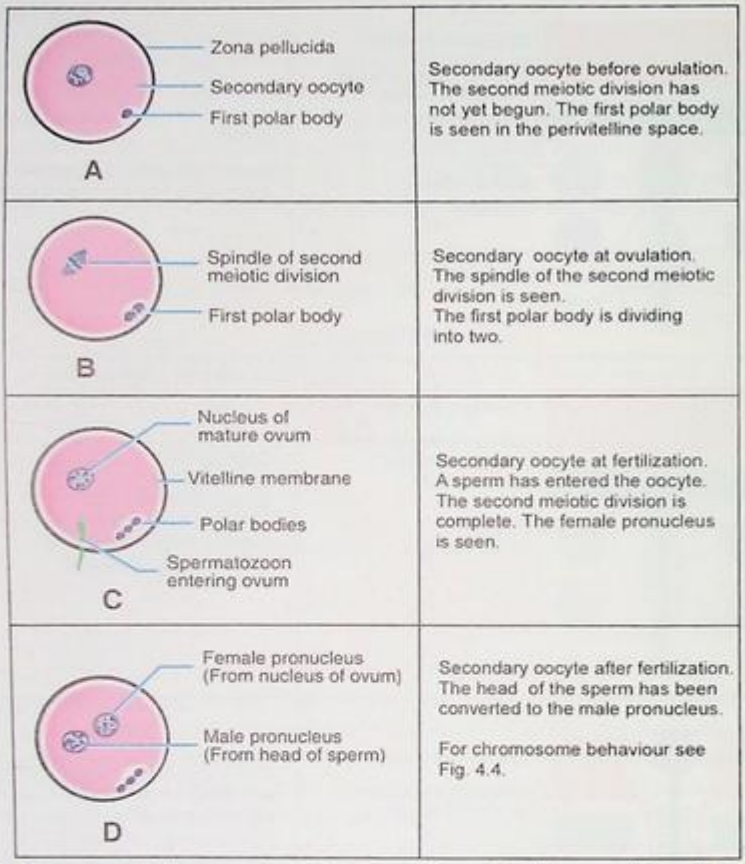

Fig. 4.3: Some stages in the maturation of the ovum: (A) Ovum just before ovulation. (B) Ovum at the time of ovulation. (C) Ovum at the time of fertilization. (D) Ovum just after fertilization.

- As soon as a spermatozoon enters the ovum the latter finishes its second meiotic division and the second polar body is formed.
- Entry of the sperm leads to metabolic changes within the ovum that facilitate its development into an embryo.
- Each chromosome in the male and female pronuclei is made up of only one chromatid. Replication of DNA takes place to form a second chromatid in each chromosome. In the cell division that follows, each chromosome splits into two (as in mitosis). Meanwhile a spindle has formed and one chromosome of each pair moves to each end of the spindle. This leads to formation of two cells, each having forty six chromosomes (Fig. 4.4).

- From what has been said above, it will be clear that as a result of fertilization:
  - the diploid chromosome number (46) is restored;
  - determination of sex takes place; and
  - the fertilized ovum begins to divide into several cells (i.e. it undergoes ***cleavage***).
- The important points to note at this stage are that:
  - the two daughter cells are still surrounded by the zona pellucida;
  - each daughter cell is much smaller than the ovum.
  - As subsequent divisions occur, the cells become smaller and smaller until they acquire the size of most cells of the body.

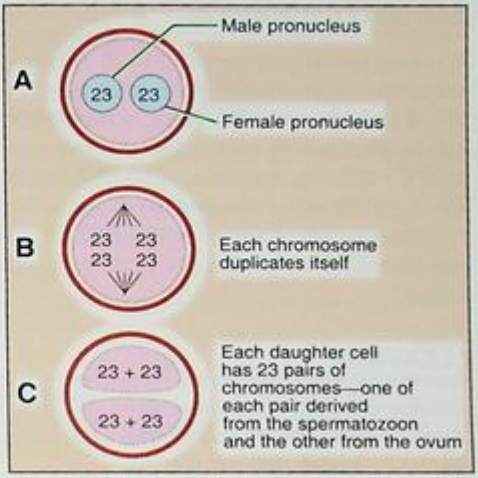

Fig. 4.4: Behaviour of chromosomes during fertilization. The female pronucleus has 22+X chromosomes. The male pronucleus may have 22+X or 22+Y chromosomes.

TEST TUBE BABIES

The so-called test tube babies are produced by the technique of ***in vitro fertilization*** (***In vitro*** = outside the body, as against ***in vivo*** = within the body). This technique is being increasingly used in couples who are not able to achieve fertilization in the normal way.

Gonadotropins are administered to the woman to stimulate growth of follicles in the ovary. Just before ovulation, the ovum is removed (using an aspirator) and is placed in a suitable medium. Spermatozoa are added to the medium. Fertilization and early development of the embryo take place in this medium. The process is carefully monitored, and when the embryo is at the 8-cell stage it is put inside the uterus. Successful implantation takes place in about 20 per cent of such trials.

The reasons for using the technique can be as follows:

- The number of spermatozoa may be inadequate (Usually about 2–5 mL of semen is ejaculated. Each millilitre contains about 100 million spermatozoa. If the count of spermatozoa is less than 20 million per mL, there may be difficulty in fertilization).
- There may be inadequate motility of spermatozoa.
- There may be obstruction of the uterine tube.
- There may be absence of ovulation.

SEX DETERMINATION

We know that all ova contain 22 + **X** chromosomes. However, we have seen that spermatozoa are of two types. Half of them have 22 + **X** chromosomes and the other half of them have 22 + **Y** chromosomes. We speak of these as '**X**-bearing' or '**Y**-bearing' spermatozoa. An ovum can be fertilized by either type of spermatozoon. If the sperm is **X**-bearing, the zygote has 44 + **X** + **X** chromosomes and the offspring is a girl. If the sperm is **Y**-bearing the zygote has 44 + **X** + **Y** chromosomes and the offspring is a boy.

Thus the sex of a child is 'determined' at the time of fertilization. It will now be clear that one chromosome of each of the 23 pairs is derived from the mother and the other from the father.

CLEAVAGE

The two cells formed as described above undergo a series of divisions. One cell divides first so that we have a '3-cell' stage of the embryo (Fig. 4.5B) followed by a '4-cell' stage (Fig. 4.5C), a '5-cell' stage, etc. This process of subdivision of the ovum into smaller cells is called ***cleavage***.

As cleavage proceeds the ovum comes to have 16 cells. It now looks like a mulberry and is called the ***morula*** (Fig. 4.5D). It is still surrounded by the zona pellucida. If we cut a section across the morula, we see that it consists of an ***inner cell mass*** that is completely surrounded by an outer layer of cells. The cells of the outer layer will later give rise to a structure called the ***trophoblast*** (Fig. 4.6A).

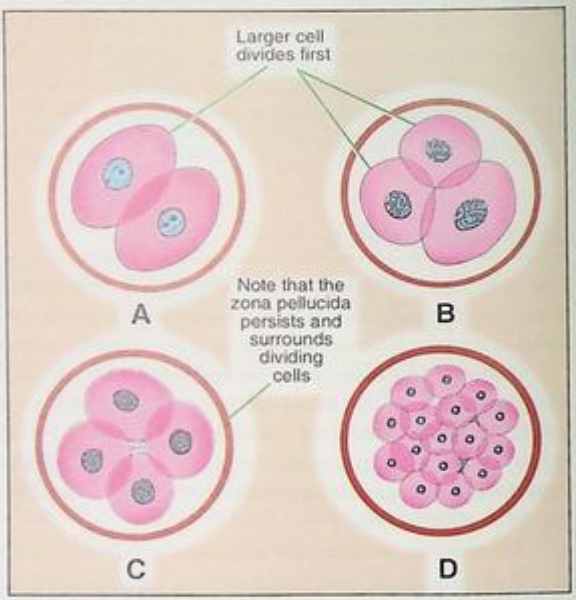

Fig. 4.5: Some stages in segmentation of the fertilized ovum. (A) Two cell stage. (B) Three cell stage. (C) Four cell stage. (D) Morula.

The inner cell mass gives rise to the embryo proper and is, therefore, also called the ***embryoblast***. The cells of the trophoblast help to provide nutrition to the embryo.

Some fluid now passes into the morula from the uterine cavity, and partially separates the cells of the inner cell mass from those of the trophoblast (Fig. 4.6B). As the quantity of fluid increases, the morula acquires the shape of a cyst. The cells of the trophoblast become flattened, and the inner cell mass gets attached to the inner side of the trophoblast on one side only (Fig. 4.6C).

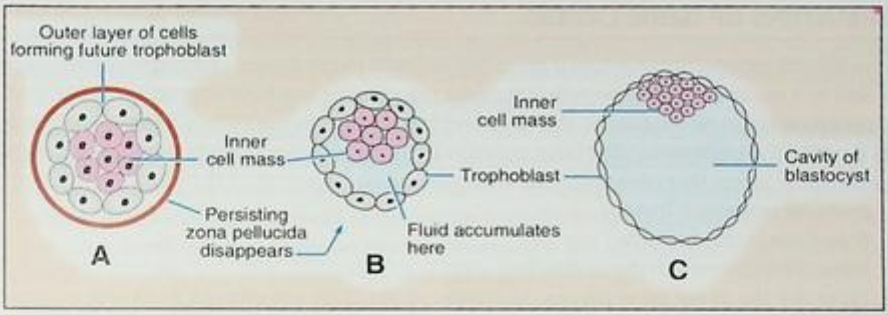

Fig. 4.6: Formation of blastocyst.

The morula has now become a ***blastocyst***. The cavity of the blastocyst is the ***blastocoele***. That side of the blastocyst to which the inner cell mass is attached is called the ***embryonic or animal pole***, while the opposite side is the ***abembryonic pole***.

Function of the Zona Pellucida

The trophoblast has the property of being able to stick to the uterine (or other) epithelium and its cells have the capacity to eat up other cells. They can, therefore, invade and burrow into tissues with which they come in contact. As the embryo travels down the uterine tube, and the uppermost part of the uterine cavity, it is prevented from 'sticking' to the epithelium by the zona pellucida. During this time, it receives nutrition, partly from the substances stored within the ovum (e.g. yolk), and partly by diffusion from uterine secretions. By the time a blastocyst is formed, it is necessary for the embryo to acquire additional sources of nutrition. This is achieved when the blastocyst 'sticks' to the uterine endometrium, and gets implanted in it. However, before this can happen, it is necessary for the zona pellucida to disappear. The zona pellucida disappears soon after the morula reaches the uterine lumen. Thus, the function of the zona pellucida is to prevent implantation of the blastocyst at an abnormal site.

- The glycoprotein of the zona pellucida is responsible for induction of the acrosomal reaction. The release of acrosomal enzymes (acrosin) helps the sperm to penetrate the zona.
- The zona pellucida allows only a sperm of the same species to fertilize the oocyte. Sperms of other species cannot pass through the zona pellucida.
- The zona pellucida is responsible for the zona reaction that prevents any additional spermatozoa from entering the fertilized ovum (zygote).
- The zona pellucida holds the blastomeres of the early embryo together.

The developing embryo is genetically different from the mother. This may evoke immunological reactions if embryonic and maternal tissues come in contact. Presence of zona pellucida (which lacks histocompatibility antigens), acts as a barrier that separates maternal tissues from the embryo. After the disappearance of zona pellucida various immunosuppressive cytokines and proteins are produced by the implanting embryo. This blocks the recognition of the embryo as a tissue foreign to the mother.

FORMATION OF GERM LAYERS

As the blastocyst develops further, it gives rise not only to the tissues and organs of the embryo but also to a number of structures that support the embryo and help it to acquire nutrition. At a very early stage in development, the embryo proper acquires the form of a three-layered disc. This is called the ***embryonic disc*** (also called embryonic area, embryonic shield, or germ disc).

The three layers that constitute this embryonic disc are:

1. ***Endoderm*** (endo = inside)
2. ***Ectoderm*** (ecto = outside)
3. ***Mesoderm*** (meso = in the middle)

These are the ***three germ layers***. All tissues of the body are derived from one or more of these layers. Much of the student's study of embryology concerns itself with learning from which of these germ layers particular tissues and organs develop. In the further development of the blastocyst that we will now consider, it is very important to have a clear conception of the formation of germ layers and of their fate.

We have seen that the blastocyst is a spherical cyst lined by flattened trophoblastic cells, and that inside it there is a mass of cells, the inner cell mass, attached eccentrically to the trophoblast.

Further changes are as follows:

- Some cells of the inner cell mass differentiate (i.e. they become different from others) into flattened cells, that come to line its free surface (lower in Fig. 4.7A). This layer is the ***hypoblast***.
- The remaining cells of the inner cell mass become columnar (Fig. 4.7B). These cells form the ***epiblast***. The embryo is now in the form of a disc having two layers.
- A space appears between the epiblast (below) and the trophoblast (above). This is the ***amniotic cavity*** (Fig. 4.7C), filled by ***amniotic fluid***, or ***liquor amnii***. The roof of this cavity is formed by ***amniogenic cells*** derived from the trophoblast, while its floor is formed by the epiblast.

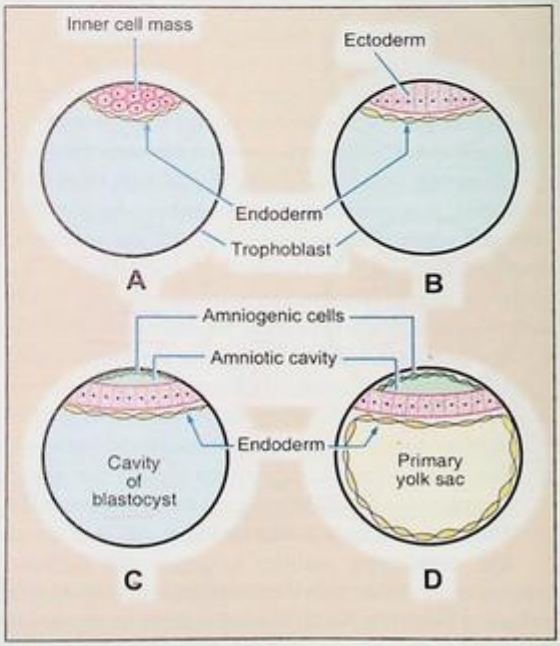

Fig. 4.7: Differentiation of endoderm and ectoderm, and the formation of the amniotic cavity and the yolk sac.

- Flattened cells arising from the hypoblast (or, according to some, from trophoblast), spread and line the inside of the blastocystic cavity. (This lining of flattened cells is called ***Heuser's membrane***). In this way, a cavity, lined on all sides by cells of endodermal origin, is formed. This cavity is called the ***primary yolk sac*** (Fig. 4.7D).
- The cells of the trophoblast give origin to a mass of cells called the ***extra-embryonic mesoderm*** (or primary mesoderm). These cells come to lie between the trophoblast and the flattened endodermal cells lining the yolk sac, thus separating them from each other. These cells also separate the wall of the amniotic cavity from the trophoblast (Fig. 4.8A). This mesoderm is called 'extra-embryonic' because it lies outside the embryonic disc. It does not give rise to any tissues of the embryo itself.
- Small cavities appear in the extra-embryonic mesoderm. Gradually, these join together to form larger spaces and, ultimately, one large cavity is formed. This cavity is called the ***extra-embryonic coelom*** (Fig. 4.8B) (also called the ***chorionic cavity***). With its formation, the extra-embryonic mesoderm is split into two layers. The part lining the inside of the trophoblast, and the outside of the amniotic cavity, is called the ***parietal or somatopleuric extra-embryonic mesoderm***. (It is also referred to as the chorionic plate). The part lining the outside of the yolk sac is called the ***visceral or splanchnopleuric extra-embryonic mesoderm*** (Fig. 4.8B).

From Fig. 4.8B it is clearly seen that the extra-embryonic coelom does not extend into that part of the extra-embryonic mesoderm which attaches the wall of the amniotic cavity to the trophoblast. The developing embryo, along with the amniotic cavity and the yolk sac, is now suspended in the extra-embryonic coelom, and is attached to the wall of the

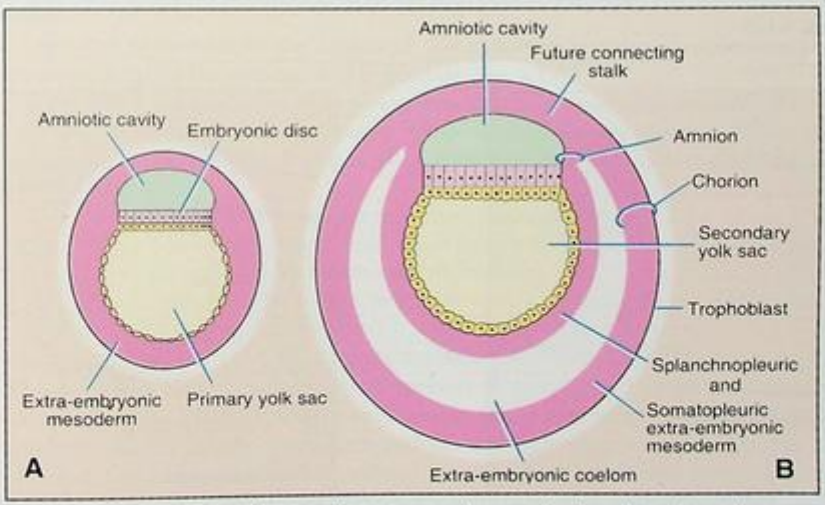

Fig. 4.8: Formation of extraembryonic mesoderm and extraembryonic coelom. Note carefully, the composition of the amnion, and of the chorion.

blastocyst (i.e. trophoblast) only by this unsplit part of the extra-embryonic mesoderm. This mesoderm forms a structure called the ***connecting stalk***.

- ***Formation of Chorion and Amnion***: At this stage, two very important membranes are formed. One is formed by the parietal extra-embryonic mesoderm (on the inside) and the overlying trophoblast (on the outside); this is called the ***chorion*** (Fig. 4.8B). The other is the ***amnion*** which is constituted by amniogenic cells forming the wall of the amniotic cavity (excluding the ectodermal floor). These cells are derived from the trophoblast. We have already seen that the amnion is covered by the parietal extra-embryonic mesoderm, and that the connecting stalk is attached to it.

  The chorion and amnion play an important role in child birth (parturition) and we will refer to them again.
- With the appearance of the extra-embryonic mesoderm, and later of the extraembryonic coelom, the yolk sac becomes much smaller than before and is now called the ***secondary yolk sac***. This alteration in size is accompanied by a change in the nature of the lining cells. They are no longer flattened but become cubical (Fig. 4.8B).
- At this stage, the embryo proper is a circular disc composed of two layers of cells: the upper layer (towards amniotic cavity) is the epiblast, the cells of which are columnar, while the lower layer (towards yolk sac) is the hypoblast, made up of cubical cells. There is no indication yet of a head or tail end of the embryonic disc (Fig. 4.9).
- However, we soon see that, at one circular area near the margin of the disc, the cubical cells of the endoderm become columnar. This area is called the ***prochordal plate***. The appearance of the prochordal plate determines the central axis of the embryo (i.e. enables us to divide it into right and left halves), and also enables us to distinguish its future head and tail ends (Fig. 4.10).

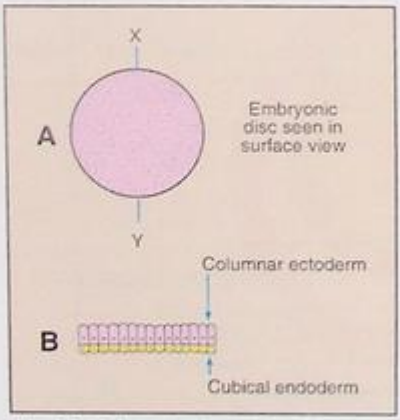

Fig. 4.9: Embryonic disc before appearance of a central axis. 'B' represents a section along the axis XY shown in 'A'.

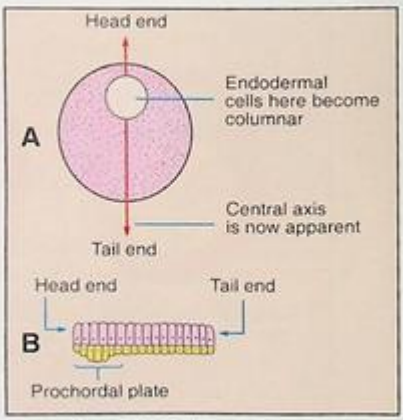

Fig. 4.10: Embryonic disc after establishment of a central axis. 'B' represents a section along the central axis.

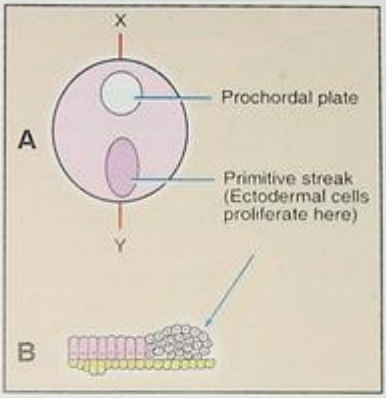

Fig. 4.11: Appearance of primitive streak. (B) is a section along axis XY shown in (A).

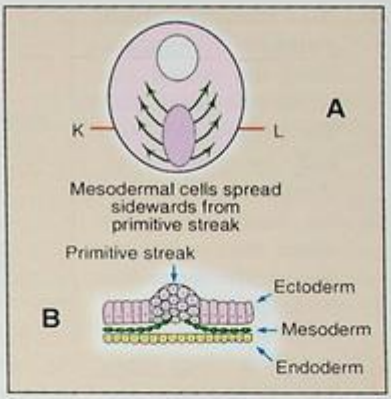

Fig. 4.12: Formation of intraembryonic mesoderm. (B) is a section along axis KL in (A).

- Soon after the formation of the prochordal plate, some of the epiblast cells lying along the central axis, near the tail end of the disc, begin to proliferate, and form an elevation that bulges into the amniotic cavity. This elevation is called the ***primitive streak*** (Figs. 4.11A, B). The primitive streak is at first a rounded or oval swelling, but with elongation of the embryonic disc it becomes a linear structure lying in the central axis of the disc.
- The cells that proliferate in the region of the primitive streak pass sideways, pushing themselves between the epiblast and hypoblast (Fig. 4.12).
  - These cells form the ***intra-embryonic mesoderm*** (or secondary mesoderm).
  - Some cells arising from the primitive streak displace the hypoblast and form the layer that is now known as ***endoderm***. Thus both endoderm and mesoderm are derived from the epiblast.
  - The remaining cells of the epiblast now form the ***ectoderm***.
  - In this way we now have a disc made up of three layers. These layers are the ectoderm (outer), endoderm (inner) and mesoderm (middle).
  - The process of formation of the primitive streak, of endoderm, and of the intra-embryonic mesoderm (by the streak), is referred to as ***gastrulation***.
- The intra-embryonic mesoderm spreads throughout the disc except in the region of the prochordal plate. Note that the mesoderm extends cranial to the prochordal plate, and here mesoderm from the two sides becomes continuous across the midline (Fig. 4.13). In the region of the prochordal plate, the ectoderm and endoderm remain in contact. In later development, the ectoderm and endoderm mostly persist as a lining epithelium. On the other hand, the bulk of the tissues of the body is formed predominantly from mesoderm. As there is no mesoderm in the prochordal plate, this region remains relatively thin, and later forms the ***bucco-pharyngeal membrane***.

- The primitive streak gradually elongates, along the central axis of the embryonic disc. The disc also elongates and becomes pear-shaped (Fig. 4.13).
- We have seen that when the embryonic disc is first formed, it is suspended (along with amniotic cavity and yolk sac) from the trophoblast by the connecting stalk (Figs. 4.8, 4.14). To begin with, the connecting stalk is very broad compared to the size of the embryo. As the embryonic disc enlarges in size, and also elongates, the connecting stalk becomes relatively small, and its attachment becomes confined to the region of the tail end of the embryonic disc (Fig. 4.14). Some intraembryonic mesoderm arising from the primitive streak, passes backwards into the connecting stalk (Figs. 4.13, 4.14). As it does so, it leaves an area caudal to the primitive streak, where ectoderm and endoderm remain in contact (i.e. mesoderm does not separate them). This region is, therefore, similar to the prochordal plate, and forms the ***cloacal membrane*** (Fig. 4.13).

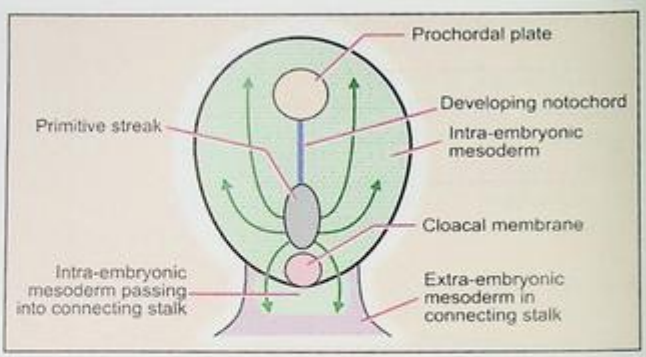

Fig. 4.13: Spread of intra-embryonic mesoderm. Note that the mesoderm comes to lie between ectoderm and endoderm in all parts of the embryonic disc except at (1) the prochordal plate, (2) the cloacal membrane, and (3) the region of the notochord.

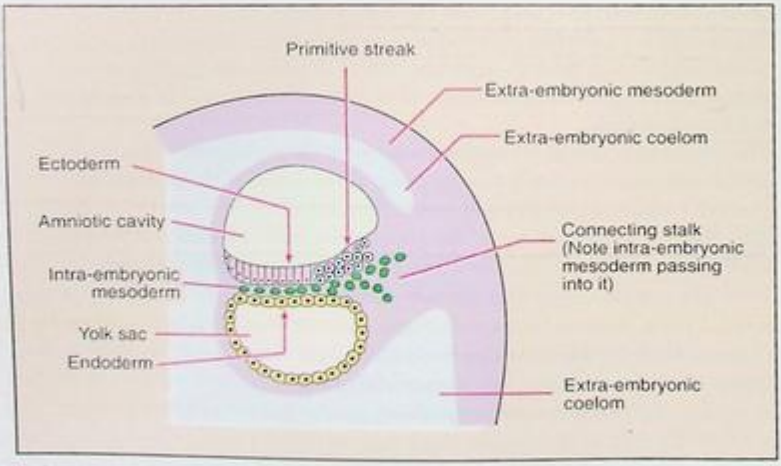

Fig. 4.14: Diagram showing the attachment of the connecting stalk to the caudal end of the embryonic disc. Note the cells of the intra-embryonic mesoderm passing into the connecting stalk.

Clinical Correlation

Use of Stem Cells in the Treatment of Diseases

By now readers must have realized that the cells of inner cell mass have the potential to differentiate into three different germ layers (ectoderm, endoderm and mesoderm). All the cells, tissues and organs of the body are formed from these three layers. Because of this the cells of the inner cell mass are called ***embryonic stem cells.*** These stem cells can be maintained and propagated in an undifferentiated state, in culture, in laboratories. If these cells are exposed to certain specific growth factors, in culture, the stem cells can form various types of adult cells e.g., neurons, muscle cells, blood cells, and cartilage cells. These cells are therefore said to be ***pleuripotent***. It has been observed that when these stem cells are introduced into the living tissues of a person, the local environment helps these stem cells to differentiate into cells similar to those of the tissue in which they are placed. This technique has tremendous potential for treatment of various diseases. Some of these are Parkinson's disease, Alzheimer disease, diabetes, myocardial infarction, blood diseases, severe burns, osteoporosis, spinal cord injury, to name but a few. However, in this procedure, the complication of immune rejection is always present as the genetic constitution of stem cell is different from that of patient. To overcome this problem scientists are working on "therapeutic stem cell cloning". In this procedure the nucleus of patient cell is introduced in the embryonic stem cell. These cells are then allowed to grow in any tissue of the patient. As the tissues arising from the stem cells are now genetically identical to those of the patient rejection is avoided.

Although the embryonic stem cells are most suitable for therapeutic purposes, stem cells can also be isolated from some adult tissues e.g., bone marrow, brain and skeletal muscle. However, adult stem cells are difficult to culture in laboratories and have less potential to differentiate in adult tissues.

As human embryos are needed for stem cell research, some authorities object to it on ethical grounds. The main objections are that it is against nature and it treats the embryo with disrespect.

TIME TABLE OF EVENTS DESCRIBED IN THIS CHAPTER

Development of the embryo from fertilization up to the formation of the bilaminar disc is described as the ***pre-organogenesis period*** as no organs are as yet recognizable. These events take place in the first 14 days of pregnancy. Anomalies produced by teratogens acting during this period usually result in death of the embryo. These anomalies are, therefore, seldom seen in babies reaching full term.

Establishment of the primitive streak and formation of intra-embryonic mesoderm mark the onset of ***gastrulation***. Gastrulation begins in the third week and most of it will be considered in the next chapter. The third week marks the beginning of what is termed the ***embryonic period*** (3rd to 8th week). Most congenital anomalies are produced by teratogens acting during this period.

The time table of some events described in this chapter is as follows.

Age in Days	Developmental Events
2	Embryo is at two cell stage
3	Morula is formed
4	Blastocyst is formed
8	Bilaminar disc is formed
14	Prochordal plate and primitive streak is seen
16	Intra-embryonic mesoderm is formed / disc is now three layered.

Chapter 5

Further Development of Embryonic Disc

HIGHLIGHTS

- The cranial end of the primitive streak enlarges to form the ***primitive knot*** (Fig. 5.1).
- Cells of the primitive knot multiply and pass cranially to form a rod-like structure reaching up to the prochordal plate. This is the ***notochordal process***.
- The notochordal process undergoes changes that convert it first into a canal and then into a plate, and finally back into a rod-like structure. This is the ***notochord***.
- Most of the notochord disappears. Remnants remain as the ***nucleus pulposus*** of each intervertebral disc.
- A wide strip of ectoderm overlying the notochord becomes thickened and forms the ***neural plate*** (Fig. 5.4C) from which the brain and spinal cord develop.
- ***Intra-embryonic mesoderm*** shows three subdivisions (Fig. 5.4D). The mesoderm next to the middle line is called the ***paraxial mesoderm***. It undergoes segmentation to form ***somites***. The mesoderm in the lateral part of the embryonic disc is called the ***lateral plate mesoderm***. A cavity called the ***intra-embryonic coelom*** appears in it and splits the mesoderm into a ***somatopleuric*** layer (in contact with ectoderm) and a ***splanchnopleuric*** layer (in contact with endoderm) (Fig. 5.5D). A strip of mesoderm between the lateral plate mesoderm and the paraxial mesoderm is called the ***intermediate mesoderm***.
- The intra-embryonic coelom later forms the pericardial, pleural and peritoneal cavities.
- The embryonic disc, which is at first flat, undergoes folding at the cranial and caudal ends. These are the ***head and tail folds*** (Fig. 5.7). Lateral folds also appear. As a result of these folds, the endoderm is converted into a tube, the gut. It is divisible into ***foregut***, ***midgut*** and ***hindgut***.
- After formation of the head fold the gut is closed cranially by the prochordal plate, which is now called the ***buccopharyngeal membrane***. Caudally, the gut is closed by the ***cloacal membrane***. The ***umbilical cord*** develops from the connecting stalk. It contains the right and left umbilical arteries, the left umbilical vein, and remnants of the vitello-intestinal duct and yolk sac. The ground substance of the umbilical cord is made up of Wharton's jelly derived from mesoderm. The cord is covered by amnion.
- The ***allantoic diverticulum*** arises from the yolk sac before formation of the gut (Fig. 5.10). After formation of the tail fold, it is seen as a diverticulum of the hindgut.
- The ***pericardial cavity*** is derived from part of the intra-embryonic coelom that lies cranial to the prochordal plate (Fig. 5.11). The developing heart lies ventral to the cavity (Fig. 5.12). After formation of the head fold the pericardial cavity lies ventral to the foregut; and the developing heart is dorsal to the pericardial cavity (Fig. 5.13).
- The ***septum transversum*** is made of intra-embryonic mesoderm that lies cranial to the pericardial cavity (Figs 5.11, 5.12). After formation of the head fold, it lies caudal to the pericardium and heart (Fig. 5.13). The liver and the diaphragm develop in relation to the septum transversum.

FORMATION OF THE NOTOCHORD

The notochord is a midline structure that develops in the region lying between the cranial end of the primitive streak and the caudal end of the prochordal plate (Figs 4.12, 5.1, 5.2). During its development, the notochord passes through several stages that are as follows:

- The cranial end of the primitive streak becomes thickened. This thickened part of the streak is called the ***primitive knot, primitive node*** or ***Henson's node*** (Figs 5.1A, 5.2A).
- A depression appears in the centre of the primitive knot. This depression is called the ***blastopore*** (Figs 5.1B, 5.2B).
- Cells in the primitive knot multiply and pass cranially in the middle line, between the ectoderm and endoderm, reaching up to the caudal margin of the prochordal plate. These cells form a solid cord called the ***notochordal process*** or ***head process*** (Figs 5.1C, 5.2C, 5.3A).

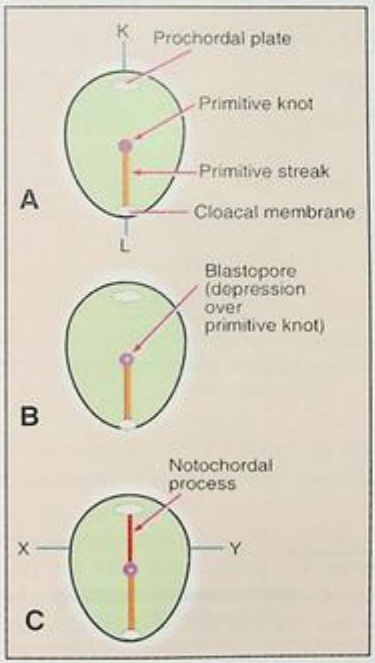

Fig. 5.1: Formation of primitive knot (A), blastopore (B) and notochordal process (C). Note that the notochordal process is deep to ectoderm and that its position is shown diagrammatically. Between the cranial end of the notochordal process and the prochordal plate there is a collection of cells lying next to endoderm. This collection of cells is the prechordal plate (not drawn)

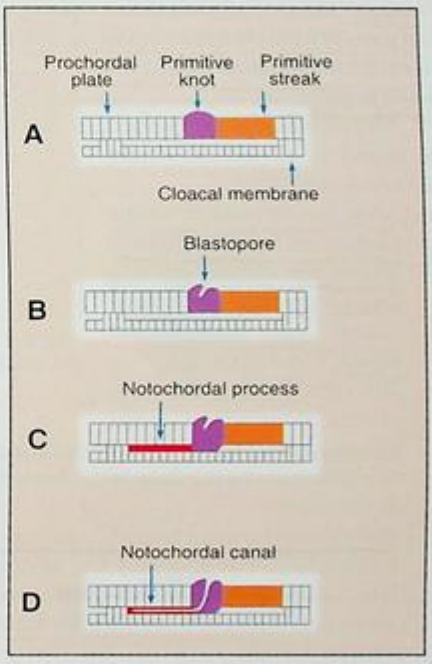

Fig. 5.2: Sections through the embryonic disc along the axis KL shown in Fig. 5.1A to illustrate the formation of the primitive knot (A), blastopore (B), notochordal process (C) and notochordal canal (D). Stages A, B and C correspond to those of Fig. 5.1.

The cells of this process undergo several stages of rearrangement (Figs 5.1, 5.2) ending in the formation of a solid rod called the ***notochord***.

As the embryo enlarges, the notochord elongates considerably and lies in the midline, in the position to be later occupied by the vertebral column. However, the notochord ***does not*** give rise to the vertebral column. Most of it disappears, but parts of it persist in the region of each intervertebral disc as the ***nucleus pulposus***.

Some details of the process of formation of the notochord are as follows:

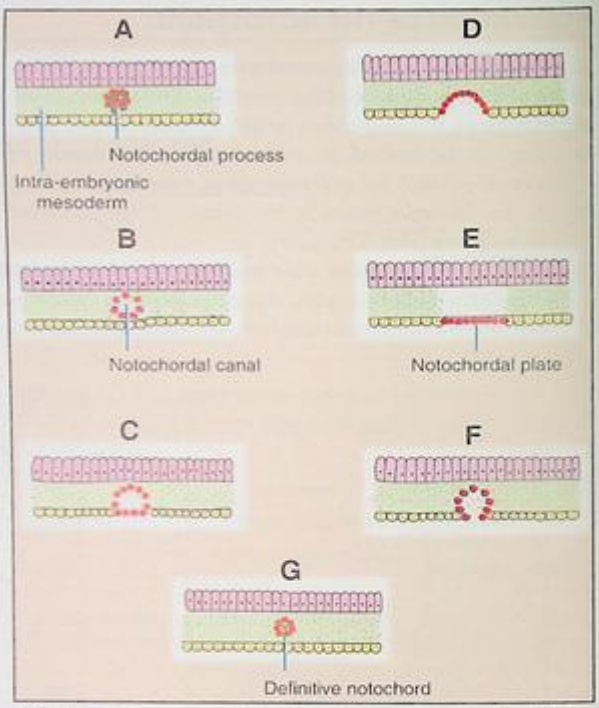

Fig. 5.3: Transverse sections through the embryonic disc (along the axis XY shown in Fig. 5.1C) to illustrate stages in the formation of the notochord.

- After the formation of the blastopore, its cavity extends into the notochordal process, and converts it into a tube called the ***notochordal canal*** (Figs 5.2D, 5.3B).
- The cells forming the floor of the notochordal canal become intercalated in (i.e. become mixed up with) the cells of the endoderm (Fig. 5.3C). The cells forming the floor of the notochordal canal now separate the canal from the cavity of the yolk sac.
- The floor of the notochordal canal begins to break down. At first, there are small openings formed in it, but gradually the whole canal comes to communicate with the yolk sac (Fig. 5.3D). The notochordal canal also communicates with the amniotic cavity through the blastopore. Thus, at this stage, the amniotic cavity and the yolk sac are in communication with each other.
- Gradually the walls of the canal become flattened so that instead of a rounded canal we have a flat plate of cells called the ***notochordal plate*** (Fig. 5.3E).
- However, this process of flattening is soon reversed and the notochordal plate again becomes curved, to assume the shape of a tube (Figs 5.3F, G). Proliferation of cells of this tube converts it into a solid rod of cells. This rod is the definitive (i.e. finally formed) ***notochord***. It gets completely separated from the endoderm.

The notochord is present in all animals that belong to the phylum Chordata. In some of them, e.g. ***Amphioxus***, it persists into adult life and forms the central axis of the body. In others, including man, it appears in the embryo but only small remnants of it remain in the adult.

FORMATION OF THE NEURAL TUBE

The details of the formation of the neural tube will be studied later. For the time being, it may be noted that:

- The neural tube gives rise to the brain and the spinal cord.
- The neural tube is formed from the ectoderm overlying the notochord and, therefore, extends from the prochordal plate to the primitive knot (Fig. 5.4C).
- The neural tube is soon divisible into: (a) a cranial enlarged part that forms the brain, and (b) a caudal tubular part that forms the spinal cord.
- In early embryos, the developing brain forms a large conspicuous mass, on the dorsal aspect. The process of formation of the neural tube is referred to as ***neurulation***.

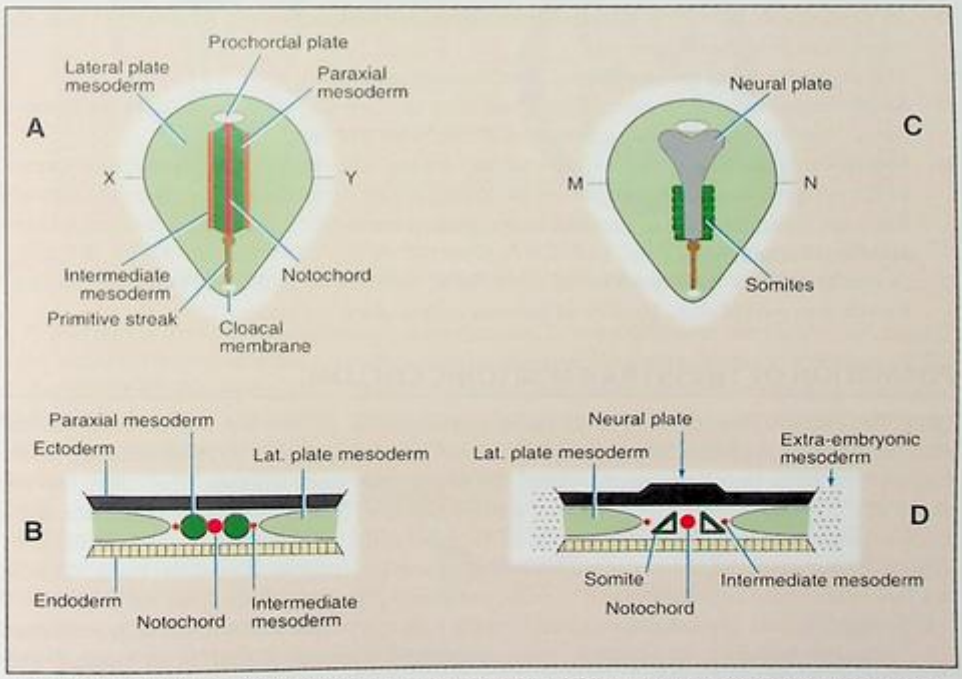

Fig. 5.4: Subdivisions of intra-embryonic mesoderm. 'B' and 'D' are transverse sections across axes XY (in A) and MN (in C) respectively. Note that the notochord and mesoderm are deep to the ectoderm. Their position is shown diagrammatically.

SUBDIVISIONS OF INTRA-EMBRYONIC MESODERM

We have seen that the intra-embryonic mesoderm is formed by proliferation of cells in the primitive streak and that it separates the ectoderm and the endoderm, except in the following regions: (a) prochordal plate (b) cloacal membrane, and (c) in the midline caudal to the prochordal plate, as this place is occupied by the notochord.

Cranial to the prochordal plate, the mesoderm of the two sides meets in the midline (Fig. 4.12). At the edges of the embryonic disc, the intra-embryonic mesoderm is continuous with the extra-embryonic mesoderm (Fig. 5.4D). The intra-embryonic mesoderm now becomes subdivided into three parts (Fig. 5.4):

A. The mesoderm, on either side of the notochord, becomes thick and is called the ***paraxial mesoderm***.
B. More laterally, the mesoderm forms a thinner layer called the ***lateral plate mesoderm***.
C. Between these two, there is a longitudinal strip called the ***intermediate mesoderm***.

Some Details about the Paraxial Mesoderm

- At first, the cells of the paraxial mesoderm are homogenously arranged. Later, the mesoderm gets segmented.
- The segments are of two categories, somitomeres and somites.
- ***Somitomeres*** lie in the region of the head. They are rounded structures. There are seven of them. They form the bones and muscles of the head and jaw..
- ***Somites*** are cubical and more distinctly segmented. The most cranial somites are formed in the occipital region. New somites are progressively formed caudal to them. Ultimately there are about 44 pairs of somites (4 occipital, 8 cervical, 12 thoracic, 5 lumbar, 5 sacral and 8 to 10 coccygeal).
- Occipital somites form muscles of the tongue. Somites form the axial skeleton, skeletal muscle and part of skin. The fate of somites is described in Chapter 7.

FORMATION OF THE INTRA-EMBRYONIC COELOM

While the paraxial mesoderm is undergoing segmentation, to form the somites, changes are also occurring in the lateral plate mesoderm. Small cavities appear in it. These coalesce (come together) to form one large cavity, called the ***intra-embryonic coelom***. The cavity has the shape of a horseshoe (Figs 5.5A, C). There are two halves of the cavity (one on either side of the midline) which are joined together cranial to the prochordal plate. At first, this is a closed cavity (Fig. 5.5A) but soon it comes to communicate with the extra-embryonic coelom (Fig. 5.5C). With the formation of the intra-embryonic coelom, the lateral plate mesoderm splits into:

1. ***Somatopleuric*** or ***parietal,*** intra-embryonic mesoderm that is in contact with ectoderm.
2. ***Splanchnopleuric***, or ***visceral***, intra-embryonic mesoderm that is in contact with endoderm (Figs 5.5B, D).

The intra-embryonic coelom gives rise to pericardial, pleural, and peritoneal cavities. Their development will be considered later. For the time being, note that the pericardium is formed

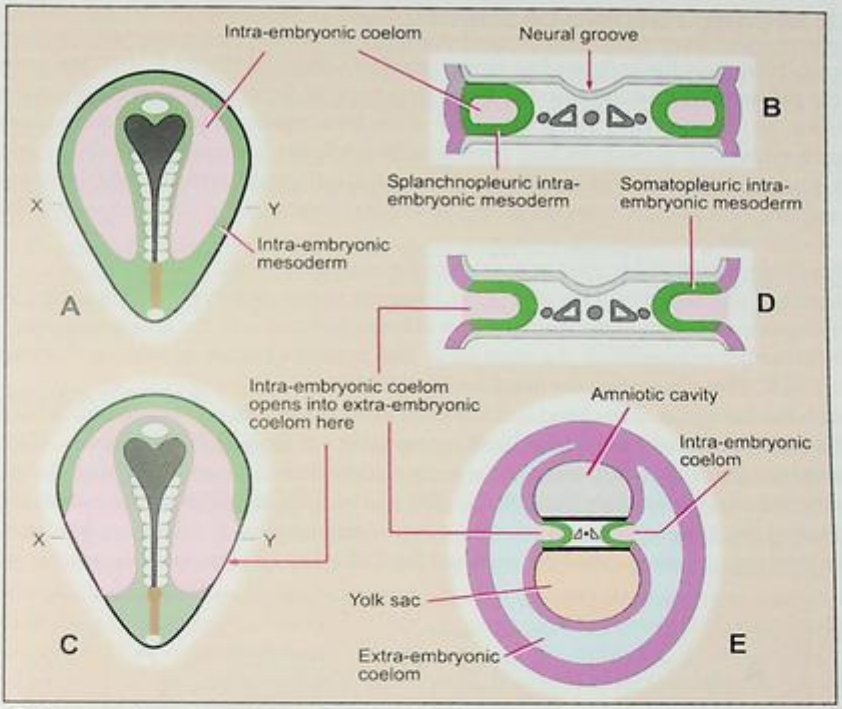

Fig. 5.5: Intra-embryonic coelom. (B) and (D) are sections across axes XY in (A) and (C) respectively. (E) shows the relationship between the intra-embryonic and the extra-embryonic coeloms.

from that part of the intra-embryonic coelom that lies, in the midline, cranial to the prochordal plate. The heart is formed in the splanchnopleuric mesoderm forming the floor of this part of the coelom (Fig. 5.6). This is, therefore, called the ***cardiogenic area*** (also called ***cardiogenic plate, heart-forming plate***). Cranial to the cardiogenic area (i.e. at the cranial edge of the embryonic disc) the somatopleuric and splanchnopleuric mesoderm are continuous with each other. The mesoderm here does not get split, as the intra-embryonic coelom has not extended into it. This unsplit mesoderm forms a structure called the ***septum transversum*** (Fig. 5.6).

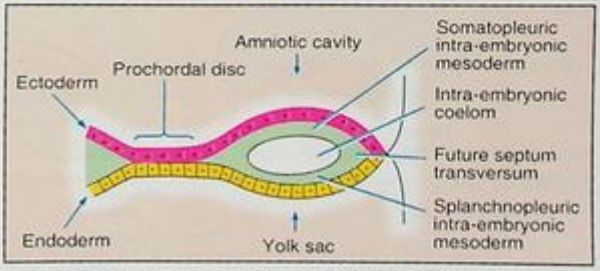

Fig. 5.6: Midline section through cranial end of the embryonic disc to show the relationship of the pericardial cavity to other structures.

YOLK SAC AND FOLDING OF EMBRYO

The early history of the yolk sac has been traced in Chapter 4 (Figs 4.6, 4.7). We have seen that the ***primary yolk sac*** is bounded above by cubical endoderm of the embryonic disc and elsewhere by flattened cells lining the inside of the blastocystic cavity. With the formation of the extra-embryonic mesoderm, and later the extra-embryonic coelom, the yolk sac becomes much smaller; it comes to be lined all round by cubical cells; and it is then called the ***secondary yolk sac***. The changes that now take place will be best understood by a careful study of Fig. 5.7. Note the following:

- There is progressive increase in the size of the embryonic disc.
- The head and tail ends of the disc (X, Y), however, remain relatively close together. Hence, the increased length of the disc causes it to bulge upwards into the amniotic cavity.
- With further enlargement, the embryonic disc becomes folded on itself, at the head and tail ends. These are called the ***head and tail folds***.
- With the formation of the head and tail folds, parts of the yolk sac become enclosed within the embryo. In this way, a tube lined by endoderm is formed in the embryo. This is the ***primitive gut***, from which most of the gastrointestinal tract is derived. At first, the gut is in wide communication with the yolk sac. The part of the gut cranial to this communication is called the ***foregut***, the part caudal to the communication is called the ***hindgut***; while the intervening part is called the ***midgut*** (Fig. 5.7E). The communication with the yolk sac

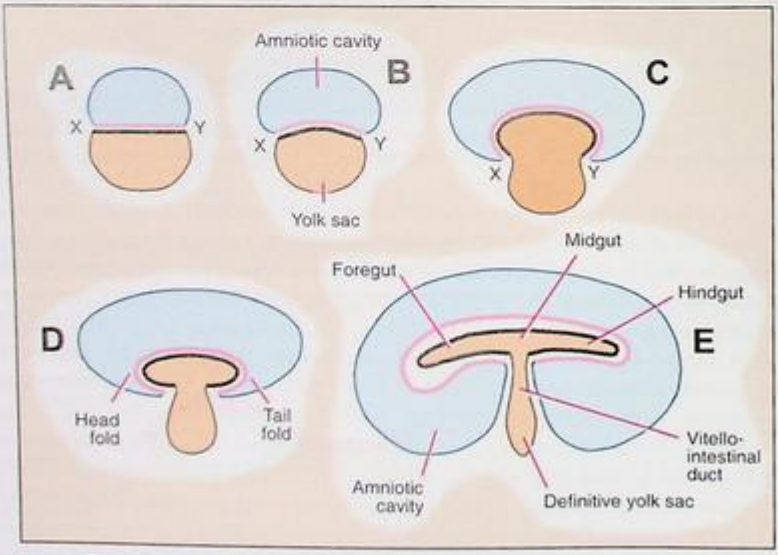

Fig. 5.7: Formation of head and tail folds and establishment of the gut.

becomes progressively narrower. As a result of these changes, the yolk sac becomes small and inconspicuous, and is now termed the ***definitive yolk sac*** (also called the ***umbilical vesicle***). The narrow channel connecting it to the gut is called the ***vitello-intestinal duct*** (also called ***vitelline duct***; ***yolk stalk*** or ***omphalomesenteric duct***). This duct becomes elongated and eventually disappears.

- As the head and tail folds are forming, similar folds are also formed on each side. These are the ***lateral folds***. As a result, the embryo comes to be enclosed all around by ectoderm except in the region through which the vitello-intestinal duct passes. Here, there is a circular aperture which may now be called the ***umbilical opening***.
- As the embryonic disc folds on itself, the amniotic cavity expands greatly, and comes to surround the embryo on all sides. In this way, the embryo now floats in the amniotic fluid, which fills the cavity.

CONNECTING STALK

While discussing the formation of the extra-embryonic coelom, we have seen that with the formation of this cavity, the embryo (along with the amniotic cavity and yolk sac) remains attached to the trophoblast only by extra-embryonic mesoderm into which the coelom does not extend (Figs 5.8A, C). This extra-embryonic mesoderm forms the ***connecting stalk***. We shall see later that the trophoblast, and the tissues of the uterus, together form an important organ, the ***placenta***, which provides the growing embryo with nutrition and with oxygen. It also removes waste products from the embryo. The importance of the connecting stalk is obvious when we see that this is the only connecting link between the embryo and the placenta.

As the embryo grows, the area of attachment of the connecting stalk to it becomes relatively smaller. Gradually this attachment is seen only near the caudal end of the embryonic disc (Figs 5.8D, E). With the formation of the tail fold, the attachment of the connecting stalk moves (with the tail end of the embryonic disc) to the ventral aspect of the embryo. It is now attached in the region of the umbilical opening (Fig. 5.8E).

By now, blood vessels have developed in the embryo, and also in the placenta. These sets of blood vessels are in communication by means of arteries and veins passing through the connecting stalk. At first, there are two arteries and two veins in the connecting stalk, but later the right vein disappears (the left vein is 'left').

It is clear from Fig. 5.8F that, at this stage, the amnion has a circular attachment to the margins of the umbilical opening and forms a wide tube in which the following lie:

- Vitello-intestinal duct and remnants of the yolk sac.
- Mesoderm (extra-embryonic) of the connecting stalk. This mesoderm gets converted into a gelatinous substance called ***Wharton's jelly***. It protects blood vessels in the umbilical cord.
- Blood vessels that pass from the embryo to placenta.
- A small part of the extra-embryonic coelom.

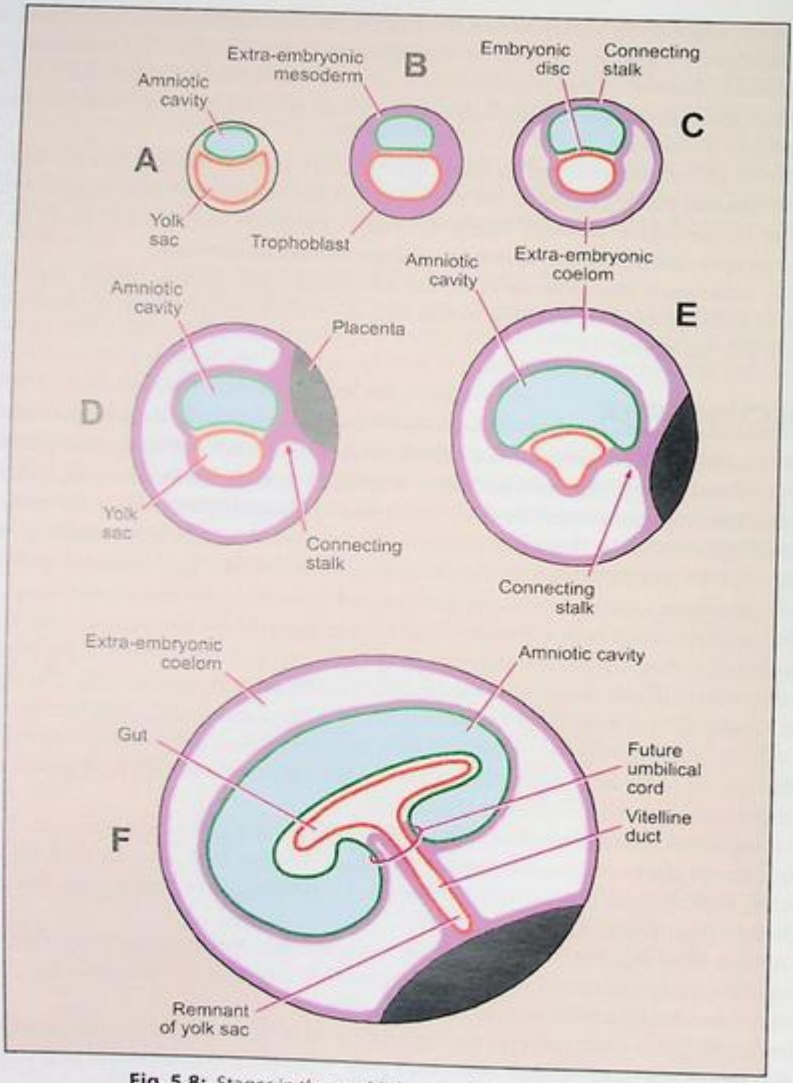

Fig. 5.8: Stages in the establishment of the umbilical cord.

This tube of amnion, and the structures within it, constitute the ***umbilical cord*** (Fig. 5.9). This cord progressively increases in length to allow free movement of the embryo within the amniotic cavity. At the time of birth of the child (i.e. at full term), the umbilical cord is about half a metre long, and about 2 cm in diameter. It shows marked torsion, which is probably due to fetal movements. An umbilical cord that is either too short or too long can cause problems during delivery of the fetus.

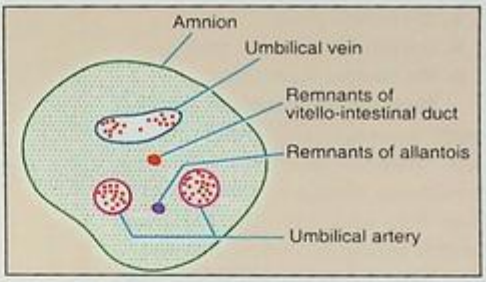

Fig. 5.9: Section through umbilical cord.

ALLANTOIC DIVERTICULUM

Before the formation of the tail fold, a small endodermal diverticulum called the ***allantoic diverticulum*** arises from the yolk sac near the caudal end of the embryonic disc (Fig. 5.10A). This diverticulum grows into the mesoderm of the connecting stalk. After the formation of the tail fold, part of this diverticulum is absorbed into the hindgut. It now passes from the ventral side of the hindgut into the connecting stalk (Fig. 5.10B). We will refer to it again while considering the development of the urinary bladder.

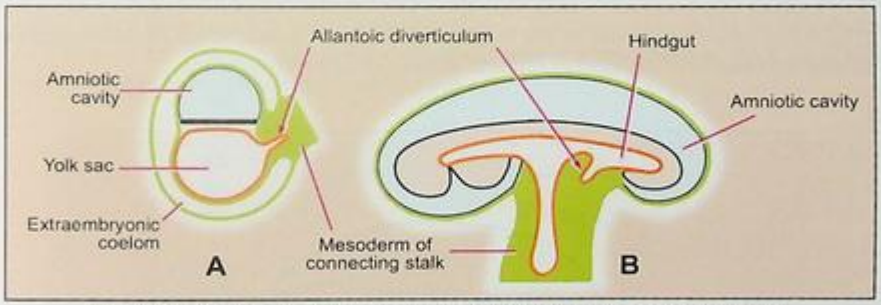

Fig. 5.10: Allantoic diverticulum, and its relationship to the connecting stalk.

EFFECT OF HEAD AND TAIL FOLDS ON POSITIONS OF OTHER STRUCTURES

Just before the formation of the head and tail folds, the structures in the embryonic disc are oriented, as shown in Fig. 5.11. A median (midline) section across the disc, at this stage, is shown in Fig. 5.12. From the cranial to the caudal side, the structures seen in the midline are

1. the septum transversum,
2. the developing pericardial cavity and the heart,
3. the prochordal plate,

4. the neural plate,
5. the primitive streak, and
6. the cloacal membrane.

Note that the primitive streak is now inconspicuous. After folding, the relative positions of these structures change to that shown in Figs 5.13 and 5.14. The important points to note here are as follows:

- With the formation of the head fold, the developing pericardial cavity comes to lie on the ventral side of the embryo, ventral to the foregut. The heart, which was developing in the splanchnopleuric mesoderm in the floor of the pericardial cavity (Fig. 5.12), now lies in the roof of the cavity (Fig. 5.13). The pericardium enlarges rapidly, and forms a conspicuous bulging on the ventral side of the embryo (Fig. 5.14).
- The septum transversum, which was the most cranial structure in the embryonic disc (Fig. 5.11), now lies caudal to the heart (Fig. 5.13). At a later stage in development, the diaphragm and liver develop in relation to the septum transversum.

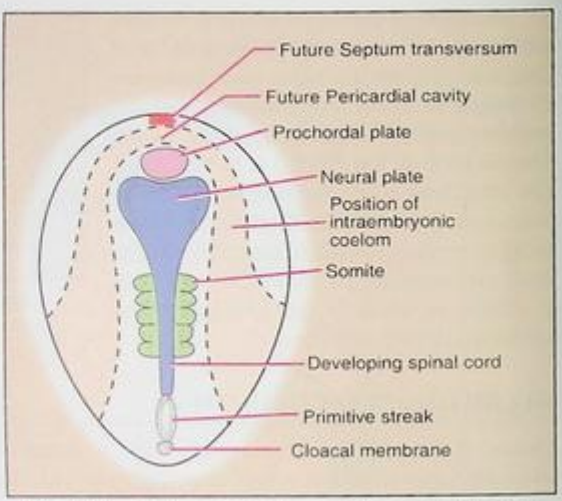

Fig. 5.11: Embryonic disc showing the neural plate and related structures.

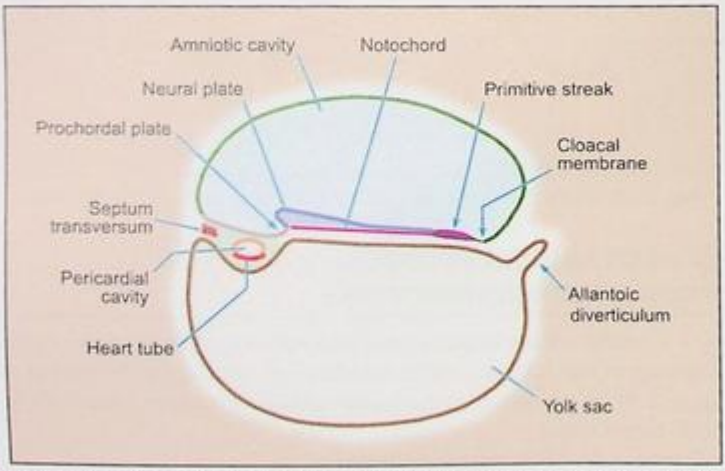

Fig. 5.12: Embryonic disc and related structures just before the formation of the head and tail folds.

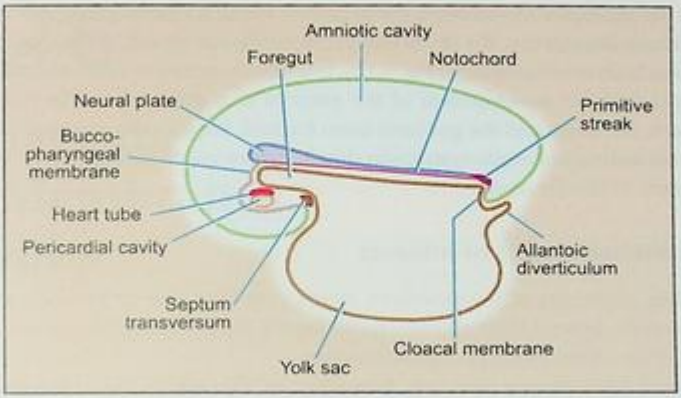

Fig. 5.13: Formation of head and tail folds. Also see Fig. 5.14.

- The region of the prochordal plate now forms the ***buccopharyngeal or oral membrane***, which closes the foregut cranially. When this membrane breaks down, the foregut communicates with the exterior.
- The most cranial structure of the embryo is now the enlarged cranial part of the neural tube, which later forms the brain (Fig. 5.13). This enlarges enormously (Fig. 5.14). There are now two big bulgings on the ventral aspect of the embryo. Cranially, there is the developing brain, and a little below it there is the bulging pericardium (Fig. 5.14). In between these two, there is a depression called the ***stomatodaeum*** or ***stomodaeum***, the floor of which is formed by the buccopharyngeal membrane.

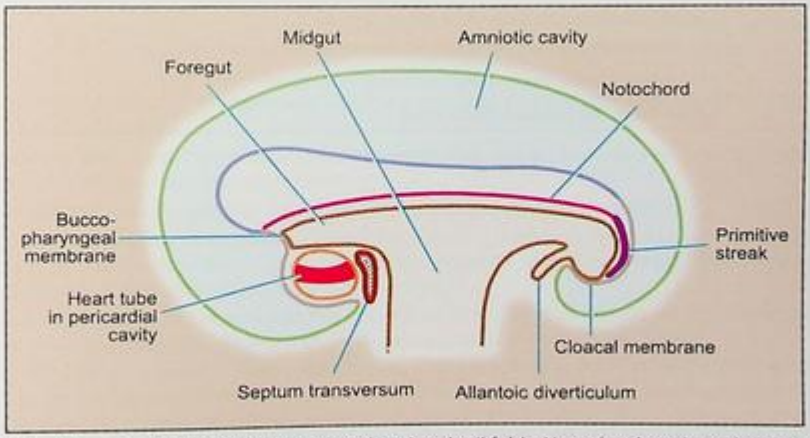

Fig. 5.14: Later stage in the formation of the head and tail folds. Note the changing relationships of septum transversum, pericardium, buccopharyngeal membrane, cloacal membrane and allantois.

- Towards the tail end of the embryo, the primitive streak is now an inconspicuous structure, that gradually disappears. The distal end of the hindgut is closed by the cloacal membrane. At first, this is directed caudally (Fig. 5.13), but later it comes to face ventrally (Fig. 5.14).

We have traced the development of the embryo to a stage when the rudiments of the nervous system, the heart and the gut have been formed. We are now in a position to trace the development of individual organ systems in detail. Before we do this, however, we must study the development of the placenta.

Some Additional Points of Interest

- In later life, remnants of the primitive streak may give rise to peculiar tumours that contain tissues derived from all three germ layers. These tumours are seen in the sacral region and are called sacrococcygeal tumours.
- Experiments have shown that the formation of the neural tube is induced by the notochord.
- Somitomeres are not confined to the region of somites. In the head region, cranial to somites, somitomeres give origin to some mesenchyme.
- Wharton's jelly is rich in proteoglycans.

TIMETABLE OF EVENTS DESCRIBED IN THIS CHAPTER

Age (in Days)	Developmental Events
15	Primitive streak appears. Definitive yolk sac is formed.
17	Notochordal process appears. Heart tube is seen in cardiogenic area. Allantoic diverticulum is seen.
19	Intra-embryonic mesoderm is being formed. Connecting stalk can be distinguished.
21	Neural groove is seen. Head fold begins to form.
23	Closure of the neural tube is seen.

Chapter 6

The Placenta
Fetal Membranes
Twinning

HIGHLIGHTS

- A developing embryo gets attached to the uterine endometrium. This is called ***implantation***.
- In human beings the embryo gets buried in the substance of the endometrium. This type of implantation is called ***interstitial*** implantation.
- After implantation the endometrium is called the ***decidua***.
- The ***placenta*** is formed partly from embryonic structures and partly from the decidua. It is responsible for transport of nutrients and oxygen to the fetus, and for removal of waste products.
- The essential elements of the placenta are ***chorionic villi***. The villi are surrounded by maternal blood. Fetal blood circulates through capillaries in villi.
- The maternal blood and the fetal blood are separated by a very thin ***placental membrane*** (or barrier). All substances passing from mother to fetus (and vice versa) traverse this membrane.
- The fetal tissue that takes part in forming the placenta is ***chorion***. It consists of trophoblast (one layer of cells) resting on extra-embryonic mesoderm.
- Proliferation of cells of the trophoblast leads to formation of two layers: ***cytotrophoblast***, which is cellular and ***syncytiotrophoblast***, which is a syncytium (cytoplasm with nuclei, but no cell boundaries).
- The first-formed villi are called ***primary villi***. They consist of a central core of cytotrophoblast covered by syncytiotrophoblast.
- ***Secondary villi*** have three layers. From inside out these are extra-embryonic mesoderm, cytotrophoblast and syncytiotrophoblast.
- In ***tertiary villi***, blood capillaries are formed in the extra-embryonic mesoderm.
- Villi are surrounded by an intervillous space that contains maternal blood. As the placenta enlarges, septa grow into the intervillous space dividing the placenta into lobes. The fully formed placenta is about six inches in diameter and about 500 g in weight.
- The placenta is normally attached to the upper part of the body of the uterus. A placenta attached lower down is called ***placenta praevia***. It can cause problems during child birth.
- The embryo is surrounded by three large cavities. These are the amniotic cavity, the extra-embryonic coelom, and the uterine cavity. Enlargement of the amniotic cavity obliterates the extra-embryonic coelom, leading to fusion of amnion and chorion. Further enlargement of amniotic cavity obliterates the uterine cavity. Fused amnion and chorion (called ***membranes***) bulge into the cervical canal (during child birth) and help to dilate it.

FORMATION OF PLACENTA

IMPLANTATION

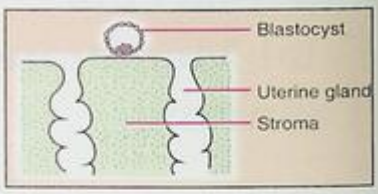

Fig. 6.1: Relationship of blastocyst to uterine endometrium.

After the ovum is shed from the ovary, it travels through the uterine tube towards the uterus. If fertilization occurs, segmentation of the ovum begins. By the time the fertilized 'ovum' reaches the uterus, it has already become a morula. The morula is still surrounded by the zona pellucida, which prevents it from 'sticking' to the wall of the uterine tube. The cells lining the surface of the morula, constitute the ***trophoblast***. The trophoblast has the property of attaching itself to, and invading, any tissue it comes in contact with. Once the zona pellucida disappears, the cells of the trophoblast stick to the uterine endometrium. This is called ***implantation*** (Fig. 6.1). In humans, implantation begins on the 6th day after fertilization. The trophoblast of the human blastocyst invades the endometrium of the uterus. The blastocyst burrows deeper and deeper into the uterine mucosa till the whole of it comes to lie within the thickness of the endometrium (Fig. 6.2). This is called ***interstitial implantation*** (Fig. 6.3).

The process of implantation is aided by proteolytic enzymes produced by the trophoblast. The uterine mucosa also aids the process. The trophoblastic cells that are situated over the inner cell mass, start penetrating the epithelium of the endometrium.

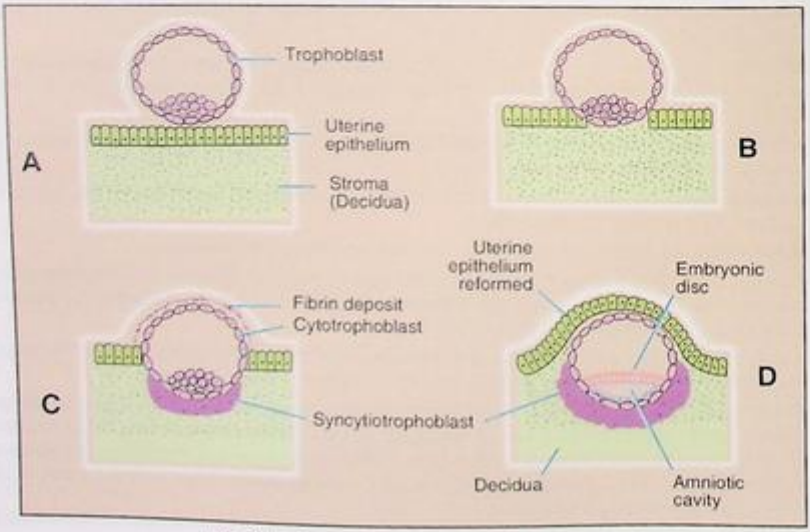

Fig. 6.2: Stages in implantation of blastocyst.

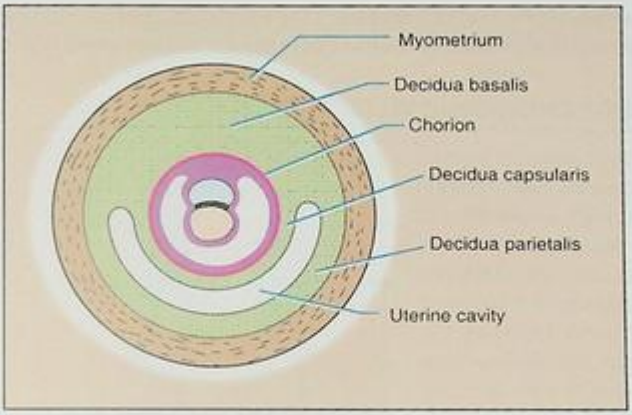

Fig. 6.3: Manner of implantation of a fetus in the human uterus. This type of implantation is described as interstitial. Various other types of implantation are seen in other mammals.

Implantation results due to the mutual interaction between trophoblastic cells and endometrium. This interaction is mediated by receptors present on uterine epithelium and by the secretion of ***L-selectin*** and ***integrins*** by trophoblastic cells.

DECIDUA

After the implantation of the embryo, the uterine endometrium is called the ***decidua***. When the morula reaches the uterus, the endometrium is in the secretory phase. After implantation, the features of the endometrium, which are seen during the secretory phase of the menstrual cycle, are maintained and intensified. The stromal cells enlarge, become vacuolated, and store glycogen and lipids. This change in the stromal cells is called the ***decidual reaction***. The portion of the decidua where the placenta is to be formed (i.e. deep to the developing blastocyst) is called the ***decidua basalis*** (Fig. 6.4). The part of the decidua that separates the embryo from the uterine lumen is called the ***decidua capsularis***, while the part lining the rest of the uterine cavity is called the ***decidua parietalis***. The decidua basalis consists predominantly of large decidual cells that contain large amounts of lipids and glycogen (that presumably provide a source of nutrition for the embryo). The decidua basalis is also referred to as the ***decidual plate***, and is firmly

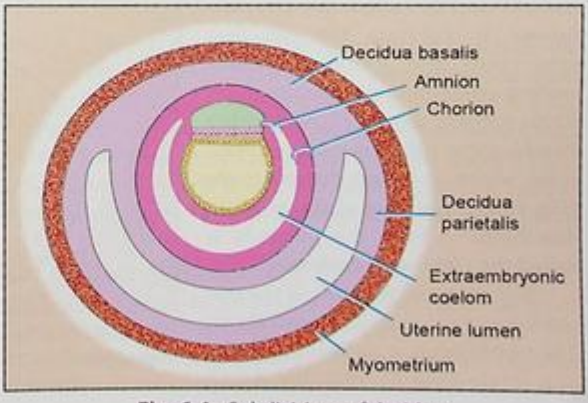

Fig. 6.4: Subdivisions of decidua.

united to the chorion. At the end of pregnancy, the decidua is shed off, along with the placenta and membranes. It is this shedding off which gives the decidua its name (*c.f.* deciduous trees).

FORMATION OF CHORIONIC VILLI

The essential functional elements of the placenta are very small finger-like processes or ***villi***. These villi are surrounded by maternal blood. In the substance of the villi, there are capillaries through which fetal blood circulates. Exchanges between the maternal and fetal circulations take place through the tissues forming the walls of the villi (Fig. 6.5). The villi are formed as offshoots from the surface of the trophoblast. As the trophoblast, along with the underlying extra-embryonic mesoderm, constitutes the chorion, the villi, arising from it, are called ***chorionic villi***.

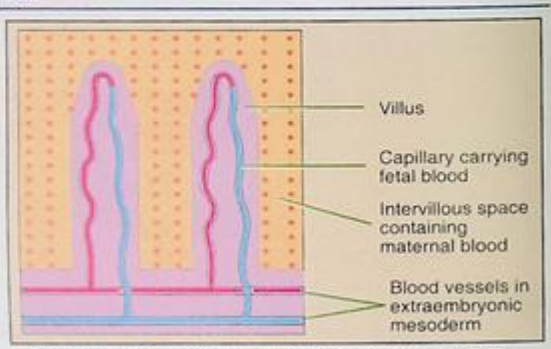

Fig. 6.5: Scheme to show that fetal blood circulating through capillaries of villi is in close relation to maternal blood in the intervillous space.

The chorionic villi are first formed all over the trophoblast and grow into the surrounding decidua (Fig. 6.6A). The villi related to the decidua capsularis are transitory. After some time, they degenerate. This part of the chorion becomes smooth and is called the ***chorion laevae***. In contrast, the villi that grow into the decidua basalis undergo considerable development. Along with the tissues of the decidua basalis, these villi form a disc-shaped mass which is called the ***placenta*** (Fig. 6.6B). The part of the chorion that helps to form the placenta is called the ***chorion frondosum***.

The essential features of the formation of chorionic villi are as follows. The trophoblast is at first made up of a single layer of cells (Fig. 6.7A).

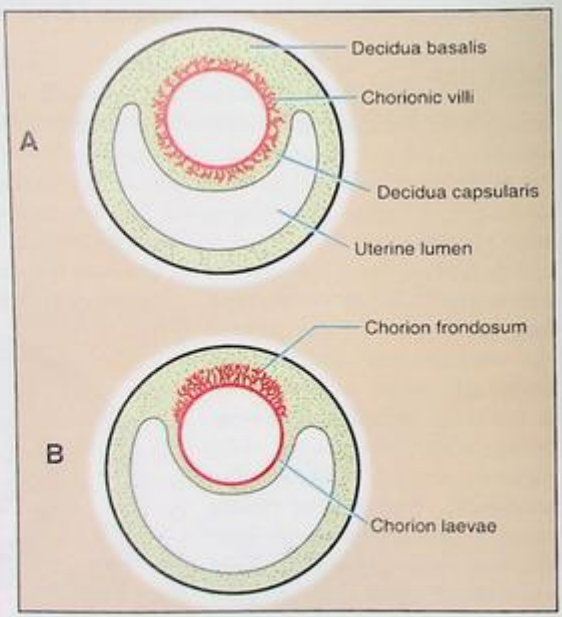

Fig. 6.6: Two stages in the formation of chorionic villi. Note their relationship to the decidua. In (B) note that the villi over the decidua capsularis have disappeared.

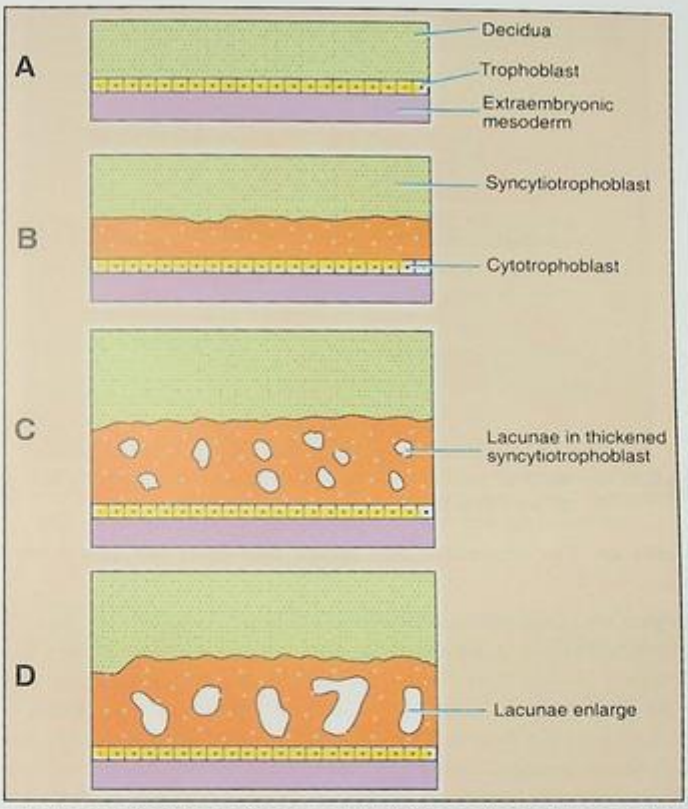

Fig. 6.7: Early stages in formation of chorionic villi: (A) Cytotrophoblast in contact with decidua; (B) Syncytiotrophoblast formed; (C) Lacunae appear in syncytiotrophoblast; (D) The lacunae enlarge.

As these cells multiply, two distinct layers are formed (Fig. 6.7B). The cells that are nearest to the decidua (i.e. the most superficial cells) lose their cell boundaries. Thus, one continuous sheet of cytoplasm containing many nuclei is formed. Such a tissue is called a syncytium. Hence, this layer of the trophoblast is called the ***syncytiotrophoblast*** or ***plasmodiotrophoblast***. Deep to the syncytium, the cells of the trophoblast retain their cell walls and form the second layer called the ***cytotrophoblast*** (also called ***Langhan's layer***). The cytotrophoblast rests on extra-embryonic mesoderm. All these elements (syncytium, cytotrophoblast and mesoderm) take part in forming chorionic villi.

The following three stages in formation of chorionic villi are seen:

1. ***Primary villi*** consist of a central core of cytotrophoblast covered by a layer of syncytiotrophoblast. Adjoining villi are separated by an intervillous space.
2. ***Secondary villi*** show three layers: outer syncytiotrophoblast, an intermediate layer of cytotrophoblast, and an inner layer of extra-embryonic mesoderm.

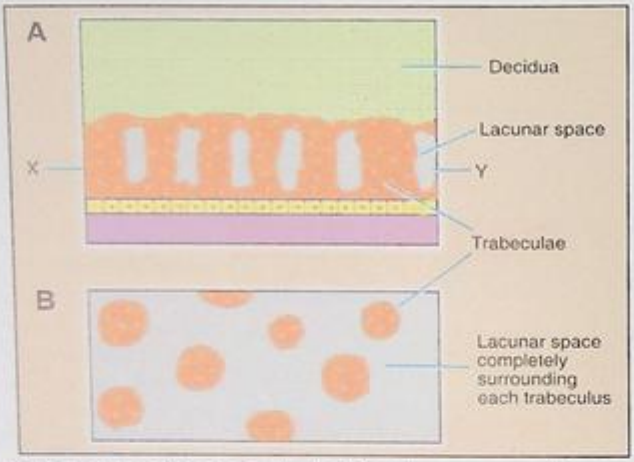

Fig. 6.8: Formation of chorionic villi. The trabeculae are now regularly arranged. (B) is a transverse section across (A) in the plane XY.

3. ***Tertiary villi*** are like secondary villi except that there are blood capillaries in the mesoderm.

Details of the process of villus formation are as follows:

- The syncytiotrophoblast grows rapidly and becomes thick. Small cavities (called ***lacunae***) appear in this layer (Fig. 6.7C). Gradually, the lacunae increase in size. At first they are irregularly arranged (Fig. 6.7D), but gradually, they come to lie radially (Figs 6.8A, 6.9) around the blastocyst. The lacunae are separated from one another by partitions of syncytium, which are called ***trabeculae***. The lacunae gradually communicate with each other, so that eventually one large space is formed. Each trabeculus is now surrounded all around by this lacunar space (Fig. 6.8B).

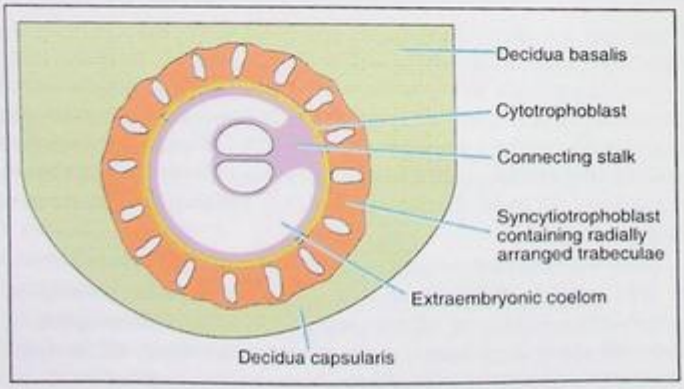

Fig. 6.9: Figure showing radial arrangement of trabeculae and lacunae around the blastocyst.

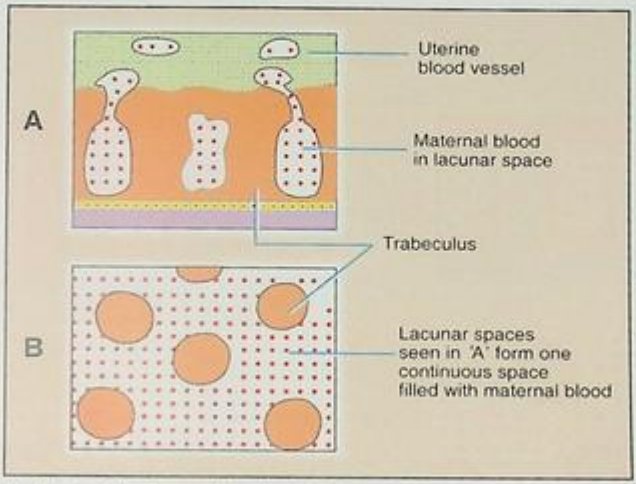

Fig. 6.10: Uterine blood vessels in the decidua open into the lacunar space and fill it with maternal blood. (B) is a transverse section through trabeculae.

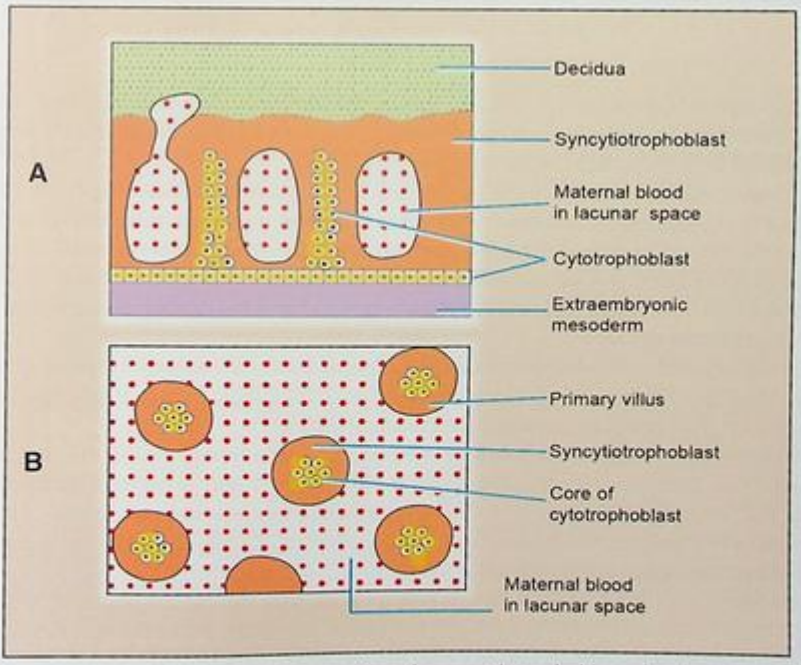

Fig. 6.11: Cells of cytotrophoblast grow into the syncytiotrophoblast of each trabeculus. The trabeculae are now called primary villi.

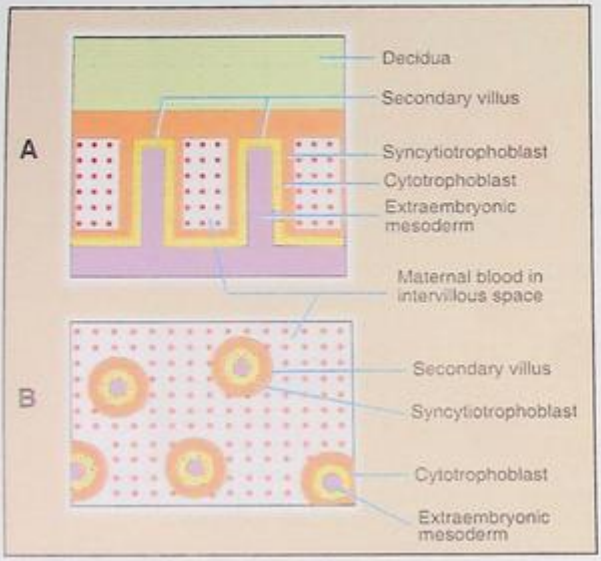

Fig. 6.12: Extra-embryonic mesoderm grows into the cytotrophoblastic core of each primary villis, converting it into a secondary villus.

- The syncytiotrophoblast (in which these changes are occurring) grows into the endometrium. As the endometrium is eroded, some of its blood vessels are opened up, and blood from them fills the lacunar space (Fig. 6.10).
- Each trabeculus is, initially, made up entirely of syncytiotrophoblast (Fig. 6.10). Now the cells of the cytotrophoblast begin to multiply and grow into each trabeculus (Fig. 6.11A). The trabeculus thus comes to have a central core of cytotrophoblast covered by an outer layer of syncytium. It is surrounded by maternal blood, filling the lacunar space. The trabeculus is now called a ***primary villus*** (Fig. 6.11) and the lacunar space is now called the ***intervillous space***.
- Extra-embryonic mesoderm invades the centre of each primary villus (Fig. 6.12A). The villus now has a core of mesoderm (Fig. 6.12B) covered by cytotrophoblast and by syncytium. This structure is called a ***secondary villus***.
- Soon thereafter, blood vessels can be seen in the mesoderm forming the core of each villus. With their appearance, the villus is fully formed and is called a ***tertiary villus*** (Fig. 6.13). The blood vessels of the villus establish connections with the circulatory system of the embryo. Fetal blood now circulates through the villi, while maternal blood circulates through the intervillous space.
- From Figs 6.11A, 6.12A and 6.13A, it will be seen that the cytotrophoblast, that grows into the trabeculus (or villus) does not penetrate the entire thickness of syncytium and, therefore, does not come in contact with the decidua.

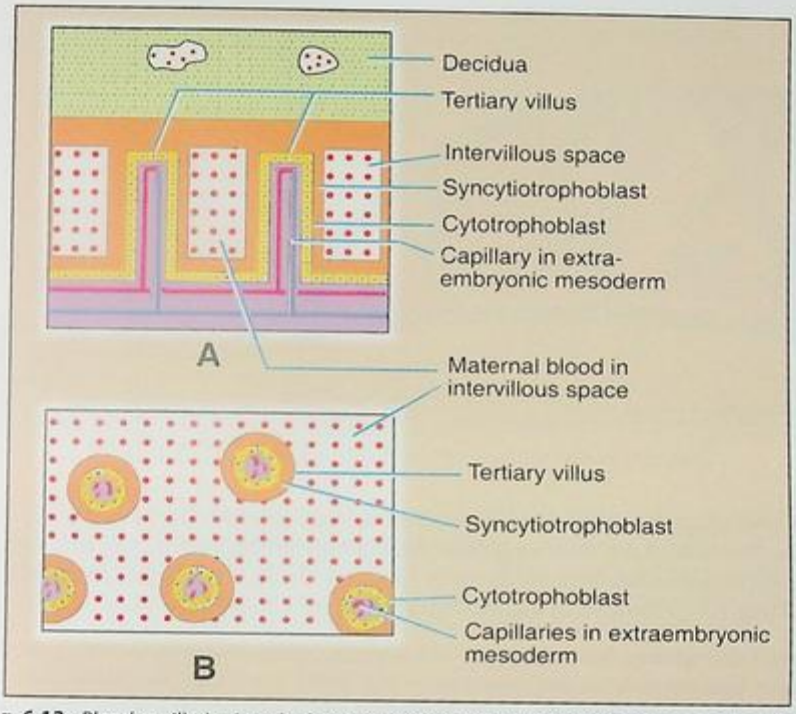

Fig. 6.13: Blood capillaries invade the extra-embryonic mesoderm of each secondary villus thus converting it into a tertiary villus.

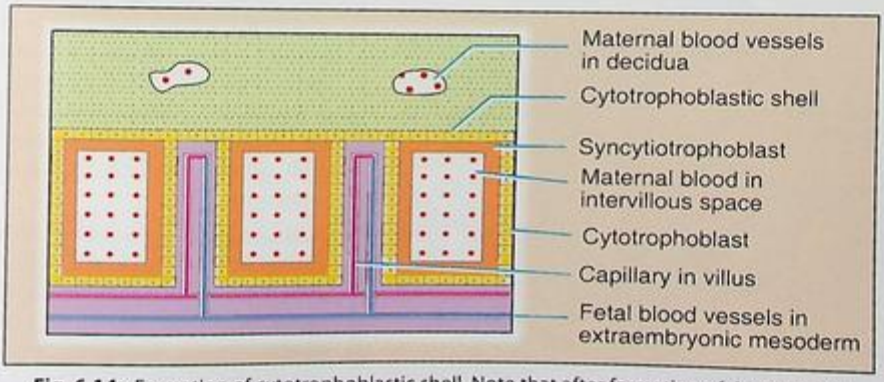

Fig. 6.14: Formation of cytotrophoblastic shell. Note that after formation of this shell the syncytiotrophoblast is no longer in contact with maternal tissues.

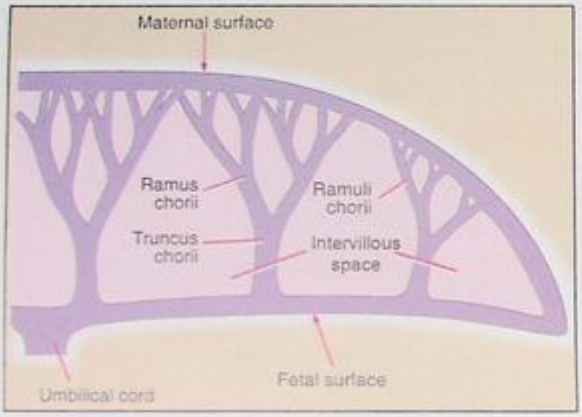

Fig. 6.15: Arrangement of anchoring villi, and of intervillous spaces within the placenta. Note the subdivisions of each anchoring villus.

At a later stage, however, the cytotrophoblast emerges through the syncytium of each villus. The cells of the cytotrophoblast now spread out to form a layer that completely cuts off the syncytium from the decidua. This layer of cells is called the ***cytotrophoblastic shell*** (Fig. 6.14). The cells of this shell multiply rapidly and the placenta increases in size.

The villi that are first formed (as described above) are attached on the fetal side (Fig. 6.15) to the embryonic mesoderm and on the maternal side to the cytotrophoblastic shell. They are, therefore, called ***anchoring villi***. Each anchoring villus consists of a stem (***truncus chorii***); this divides into a number of branches (***rami chorii***) which in turn divide into finer branches (***ramuli chorii***). The ramuli are attached to the cytotrophoblastic shell. The anchoring villi give off numerous branches that grow into the intervillous space as free villi (Fig. 6.16). New villi also sprout from the chorionic side of the intervillous space. Ultimately, almost the whole intervillous space becomes filled with villi. As a result, the surface area available for exchanges between maternal and fetal circulations becomes enormous.

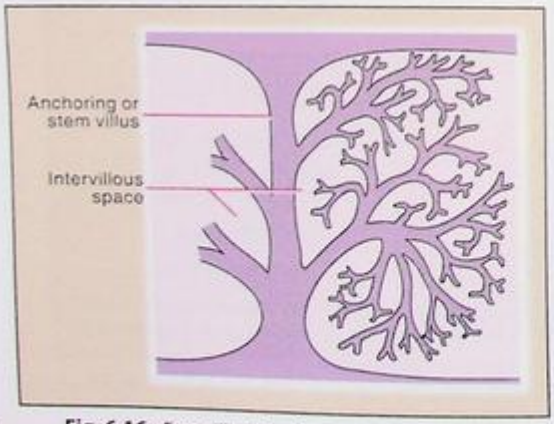

Fig. 6.16: Free villi arising from an anchoring villus

These, newly formed, villi at first consist only of syncytiotrophoblast. They are subsequently invaded by cytotrophoblast, mesoderm, and blood vessels, and pass through the stages of primary, secondary and tertiary villi, as described above.

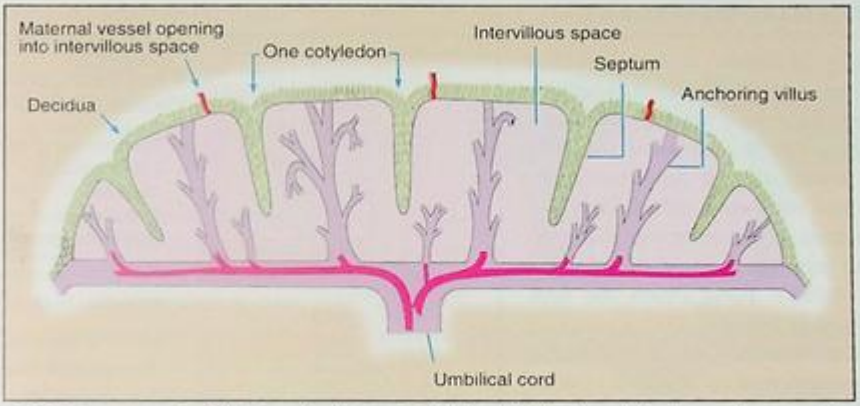

Fig. 6.17: Structure of a fully formed placenta. Each lobe (labelled cotyledon) contains a number of anchoring villi, but only one is shown here for the sake of simplicity.

FURTHER DEVELOPMENT OF THE PLACENTA

The placenta now becomes subdivided into a number of lobes, by septa that grow into the intervillous space from the maternal side (Fig. 6.17). Each such lobe of the placenta is often called a ***maternal cotyledon***. If the placenta is viewed from the maternal side, the bases of the septa are seen as grooves (Fig. 6.18) while the cotyledons appear as convex areas bounded by the grooves. The number of lobes generally varies between 15 and 20. Each lobe contains a number of anchoring villi and their branches. One such villus and its branches constitute a ***fetal cotyledon***. The fully formed placenta has 60–100 such fetal cotyledons. The placenta now forms a compact mass and is disc-shaped (Figs 6.17, 6.18).

At full term (9 months after onset of pregnancy), the placenta has a diameter of 6 to 8 inches and weighs about 500 g. After the birth of the child, the placenta is shed off along with the decidua. The maternal surface (formed by the decidual plate) is rough and is subdivided into cotyledons. The fetal surface (chorionic plate) is lined by amnion. It is smooth and is not divided into cotyledons. The umbilical cord is attached to this surface.

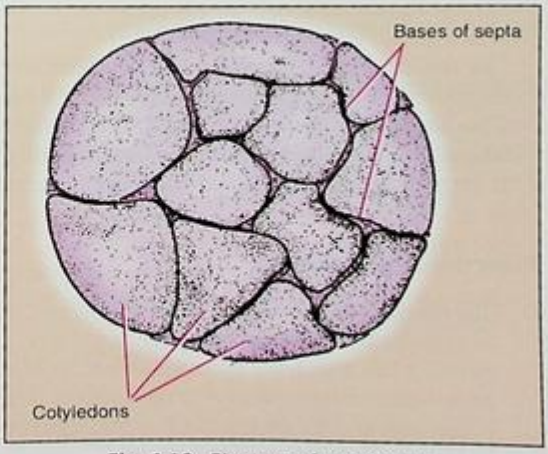

Fig. 6.18: Placenta, after shedding, viewed from the maternal aspect.

PLACENTAL MEMBRANE

In the placenta, maternal blood circulates through the intervillous space and fetal blood circulates through blood vessels in the villi. The maternal and fetal blood do not mix with each other. They are separated by a membrane, made up of the layers of the wall of the villus (Fig. 6.19A). These (from the fetal side) are as follows:

1. the endothelium of fetal blood vessels, and its basement membrane.
2. surrounding mesoderm (connective tissue).
3. cytotrophoblast, and its basement membrane.
4. syncytiotrophoblast.

These structures constitute the ***placental membrane*** or ***barrier***. All interchanges of oxygen, nutrition and waste products take place through this membrane.

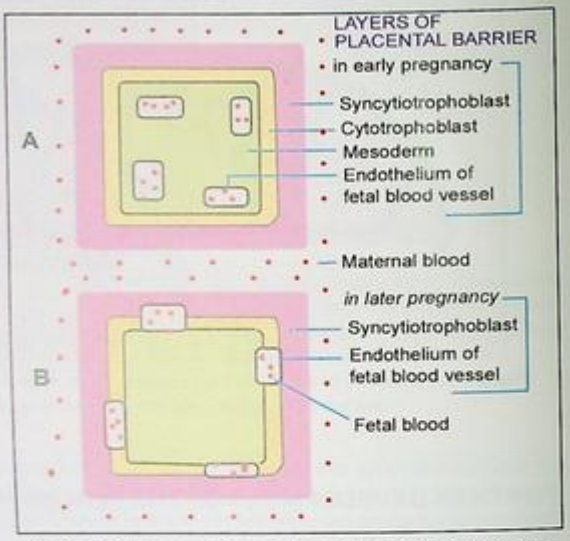

Fig. 6.19: Diagrams of placental barrier: (A) in early part of pregnancy, and (B) in later part.

The total area of this membrane varies from 4 to 14 square metres. It is interesting to note that this is equal to the total absorptive area of the adult intestinal tract. As in the gut, the effective absorptive area is greatly increased by the presence of numerous microvilli on the surface of the syncytiotrophoblast.

In the later part of pregnancy, the efficiency of the membrane is increased, by disappearance of the cytotrophoblastic layer from most villi, and by considerable thinning of the connective tissue (Fig 6.19B). This membrane, which is at first 0.025 mm thick, is reduced to 0.002 mm. However, towards the end of pregnancy, a fibrinoid deposit appears on the membrane, and this reduces its efficiency.

Functions of Placenta

- The placenta enables the transport of oxygen, water, electrolytes and nutrition (in the form of carbohydrates, lipids, polypeptides, amino acids and vitamins) from maternal to fetal blood. A full term fetus takes up about 25 ml of oxygen per minute from maternal blood. Even a short interruption of oxygen supply is fatal for the fetus.
- It also provides for excretion of carbon dioxide, urea and other waste products produced by the fetus into the maternal blood.

- Maternal antibodies (IgG, gamma globulins or Immunoglobulins) reaching the fetus through the placenta give the fetus immunity against some infections (e.g. diphtheria and measles).
- The placenta acts as a barrier and prevents many bacteria and other harmful substances from reaching the fetus. However, most viruses (including poliomyelitis, measles and rubella) and some bacteria can pass across it. Drugs taken by the mother may also enter the fetal circulation and can produce congenital malformations. As a rule, maternal hormones do not reach the fetus. However, synthetic progestins and synthetic oestrogens (e.g. diethylstilbestrol) easily cross the placenta and can have adverse effects on the fetus (including carcinoma in later life).
- While permitting the exchange of several substances between the maternal and fetal blood, it keeps these blood streams separate, thereby preventing antigenic reactions between them.
- The placenta synthesizes several hormones. These are probably produced in the syncytiotrophoblast.

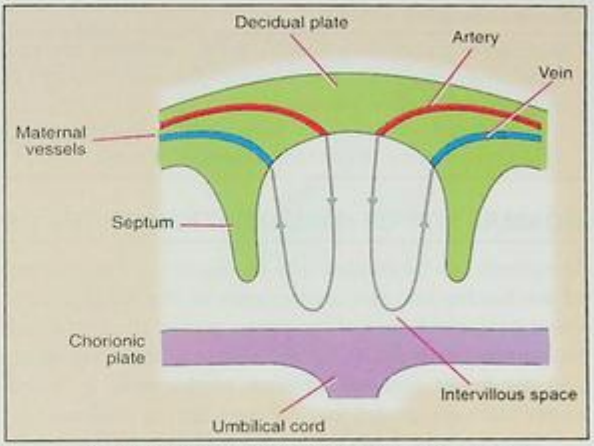

Fig. 6.20: Scheme to show how maternal blood circulates through the placenta. Villi are not drawn for the sake of simplicity.

Progesterone secreted by the placenta is essential for maintenance of pregnancy after the fourth month (when the corpus luteum degenerates).

Oestrogens (mainly estriol) produced by the placenta reach maternal blood and promote uterine growth and development of the mammary gland.

Clinical Correlation

Human chorionic gonadotropin (hCG) produced by the placenta is similar in its actions to the luteinizing hormone of the hypophysis cerebri. Gonadotropins are excreted through maternal urine where their presence is used as a test to detect a pregnancy in its early stages.

Somatomammotropin (hCS) has an anti-insulin effect on the mother. This leads to increased plasma levels of glucose and amino acids in the maternal circulation. In this way it increases availability of these materials for the fetus. It also enhances glucose utilization by the fetus.

Circulation of Blood through the Placenta

Blood flow through lacunar spaces in the syncytiotrophoblast begins as early as the 9th day of pregnancy. Thereafter, the maternal blood in the intervillous spaces is constantly in circulation.

Clinical Correlation *contd...*

Blood enters the intervillous space through maternal arteries that open into the space. The pressure of blood drives it right up to the chorionic plate. Blood from the intervillous spaces is drained by veins that also open into the same spaces.

In the fully formed placenta, the intervillous spaces contain about 150 ml of blood that is replaced in 15 to 20 seconds (i.e. three to four times per minute).

NORMAL SITE OF IMPLANTATION OF THE OVUM

The uterus can be divided into an upper part, consisting of the fundus and the greater part of the body, and a lower part, consisting of the lower part of the body and the cervix. These are called the ***upper uterine segment***, and the ***lower uterine segment***, respectively. It is the upper uterine segment that enlarges during pregnancy.

The placenta is normally attached only to the upper uterine segment (Fig. 6.21).

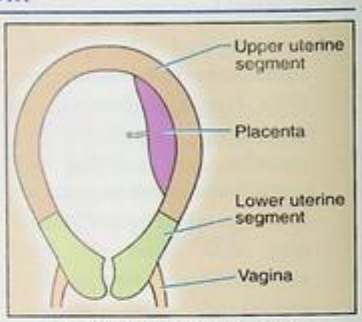

Fig. 6.21: Upper and lower uterine segments and their normal relationship to the placenta.

Clinical Correlation

Abnormal Sites of Implantation of the Ovum

Abnormal Implantation within the Uterus

The attachment of the placenta may extend partially, or completely, into the lower uterine segment. This condition is called ***placenta praevia***. It causes difficulty during childbirth and may cause severe bleeding. Various degrees of placenta praevia may be recognized, as given below:

- ***First degree:*** The attachment of the placenta extends into the lower uterine segment, but does not reach the internal os (Fig. 6.22A).
- ***Second degree:*** The margin of the placenta reaches the internal os, but does not cover it (Fig. 6.22B)
- ***Third degree:*** The edge of the placenta covers the internal os, but when the os dilates during childbirth, the placenta no longer occludes it (Fig. 6.22C).
- ***Fourth degree:*** The placenta completely covers the internal os, and occludes the os even after it has dilated (Fig. 6.22D).

Implantation Outside the Uterus

When the ovum gets implanted at any site outside the uterus, this is called an ***ectopic pregnancy***. This may be as follows:

- ***Tubal pregnancy***: The blastocyst gets implanted in the uterine tube. Such a pregnancy cannot go on to full term, and may result in rupture of the tube. After rupture, the blastocyst may acquire a secondary implantation in the abdominal cavity (Fig. 6.23), giving rise to an ***abdominal pregnancy***.
- ***Interstitial tubal implantation:*** The blastocyst may get implanted in the part of the uterine tube passing through the uterine wall.
- ***Implantation in the ovary:*** Fertilization and implantation may occur while the ovum is still in the ovary.

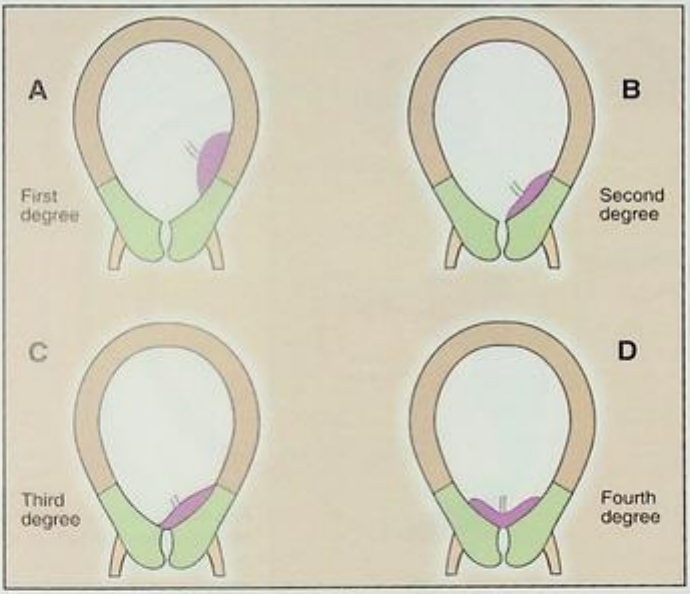

Fig. 6.22: Types of placenta praevia.

Other Anomalies of Placenta

Instead of being shaped like a disc, the placenta may be:

- ***bidiscoidal***, when it consists of two discs (Fig. 6.24A);
- ***lobed***, when it is divided into lobes (Fig. 6.24B);
- ***diffuse***, when chorionic villi persist all round the blastocyst: the placenta is thin and does not assume the shape of a disc (Fig. 6.24C);
- ***placenta succenturiata***, when a small part of the placenta is separated from the rest of it (Fig. 6.24D);

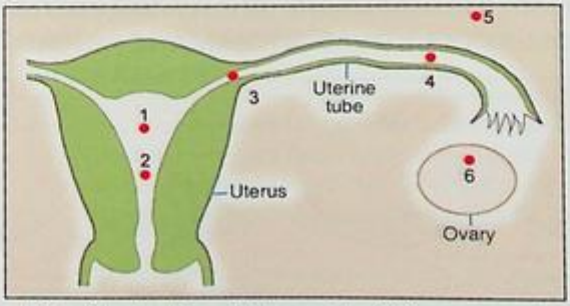

Fig. 6.23: Abnormal sites of implantation: (1) Normal site, (2) Placenta praevia, (3) Interstitial tubal implantation, (4) Tubal implantation, (5) Abdominal implantation, (6) Ovarian implantation.

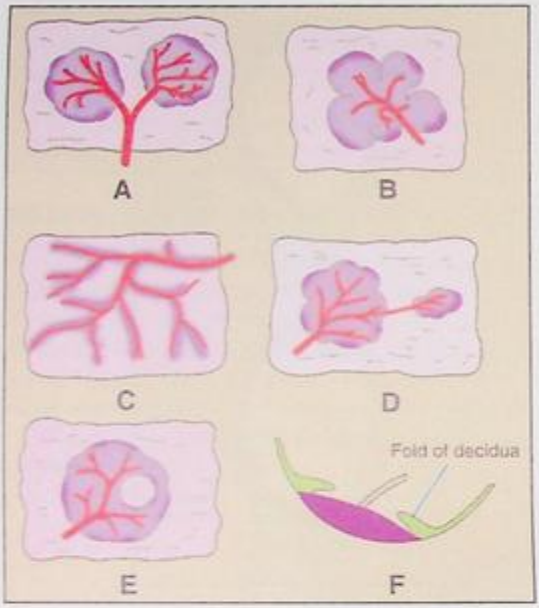

Fig. 6.24: Anomalies of placenta: (A) Bidiscoidal, (B) Lobed, (C) Diffuse, (D) Placenta succenturiata, (E) Fenestrated placenta, (F) Circumvallate placenta.

- ***fenestrated***, when there is a hole in the disc (Fig. 6.24E); and
- ***circumvallate***, when the peripheral edge of the placenta is covered by a circular fold of decidua (Fig. 6.24F).

The umbilical cord is normally attached to the placenta near the centre (Fig. 6.25A). However, this attachment may be:

- ***marginal***, when the cord is attached at the margin of the placenta (Fig. 6.25B) (this type of placenta is called ***Battledore placenta***); or
- ***furcate***, when blood vessels divide before reaching the placenta (Fig. 6.25C).
- When blood vessels are attached to amnion, where they ramify before reaching the placenta (Fig. 6.25D), the condition is referred to as ***velamentous insertion***.

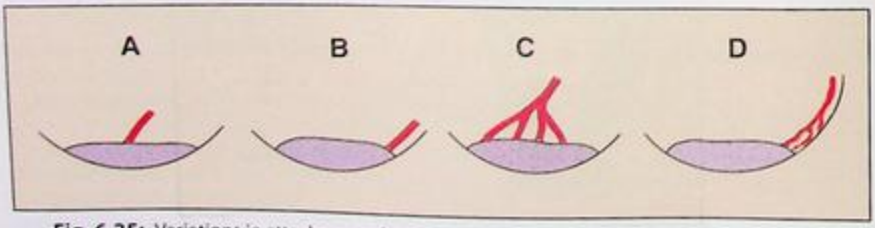

Fig. 6.25: Variations in attachment of umbilical cord to placenta: (A) Normal, (B) Marginal, (C) Furcate, (D) Velamentous insertion.

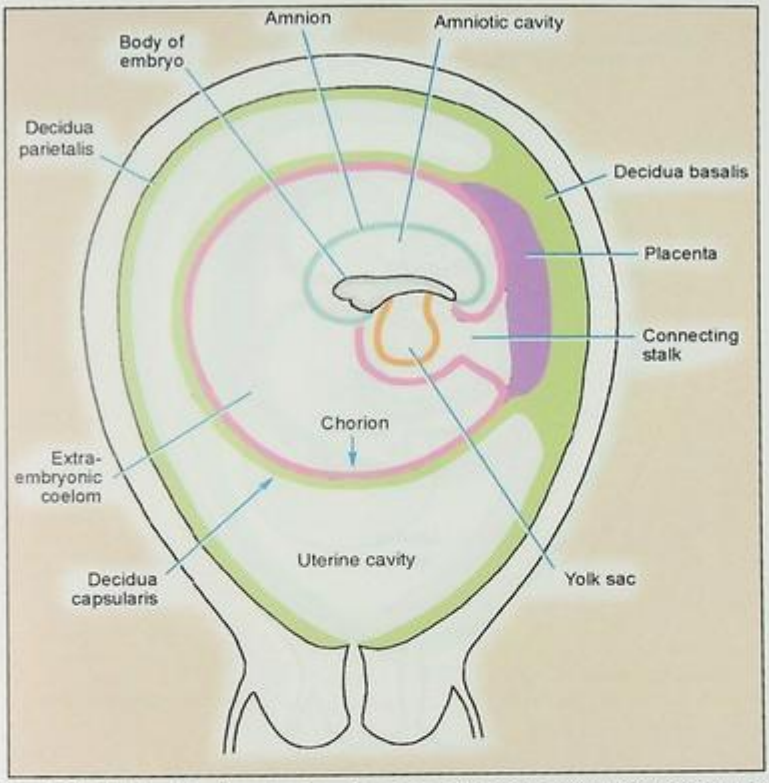

Fig. 6.26: Relationship of amniotic cavity, extra-embryonic coelom and uterine cavity. For description see text.

FETAL MEMBRANES

MUTUAL RELATIONSHIP OF AMNIOTIC CAVITY, EXTRA-EMBRYONIC COELOM AND UTERINE CAVITY

We have so far considered the fetal membranes (amnion and chorion), and the placenta, mainly in relation to the fetus. Let us now see their relationships to the uterine cavity. These are important, as they help us to understand some aspects of the process of childbirth. The changing relationships will be best understood by first reviewing Figs 4.6, 4.7 and 4.13 and then by studying Figs 6.26 to 6.28.

In Fig. 6.26 we see three cavities, namely, the uterine cavity, the extra-embryonic coelom, and the amniotic cavity. The outer wall of the extra-embryonic coelom is formed by chorion and the inner wall by amnion.

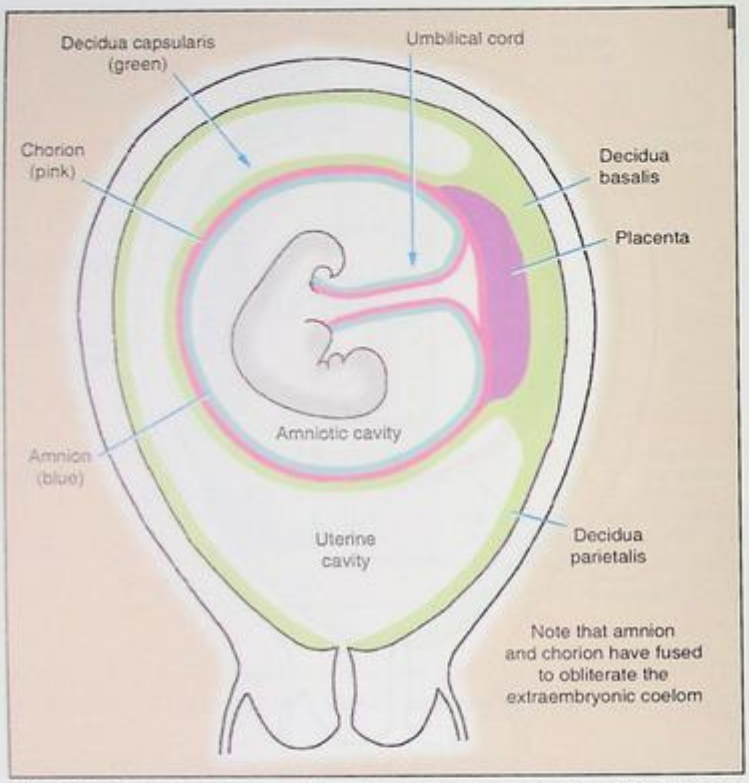

Fig. 6.27: Relationship of amniotic cavity and uterine cavity after obliteration of the extra-embryonic coelom.

As the amniotic cavity enlarges, the extra-embryonic coelom becomes smaller and smaller. It is eventually obliterated, by fusion of amnion and chorion. The fused chorion and amnion form the ***amniochorionic membrane***. From Fig. 6.27 it will be seen that the wall of the amniotic cavity is now formed by (i) amnion, (ii) chorion, and (iii) decidua capsularis, all three being fused to one another.

Further expansion of the amniotic cavity occurs at the expense of the uterine cavity. Gradually, the decidua capsularis fuses with the decidua parietalis, and the uterine cavity is also obliterated (Fig. 6.28). Still, further expansion of the amniotic cavity is achieved by enlargement of the uterus. Enlargement of the amniotic cavity is accompanied by an increase in the amount of amniotic fluid.

At the time of parturition (childbirth), the fused amnion and chorion (amniochorionic membrane) (along with the greatly thinned out decidua capsularis), constitute what are called the ***membranes***. As the uterine muscle contracts, increased pressure in the amniotic fluid

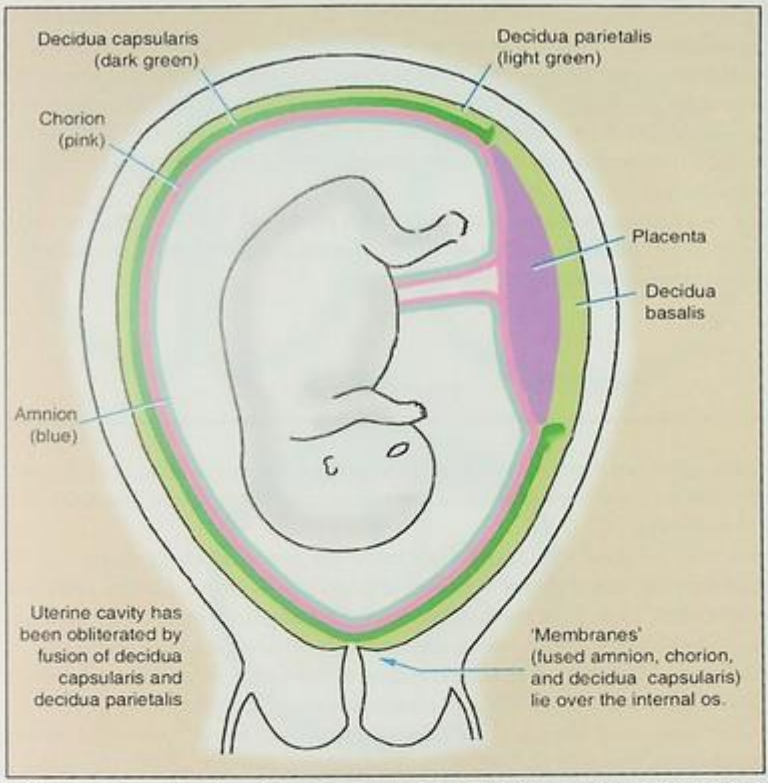

Fig. 6.28: Amniotic cavity after obliteration of the extra-embryonic coelom and uterine cavity.

causes these membranes to bulge into the cervical canal. This bulging helps to dilate this canal. The bulging membranes can be felt through the vagina and are referred to as the ***bag of waters***. Ultimately the membranes rupture. Amniotic fluid flows out into the vagina. After the child is delivered, the placenta and the membranes, along with all parts of the decidua, separate from the wall of the uterus and are expelled from it.

AMNIOTIC FLUID

Amniotic fluid provides support for the delicate tissues of the growing embryo or fetus. It allows free movement and protects the fetus from external injury. It also avoids adhesion of the fetus to amnion. As pregnancy advances, the quantity of this fluid increases, till at full term it is about one litre.

The condition in which there is too much amniotic fluid (over 1500 ml) is called ***hydramnios***; and when the fluid is too little it is called ***oligamnios***. Both conditions can cause abnormalities in the fetus. They can also cause difficulties during childbirth.

There is constant exchange of water between the amniotic fluid and maternal blood, the water being completely replaced every three hours. Some time in the fifth month the fetus begins to swallow amniotic fluid. This fluid is absorbed (through the gut) into fetal blood and is transferred through the placenta to maternal blood. When the fetal kidneys start working the fetus passes urine into the amniotic fluid. This does not cause harm because fetal urine is made up mostly of water (metabolic wastes being removed from blood by the placenta and not through the kidneys).

In some cases, hydramnios is associated with atresia of the oesophagus, which prevents swallowing of amniotic fluid by the fetus. Oligamnios is sometimes associated with renal agenesis, as no urine is added to the amniotic fluid.

TWINNING

When a mother gives birth to two infants at the same time, they are called twins. Three (triplets), four (quadruplets) or even more infants are sometimes born simultaneously. Twins can be produced in two ways.

- Two ova may be shed simultaneously from the ovary. Each of them may be fertilized and may develop in the usual manner. This results in twins that are called ***dizygotic*** or ***fraternal twins***. As each of them develops from a separate ovum, they have independent genetic constitutions. These twins, therefore, need not be of the same sex, nor do they resemble each other any more than children of the same parents that are born separately. Each fetus has its own chorionic and amniotic sacs (Fig. 6.29A).
- Twins can also arise from a single fertilized ovum. These are called ***monozygotic*** or ***maternal twins***. The genetic constitution of the two twins is exactly the same. Hence they are of the same sex. They are also exactly alike in appearance.

Monozygotic twins are produced in one of the following ways:

- The cells formed in the first few divisions of the zygote are ***totipotent***, i.e. each cell is capable of developing into a complete embryo. The two cells formed by the first division may separate and develop independently. In such a case, the fetuses will have separate chorionic and amniotic sacs, as in dizygotic twins.
- The embryo may develop normally up to the stage of the morula. However, when the blastocyst is formed, two inner cell masses form within it and each develops into a complete fetus. In this case the two fetuses have a common chorionic sac but each lies in an independent amniotic cavity (Fig. 6.29B).
- Lastly, the inner cell mass may split into two; or two embryonic axes may be established in one inner cell mass. By this we mean that two separate embryonic discs are formed within it, each with its own prochordal plate and primitive streak. In this case the two fetuses share a common chorion as well as a common amniotic cavity (Fig. 6.29C).

In those instances where the fetuses share a common chorion, there is one placenta to which two umbilical cords are attached. Where the chorionic sacs are separate, two

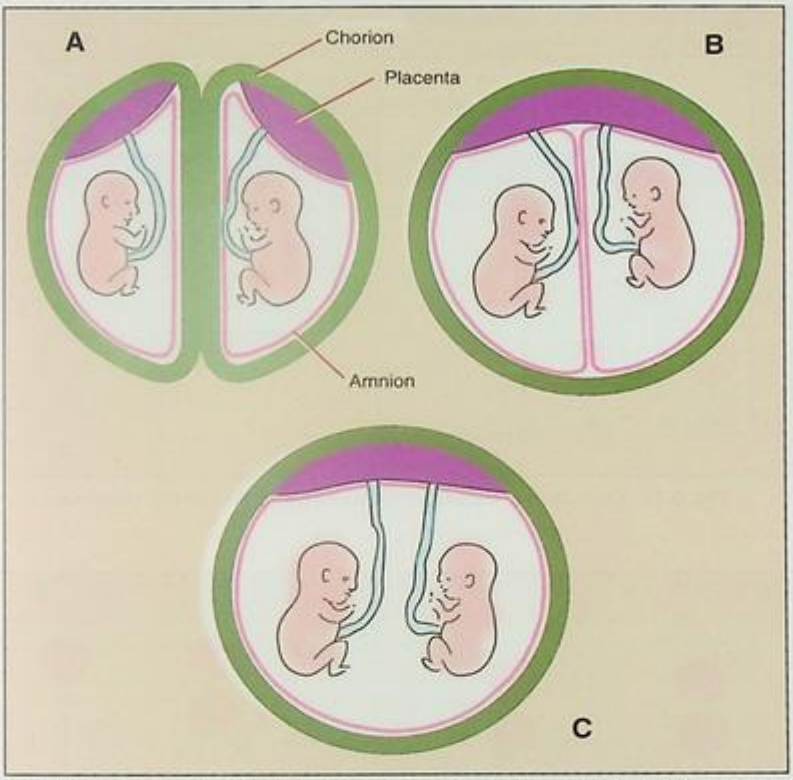

Fig. 6.29: (A) Dizygotic twins. Each twin has its own chorion and amnion. (B) and (C) Monozygotic twins. The chorion is common. The amnion can be common or separate.

independent placentae are formed. Such placentae may secondarily fuse with each other, but normally there are no anastomoses between the vessels of the two placentae. Rarely, the placentae can fuse and there may be mixing of blood of the two fetuses. In that case the blood of each fetus may contain two types of erythrocytes. The condition is known as ***erythrocyte mosaicism***.

Multiple births may occur by subdivision of one zygote into more than two parts, by the simultaneous fertilization of more than two ova, or by a combination of both these factors (Figs 6.30, 6.31).

Incomplete separation of monozygotic twins results in the birth of two infants that are joined together in some part of the body. In some cases, it is possible to separate them by operation, but most of them are born dead. These are called ***conjoined twins*** or ***Siamese twins***.

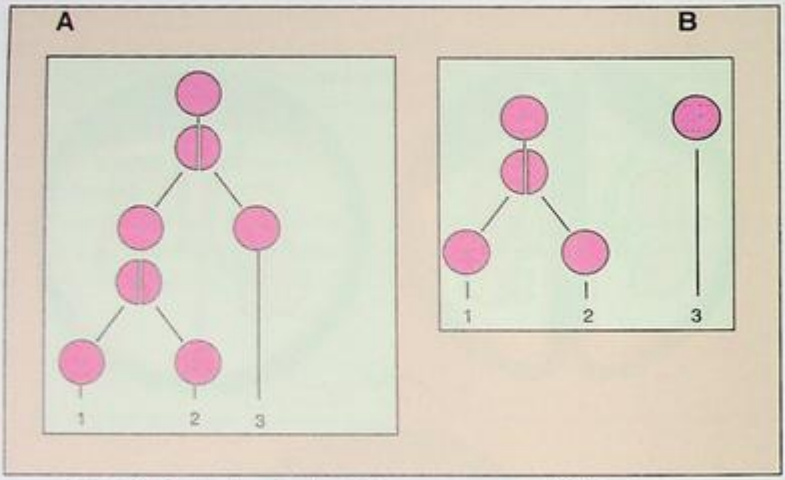

Fig. 6.30: Derivation of triplets (A) from one ovum; and (B) from two ova.

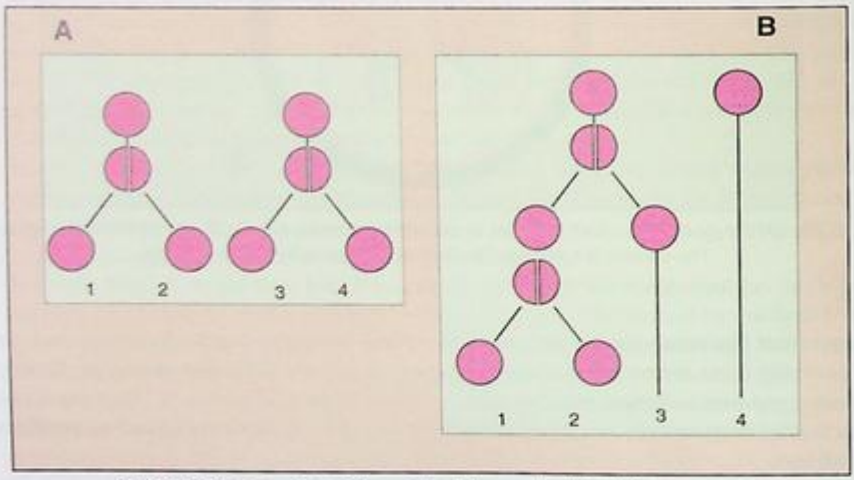

Fig. 6.31: Two ways in which quadruplets may be derived from two ova.

Not infrequently, the two twins do not undergo equal development, possibly as a result of unequal blood supply. The underdeveloped fetus may possess no heart of its own and may depend upon the other fetus for its blood supply. Sometimes, it may be represented by just a mass attached to the other fetus, or may even be embedded within its body.

The incidence of twinning differs in different races and in different countries. Twins occur in one to two per cent of pregnancies and about 70 per cent of them are dizygotic.

TIMETABLE OF SOME EVENTS DESCRIBED IN THIS CHAPTER

Age (in days)	Developmental Events
8th day	Trophoblast differentiates into cytotrophoblast and syncytiotrophoblast.
9th day	Lacunae appear in the syncytium.
11th day	Embryo gets completely implanted in the endometrium.
13th day	Primary villi are formed.
16th day	Secondary and tertiary villi are seen.
2nd month	Villi are seen all around the trophoblast.
4th month	A definitive placenta is formed.
Full term	Placenta is shed about half an hour after birth of the baby.

Chapter 7

Formation of Tissues of the Body

Highlights

- ***Epithelia*** may originate from ectoderm, endoderm or mesoderm.
- Epithelia lining ***external surfaces*** of the body, and terminal parts of passages opening to the outside are derived from ectoderm.
- Epithelium lining the ***gut***, and of organs that develop as diverticula of the gut, is endodermal in origin.
- Epithelium lining most of the ***urogenital tract*** is derived from mesoderm. In some parts, it is endodermal in origin.
- ***Mesenchyme*** is made up of cells that can give rise to cartilage, bone, muscle, blood and connective tissues.
- ***Blood cells*** are derived from mesenchyme in bone marrow, liver, and spleen. Lymphocytes are formed mainly in lymphoid tissues.
- Most ***bones*** are formed by ***endochondral ossification***, in which a cartilaginous model is first formed and is later replaced by bone. Some bones are formed by direct ossification of membrane (***intramembranous ossification***).
- An area where ossification starts is called a ***centre of ossification***. In the case of long bones the shaft (or diaphysis) is formed by extension of ossification from the ***primary centre of ossification***. Secondary centres (of variable number) appear for bone ends. The part of bone ossified from a secondary centre is called an ***epiphysis***.
- In growing bone the diaphysis and epiphysis are separated by the ***epiphyseal plate*** (which is made up of cartilage). Growth in length of a bone takes place mainly at the epiphyseal plate.
- The portion of diaphysis adjoining the epiphyseal plate is called the ***metaphysis***.
- ***Somites*** undergo division into three parts. These are: (a) the ***dermatome*** which forms the dermis of the skin; (b) ***myotome*** which forms skeletal muscle; and (c) ***sclerotome*** which helps to form the vertebral column and ribs.
- ***Skeletal muscle*** is derived partly from somites and partly from mesenchyme of the region.
- Most ***smooth muscle*** is formed from mesenchyme related to viscera, and blood vessels.
- ***Cardiac muscle*** is formed from mesoderm related to the developing heart.
- ***Neurons*** and many ***neuroglial cells*** are formed in the neural tube. The myelin sheaths of peripheral nerves are derived from ***Schwann cells,*** while in the central nervous system they are derived from ***oligodendrocytes.***

The human body is made up of many types of tissue. These are known as basic tissues of the body. They are as follows:

- **Epithelial tissue** – Epithelium consists of cells arranged in the form of continuous sheets. Epithelia line the external and internal surfaces of the body and of body cavities.
- **Connective tissue** – Connective tissue proper includes loose connective tissue, dense connective tissue and adipose tissue. Blood, cartilage and bone are special connective tissues.
- **Muscular tissue** – This is of three types: striated, cardiac and smooth.
- **Nervous tissue** – This tissue consists of neurons (nerve cells), nerve cell processes (axons and dendrites) and cells of neuroglia.

In the present chapter we shall study the formation of these basic tissues.

EPITHELIA

An epithelium may be derived from ectoderm, endoderm or mesoderm. In general, ectoderm gives rise to epithelia covering the external surfaces of the body; and some surfaces near the exterior. Endoderm gives origin to the epithelium of most of the gut; and of structures arising as diverticula from the gut (e.g. the liver and pancreas). Mesoderm gives origin to the epithelial lining of the greater part of the urogenital tract.

Some Epithelia Derived from Ectoderm

- Epithelium of skin, hair follicles, sweat glands, sebaceous glands, and mammary glands.
- Epithelium over cornea and conjunctiva, external acoustic meatus and outer surface of tympanic membrane.
- Epithelium of some parts of the mouth, lower part of anal canal, terminal part of male urethra, parts of female external genitalia.

Some Epithelia Derived from Endoderm

- Epithelium of the entire gut except part of the mouth and anal canal (lined by ectoderm).
- Epithelium of auditory tube and middle ear.
- Epithelium of respiratory tract.
- Epithelium over part of urinary bladder, urethra and vagina.

Some Epithelia Derived from Mesoderm

- Tubules of kidneys, ureter, trigone of urinary bladder.
- Uterine tubes, uterus, part of vagina.
- Testis and its duct system.
- Endothelium lining the heart, blood vessels and lymphatics.
- Mesothelium lining the pericardial, peritoneal and pleural cavities; and cavities of joints.

GLANDS

Almost all glands, both exocrine and endocrine, develop as diverticula from epithelial surfaces (Fig. 7.1A). The gland may be derived from elements formed by branching of one diverticulum (e.g. parotid) or may be formed from several diverticula (e.g. lacrimal gland, prostate). The opening of the duct (or ducts) is usually situated at the site of the original outgrowth. In the case of endocrine glands (e.g. thyroid, anterior part of hypophysis cerebri) the gland loses all contact with the epithelial surface from which it takes origin.

The diverticula are generally solid to begin with (Figs. 7.1A, B) and are canalised later (Fig. 7.1C). The proximal parts of the diverticula form the duct system. The distal parts of the diverticula form the secretory elements (Fig. 7.1D).

Depending on the epithelium from which they take origin, glands may be ectodermal (e.g. sweat glands, mammary glands), endodermal (e.g. pancreas, liver), mesodermal (e.g. adrenal cortex), or of mixed origin (e.g. prostate).

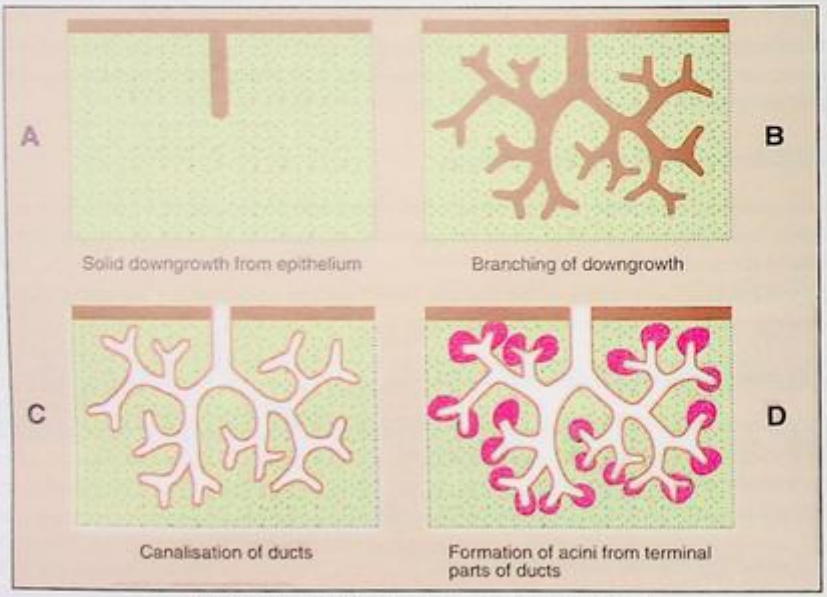

Fig. 7.1: Stages in the development of a typical gland.

MESENCHYME

We have seen above that a small proportion of mesodermal cells give rise to epithelia. The remaining cells, that make up the bulk of mesoderm, get converted into a loose tissue called ***mesenchyme*** (Fig. 7.2). Mesenchymal cells have the ability to form many different kinds of

cells that in turn give rise to various tissues (Fig. 7.3). ***Chondroblasts*** arising from mesenchymal cells form cartilage, ***osteoblasts*** form bone, ***myoblasts*** form muscle, while ***lymphoblasts*** and ***haemocytoblasts*** form various cells of blood. Mesenchymal cells also give rise to ***endothelial cells*** from which blood vessels and the primitive heart tubes are formed. However, after all these tissues have been formed many mesenchymal cells are still left and they give rise to cells of various types of connective tissue.

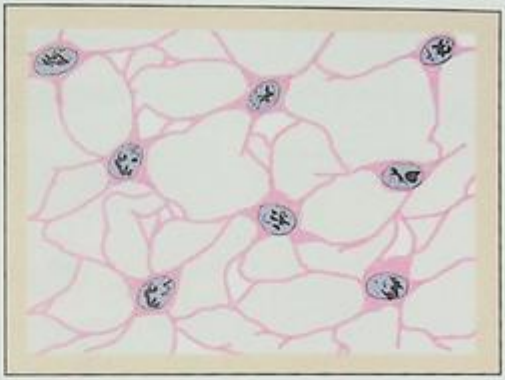

Fig. 7.2: Mesenchymal cells. Note the delicate cytoplasmic processes joining the cells to one another.

CONNECTIVE TISSUE

As the name suggests, connective tissue serves as a connecting system binding, supporting and strengthening all other body tissues together. Connective tissue consists of three components i.e., cells, fibres and ground substance. The fibres and ground substance are synthesized by the cells of the connective tissue.

Formation of Loose Connective Tissue

At the site of formation of loose connective tissue the mesenchymal cells get converted into fibroblasts. Fibroblasts secrete the ground substance and synthesize the collagen, reticular and elastic fibres. Some mesenchymal cells present in the developing connective tissue also get converted into histiocytes, mast cells, plasma cells and fat cells (Fig. 7.3).

FORMATION OF BLOOD

Blood is a specialized fluid connective tissue, which acts as a major transport system within the body. The formation of the cells of blood begins very early in embryonic life (before somites have appeared) and continues throughout life. Blood formation is specially rapid in the embryo to provide for increase in blood volume with the growth of the embryo.

In the third week of embryonic life, formation of blood vessels and blood cells is first seen in the wall of the yolk sac, around the allantoic diverticulum and in the connecting stalk. In these situations, clusters of mesodermal cells aggregate to form ***blood islands***. These mesodermal cells are then converted to precursor cells (***haemangioblasts***) that give rise to blood vessels and blood cells (Fig. 7.4). Cells, which are present in the centre of the blood island, form the precursors of all blood cells (***haematopoietic stem cells***). Cells at the periphery of the island form the precursors of blood vessels (***angioblasts***).

Blood cells arising in the blood islands of the yolk sac are temporary. They are soon replaced by permanent stem cells, which arise from the mesoderm surrounding the developing aorta. These stem cells first form colonies in the liver.

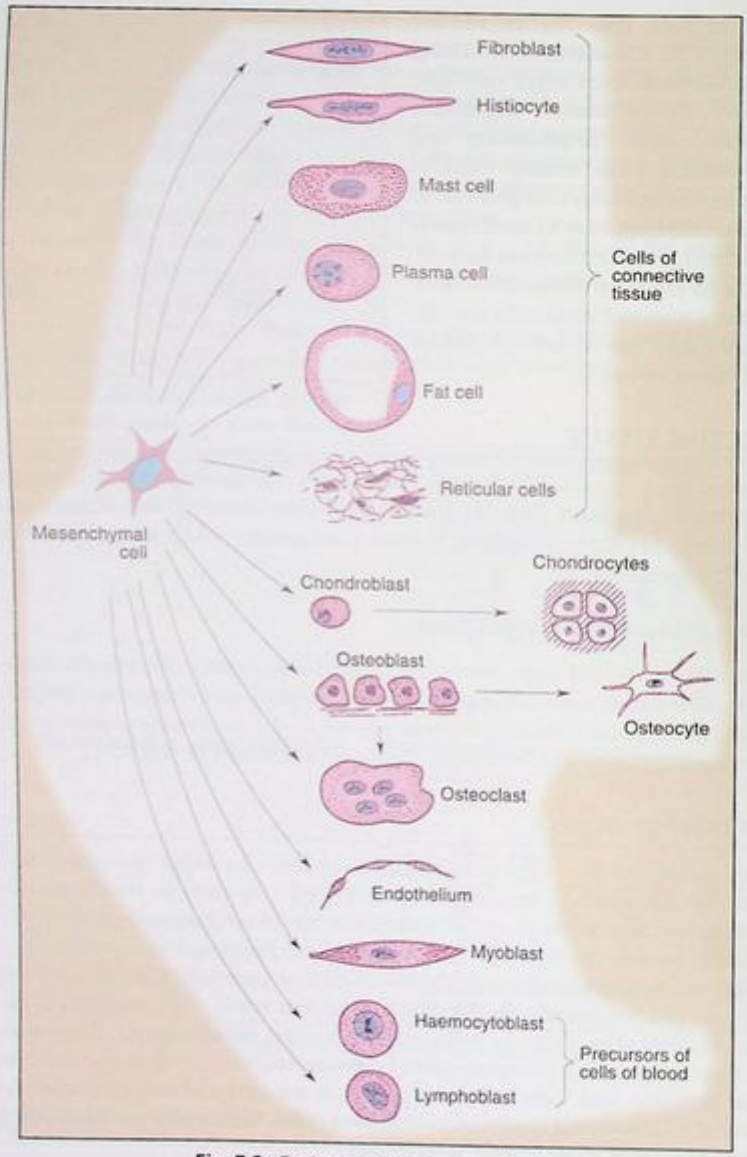

Fig. 7.3: Derivatives of mesenchymal cells.

In the late embryonic period the formation of blood starts in the liver, which remains an important site of blood cell formation till the sixth month of intrauterine life.

Almost near the middle of prenatal life, definitive hematopoietic stem cells from the liver migrate to colonise the bone marrow. At the time of the birth, blood formation is mainly in the bone marrow. Here totipotent haemal stem cells give rise to pleuripotent lymphoid stem cells and pleuripotent haemal stem cells (Fig. 7.5). These stem cells form ***colony forming units (CFU).*** Cells of one particular colony forming unit are committed to differentiate only into one line of blood cells i.e., erythrocytes, megakaryocyte, granulocytes, monocytes, macrophages and lymphocytes (Fig. 7.5). In the case of erythrocytes stem cells divide so rapidly that they seem to burst. They are therefore called ***burst forming units (BFU)***. Their daughter cells then form colony forming units.

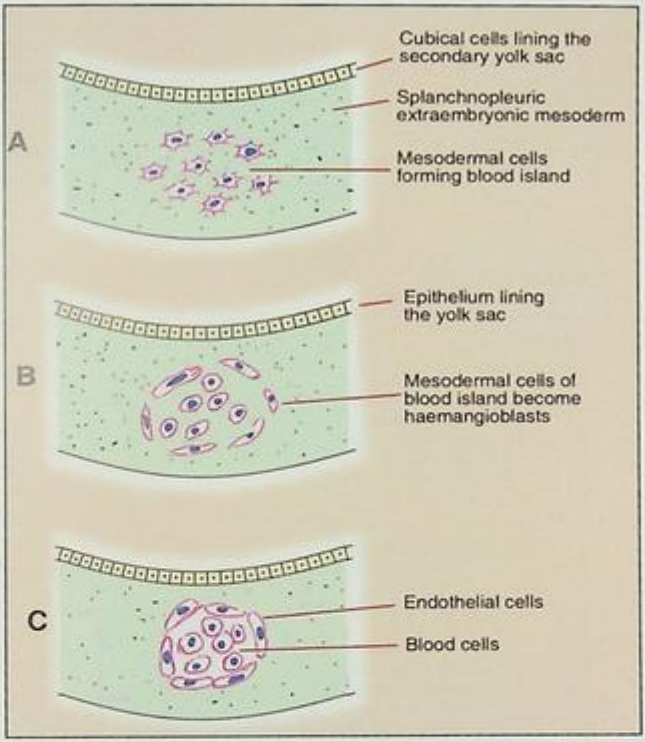

Fig. 7.4: Formation of blood cells and blood vessel from a blood island.

In the adult, main sites of blood formation are bone marrow, lymph nodes, thymus and spleen.

As stated above, the precursors of the various types of blood cells are generally regarded as being of mesodermal in origin. However, blood forming cells differentiating in relation to the wall of the yolk sac and probably in the liver, may be endodermal in origin.

FORMATION OF CARTILAGE

Cartilage is formed from mesenchyme. At a site where cartilage is to be formed, mesenchymal cells become closely packed. This is called a ***mesenchymal condensation***. The mesenchymal cells then become rounded and get converted into cartilage forming cells or ***chondroblasts*** (Fig. 7.3).

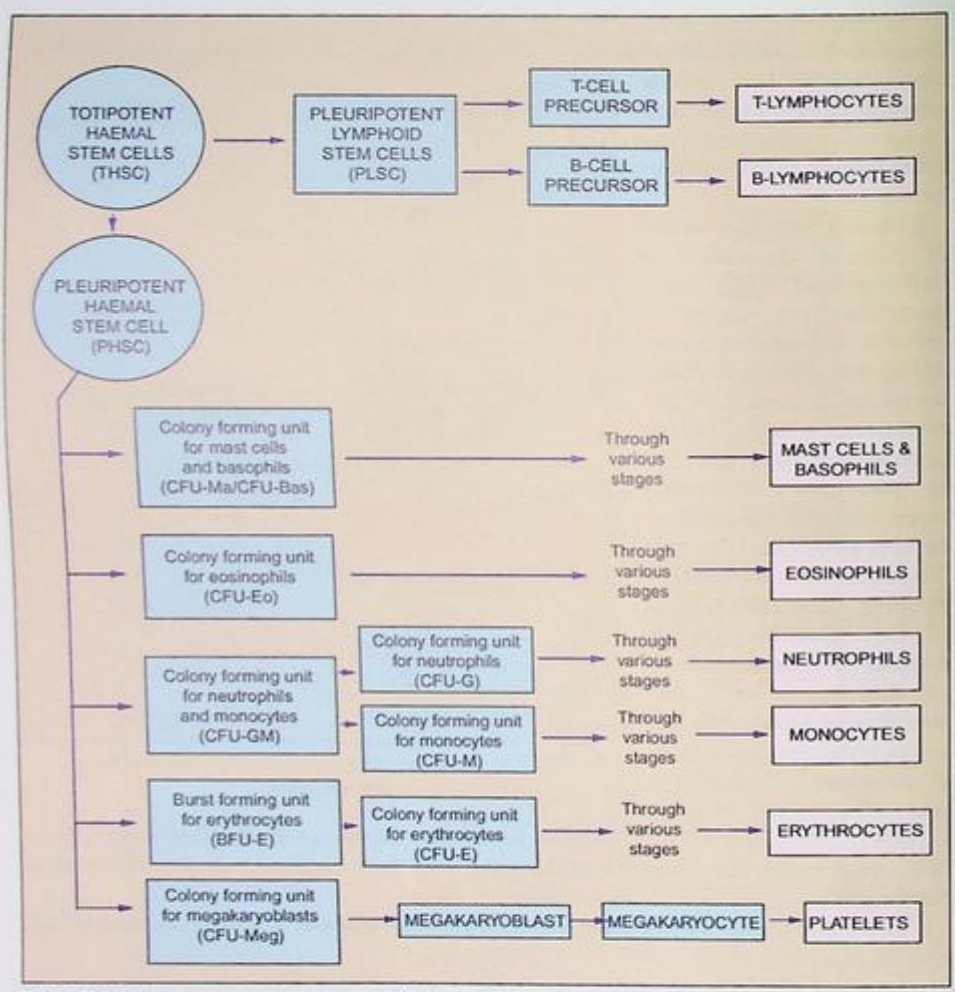

Fig. 7.5: Scheme showing the terms applied to precursors of various blood cells. CFU = Colony Forming Unit. BFU = Burst Forming Unit. Note the other abbreviations used for other precursor cells.

Under the influence of chondroblasts, the ***intercellular substance*** of cartilage is laid down. Some chondroblasts get imprisoned within the substance of this developing cartilage and are called ***chondrocytes***. Some fibres also develop in the intercellular substance. In ***hyaline cartilage***, collagen fibres are present, but are not seen easily. In ***fibrocartilage***, collagen fibres are numerous and very obvious. In some situations, the intercellular substance is permeated by elastic fibres, forming ***elastic cartilage***.

Mesenchymal cells surrounding the surface of the developing cartilage form a fibrous membrane, the ***perichondrium***.

BONE

To understand the formation of bone, it is necessary for students to know its normal structure. This can be read up from the author's Textbook of Human Histology. Some features are shown in Figs. 7.6 to 7.8.

Cells of Bone

Three main types of cells are present in bone.

- ***Osteocytes*** are cells that are seen in mature bone.
- ***Osteoblasts*** are bone forming cells. These cells are, therefore, seen wherever bone is being laid down. They have abundant basophilic cytoplasm and are arranged in regular rows, looking very much like an epithelial lining (Fig. 7.9).
- ***Osteoclasts*** are, on the other hand, responsible for bone removal. They are large multinucleated cells and are seen in regions where bone is being absorbed (Fig. 7.9).

Formation of Bone

All bone is of mesodermal origin. The process of bone formation is called ***ossification***. In most parts of the embryo, bone formation is preceded by the formation of a ***cartilaginous model*** that closely resembles the bone to be formed. This cartilage is

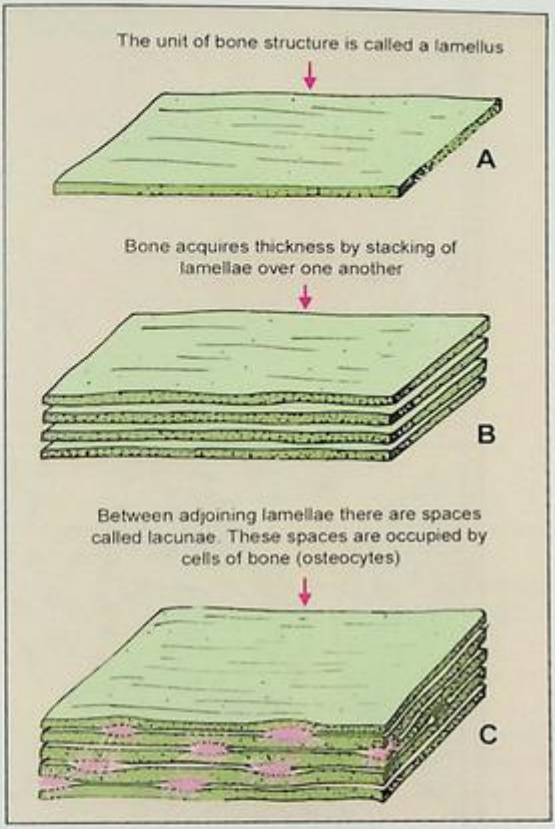

Fig. 7.6: Scheme to show that bone is made up of lamellae.

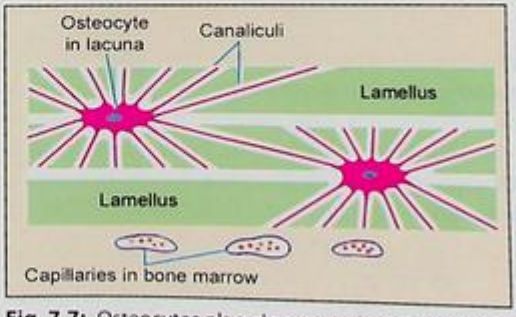

Fig. 7.7: Osteocytes placed amongst lamellae of bone.

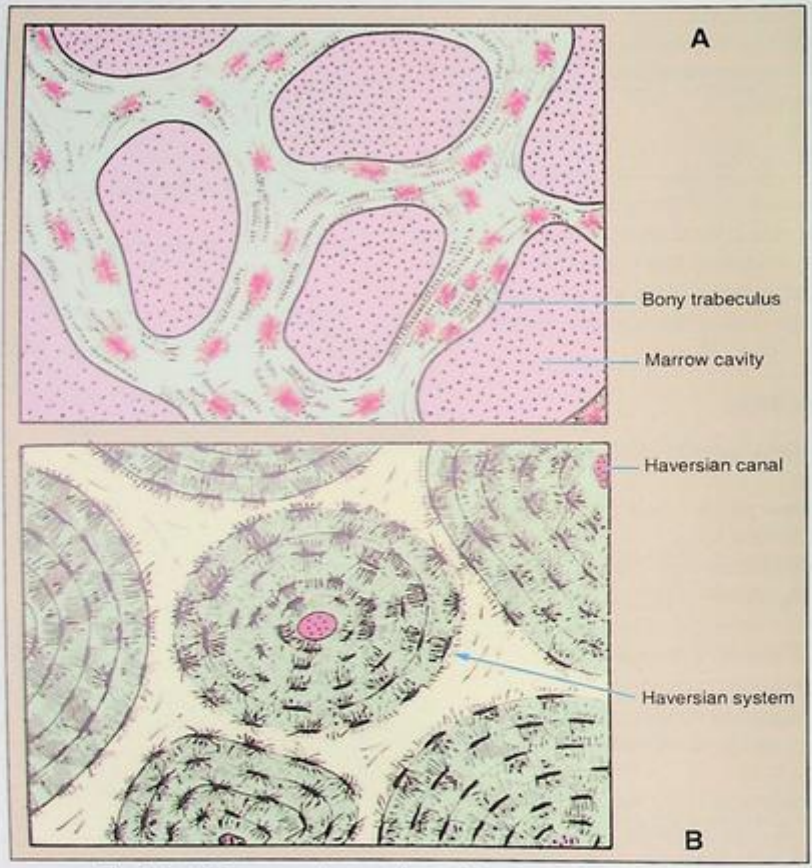

Fig. 7.8: (A) Structure of spongy bone. (B) Structure of compact bone.

subsequently replaced by (not converted into) bone. This kind of bone formation is called ***endochondral ossification***. Bones formed in this way are, therefore, called ***cartilage bones***. In some situations (e.g. the vault of the skull), formation of bone is not preceded by formation of a cartilaginous model. Instead, bone is laid down directly in a fibrous membrane. This is called ***intramembranous ossification*** and these bones are called ***membrane bones***. These include the bones of the vault of the skull, the mandible and the clavicle.

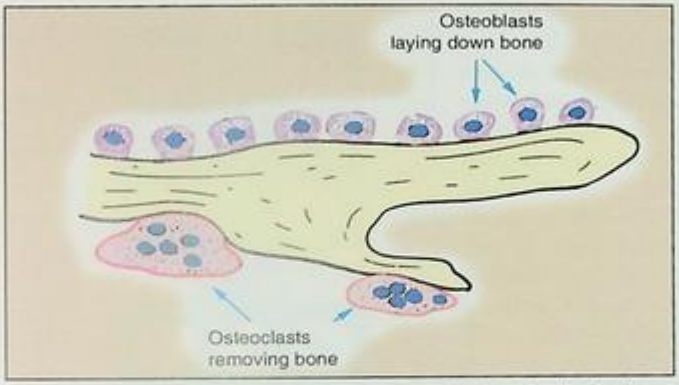

Fig. 7.9: Relationship of osteoblasts and osteoclasts to developing bone.

Endochondral Ossification

The essential steps in the formation of bone by endochondral ossification are as follows:

- At the site where the bone is to be formed, the mesenchymal cells become closely packed to form a mesenchymal condensation (Figs. 7.10 A, B).
- Some mesenchymal cells become chondroblasts and lay down hyaline cartilage (Fig. 7.10C). Mesenchymal cells on the surface of the cartilage form a membrane called the ***perichondrium***. This membrane is vascular and contains osteogenic cells.
- The cells of the cartilage are at first small and irregularly arranged. However, in the area where bone formation is to begin, the cells enlarge considerably (Fig. 7.10D).
- The intercellular substance between the enlarged cartilage cells becomes calcified, under the influence of an enzyme called ***alkaline phosphatase***, which is secreted by the cartilage cells. The nutrition to the cells is thus cut off and they die, leaving behind empty spaces called ***primary areolae*** (Figs. 7.11 A, B).

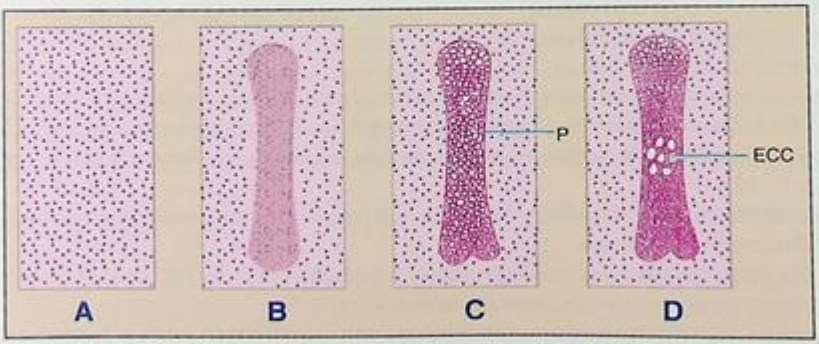

Fig. 7.10: Endochondral ossification: Formation of cartilaginous model.
P = Perichondrium; ECC = Enlarged cartilage cells.

- Some blood vessels of the perichondrium (which may be called ***periosteum*** as soon as bone is formed) now invade the calcified cartilaginous matrix. They are accompanied by osteogenic cells. This mass of vessels and cells is called the ***periosteal bud***. It eats away much of the calcified matrix forming the walls of the primary areolae, and thus creates large cavities called ***secondary areolae*** (Fig. 7.11 C).
- The walls of the secondary areolae are formed by thin layers of calcified matrix that have not been dissolved. The osteogenic cells become osteoblasts and arrange themselves along the surfaces of these bars, or plates, of calcified cartilaginous matrix (Fig. 7.12 A).
- These osteoblasts now lay down a layer of ossein fibrils embedded in a gelatinous intercellular matrix (7.12B). This material is called ***osteoid***. It is calcified and a ***lamellus*** of bone is formed (Fig. 7.12 C).

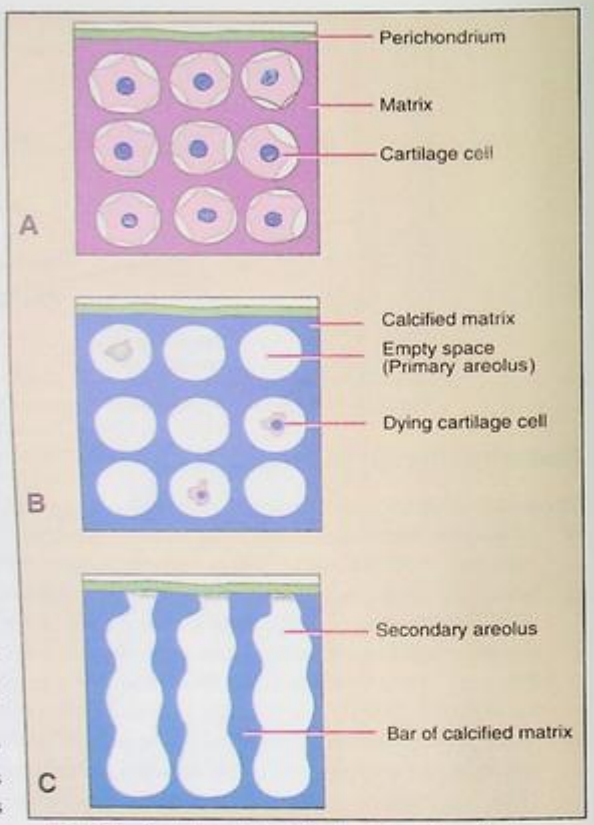

Fig. 7.11: Endochondral ossification: Formation of primary and secondary areolae.

- The osteoblasts now lay down another layer of osteoid over the first lamellus. This is also calcified. Thus two lamellae of bone are formed. Some osteoblasts that get caught between the lamellae form ***osteocytes***. As more lamellae are laid down, bony trabeculae are formed (Fig. 7.12 D).

The calcified matrix of cartilage only acts as a support for the developing trabeculae and is not itself converted into bone.

At this stage the ossifying cartilage shows a central area (1 in Fig. 7.13A) where bone has been formed. As we move away from this area we see:

- a region where the cartilaginous matrix has been calcified and surrounds dead, and dying, cartilage cells (2 in Fig. 7.13A);

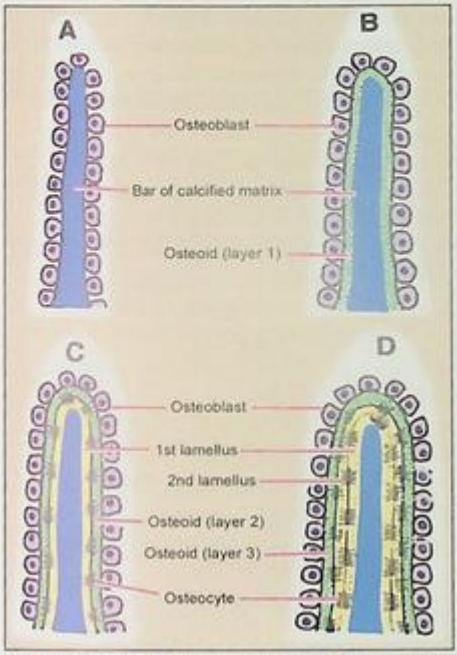

Fig. 7.12: Endochondral ossification: Stages in the formation of bony lamellae.

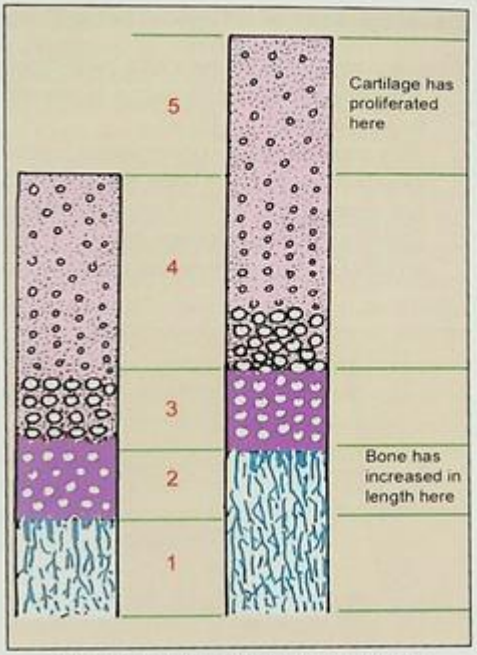

Fig. 7.13: Scheme to show how a bone grows in length.

- a zone of hypertrophied cartilage cells, in an uncalcified matrix (3 in figure 7.13A); and
- normal cartilage (4 in figure 7.13A) in which there is considerable mitotic activity.

If we see the same cartilage a little latter (Fig. 7.13B), we find that ossification has now extended into zone 2, and simultaneously the matrix in zone 3 has become calcified. The deeper cells of zone 4 have meanwhile hypertrophied, while the more superficial ones have multiplied to form zone 5. In this way, formation of new cartilage keeps pace with the loss due to replacement by bone. The total effect is that the ossifying cartilage progressively increases in size.

Development of a Typical Long Bone

We may now consider how a long bone develops.

- A mesenchymal condensation is seen in the limb-bud in the region where the bone is to be formed (Figs. 7.14A, B).
- This mesenchymal condensation is converted into a cartilaginous model. This model closely resembles the bone to be formed. It is covered by perichondrium (Fig. 7.14C) that has a superficial fibrous layer and a deeper layer that has osteogenic cells.
- Endochondral ossification starts in a small area of the shaft as described above. This area is called the ***primary centre of ossification*** (Fig. 7.15).

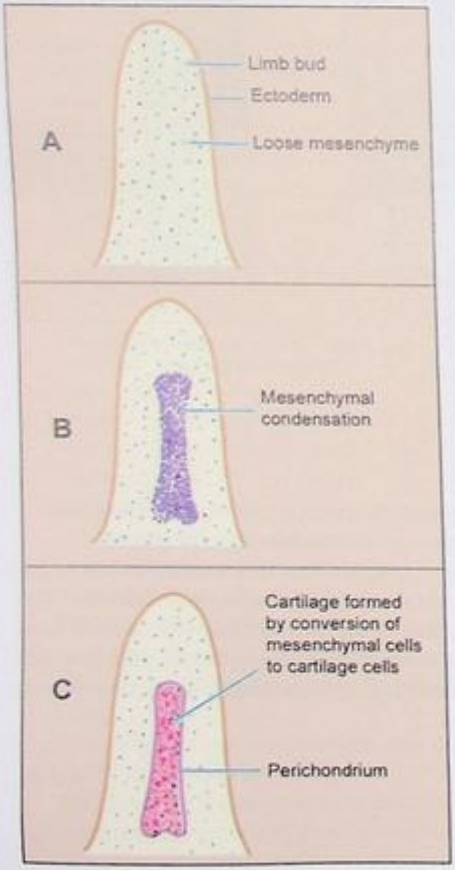

Fig. 7.14: Formation of a typical long bone: Establishment of cartilaginous model.

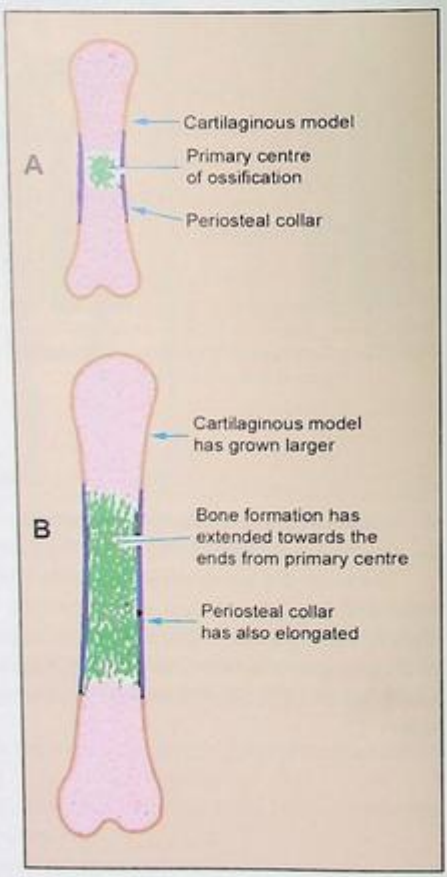

Fig. 7.15: Formation of a typical long bone: Primary centre of ossification and periosteal collar.

- Gradually, bone formation extends from the primary centre towards the ends of the shaft. This is accompanied by enlargement of the cartilaginous model (Fig. 7.15).
- Soon after the appearance of the primary centre, and onset of endochondral ossification in it, the perichondrium (which may now be called ***periosteum***) becomes active. The osteogenic cells in its deeper layer lay down bone ***on the surface of*** the cartilaginous model by ***intramembranous ossification***. This periosteal bone completely surrounds the cartilaginous shaft and is, therefore, called the ***periosteal collar*** (Fig. 7.15). It is first formed only around the region of the primary centre but rapidly extends towards the ends of the cartilaginous model. The periosteal collar acts as a splint, and gives strength to the cartilaginous model, at the site where it is weakened by the formation of secondary areolae. We shall see that most of the shaft of the bone is derived from this periosteal collar and is, therefore, intramembranous in origin.
- At about the time of birth, the developing bone consists of a part called the ***diaphysis*** (or shaft) (that is bony, and has been formed by extension of the primary centre of ossification); and ends that are cartilaginous (Fig. 7.16A). At varying times after birth, ***secondary centres*** of endochondral ossification appear in the cartilages forming the ends of the bone (Fig. 7.16B). These centres enlarge until the ends become bony (Fig. 7.16C). More than one secondary centre of ossification may appear at either end. The portion of bone formed from one secondary centre is called an ***epiphysis***.

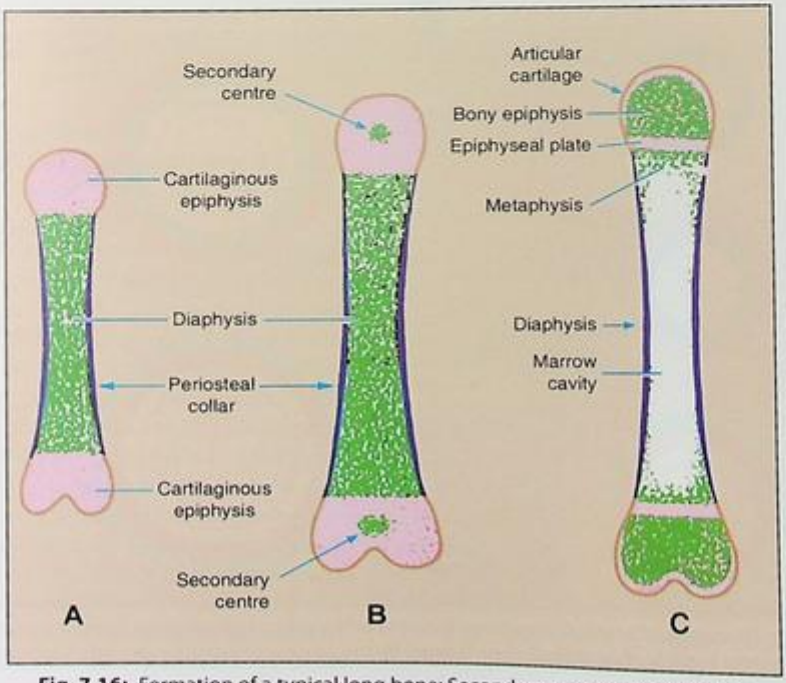

Fig. 7.16: Formation of a typical long bone: Secondary centres of ossification.

For a considerable time after birth, the bone of the diaphysis and the bone of the epiphysis are separated by a plate of cartilage called the ***epiphyseal cartilage***, or ***epiphyseal plate***. This is formed by cartilage into which ossification has not extended either from the diaphysis or from the epiphysis. We shall see that this plate plays a vital role in growth of the bone.

Growth of a Long Bone

A growing bone increases both in length and in thickness.

We have seen that the periosteum lays down a layer of bone around the shaft of the cartilaginous model. This periosteal collar gradually extends over the whole length of the diaphysis. As more layers of bone are laid down over it, the periosteal bone becomes thicker and thicker. However, it is neither necessary nor desirable for it to become too thick. Hence, osteoclasts come to line the internal surface of the shaft and remove bone from this aspect. As bone is laid down outside the shaft it is removed from the inside. The shaft thus grows in diameter, and at the same time, its wall does not become too thick (Fig. 7.17). The osteoclasts also remove the trabeculae lying in the centre of the bone that were formed by endochondral ossification. In this way, a *marrow cavity* is formed.

As the shaft increases in diameter, there is a corresponding increase in the size of the marrow cavity. This cavity also extends towards the ends of the diaphysis but does not reach

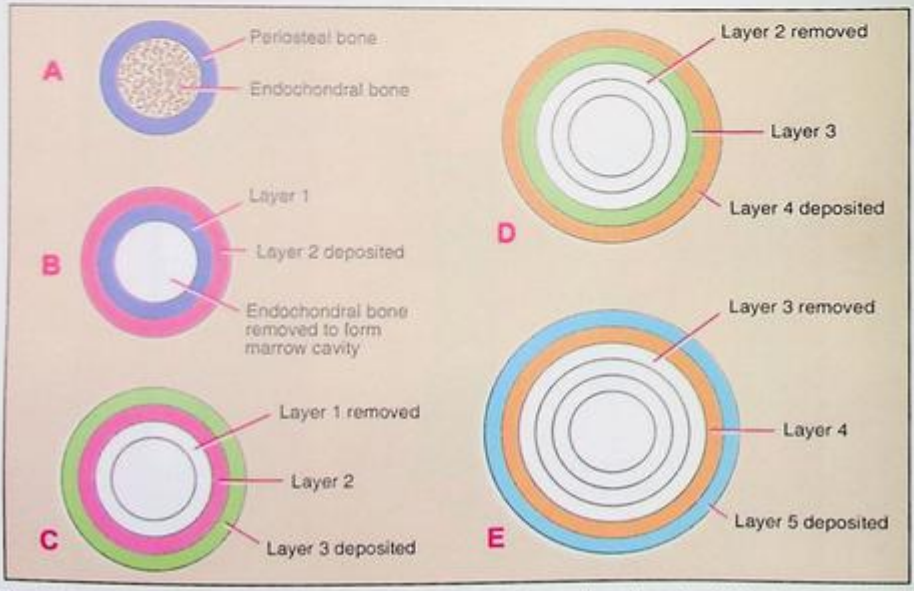

Fig. 7.17: Formation of a typical long bone: Increase in thickness. Note that the shaft is ultimately made up almost entirely of periosteal bone formed by the process of intramembranous ossification.

the epiphyseal plate. Gradually, most of the bone formed from the primary centre (i.e. of endochondral origin) is removed, except near the ends, so that the wall of the shaft is made up purely of periosteal bone formed by the process of intramembranous ossification.

To understand how a bone grows in length, we will now have a closer look at the epiphyseal plate. Depending on the arrangement of its cells, three zones can be recognized (Fig. 7.18).

1. *Zone of resting cartilage*: Here, the cells are small and irregularly arranged.
2. *Zone of proliferating cartilage*: Here, the cells are larger and are undergoing repeated mitosis. As they multiply, they come to be arranged in parallel columns, separated by bars of intercellular matrix.
3. *Zone of calcification*: Here, the cells become still larger and the matrix becomes calcified.

Next to the zone of calcification, there is a zone where cartilage cells are dead and the calcified matrix is being replaced by bone. Growth in length of the bone takes place by continuous transformation of the epiphyseal cartilage to bone (Figs. 7.18, 7.19) in this zone (i.e. on the diaphyseal surface of the epiphyseal cartilage). At the same time, the thickness of the epiphyseal cartilage is maintained by active multiplication of cells in the zone of proliferation. When the bone has attained its full length, cells in the epiphyseal cartilage stop proliferating. The process of ossification, however, continues to extend

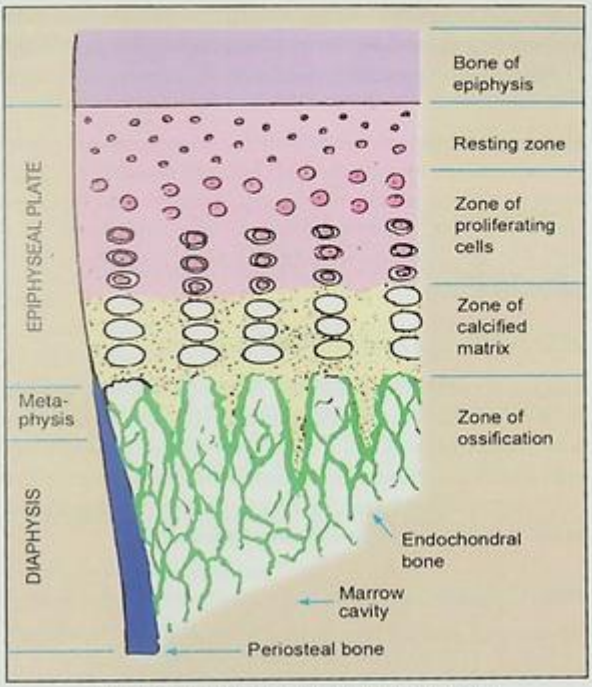

Fig. 7.18: Structure of epiphyseal cartilage.

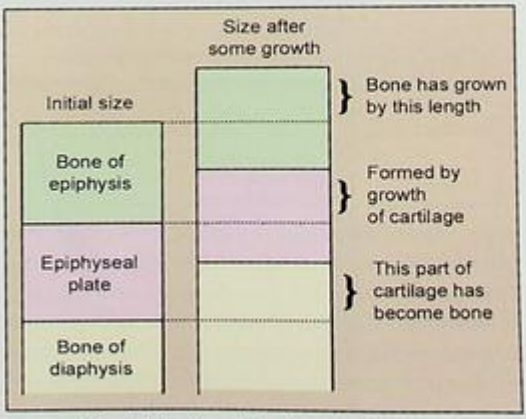

Fig. 7.19: Growth in length of bone at epiphyseal cartilage.

into it until the whole of the epiphyseal plate is converted into bone. The bone of the diaphysis and epiphysis then becomes continuous. This is called ***fusion of epiphysis***.

Metaphysis

The portion of diaphysis adjoining the epiphyseal plate is called the ***metaphysis***. It is a region of active bone formation and, for this reason, it is highly vascular. The metaphysis does not have a marrow cavity. Numerous muscles and ligaments are usually attached to the bone in this region. Even after bone growth has ceased, the calcium-turnover function of bone is most active in the metaphysis, which acts as a storehouse of calcium. This region is frequently the site of infection.

Interstitial and Appositional Growth

Tissues grow by two methods. In some of them, growth takes place by multiplication of cells (or by increase in intercellular material) throughout the substance of the tissue. This is called ***interstitial growth***. As a result, the tissue expands equally in all directions and its shape is maintained. Cartilage (and most other tissues) grow in this way.

On the other hand, bone grows only by deposition of more bone on its surface, or at its ends. This is called ***appositional growth***.

Remodelling

We have seen above that when a tissue grows by interstitial growth it is easy for it to maintain its shape. However, this is not true of bone which can grow only by apposition. This will be clear from Fig. 7.20. In this figure the brown line represents the shape of a bone end. The green line represents the same bone end after it has grown for some time. It will be clear that some areas of the original bone have to disappear if proper shape is to be maintained. This process of removal of unwanted bone is called ***remodelling***.

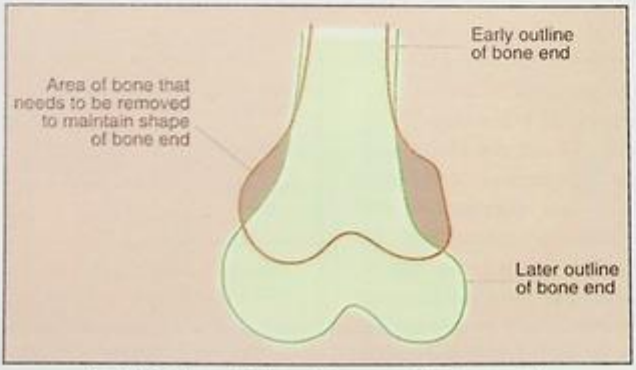

Fig. 7.20: Remodelling of bone ends during growth.

The trabeculae of spongy bone and the Haversian systems of compact bone are so arranged that they are best fitted to bear the stresses imposed on them. This arrangement can change with change in stresses acting on the bone. This process is often called ***internal remodelling***.

Clinical Correlation

Anomalies of Bone Formation

Bone and cartilage formation may sometimes be abnormal as a result of various genetic and environmental factors. The anomalies may be localised to a particular part of the skeleton, or may be generalised. Anomalies of individual parts of the skeleton are considered in Chapter 10. Some anomalies that affect the skeleton as a whole are as follows:

- Disorderly and excessive proliferation of cartilage cells in the epiphyseal plate, or the failure of normally formed cartilage to be replaced by bone, leads to the formation of irregular masses of cartilage within the metaphysis. This is called ***dyschondroplasia*** or ***enchondromatosis***.
- Abnormal masses of bone may be formed in the region of the metaphysis and may protrude from the bone. Such a protrusion is called an ***exostosis***, and the condition is called ***multiple exostoses*** or ***diaphyseal aclasis***. This condition may be a result of interference with the process of remodelling of bone ends.
- Calcification of bone may be defective (***osteogenesis imperfecta***) and may result in multiple fractures.
- Parts of bone may be replaced by fibrous tissue (***fibrous displasia***).
- Bones may show increased density or ***osteosclerosis***. One disease characterised by increased bone density is known as ***osteopetrosis***, or ***marble bone disease***.
- In the condition called ***achondroplasia***, there is insufficient, or disorderly, formation of bone in the region of the epiphyseal cartilage. This interferes with growth of long bones. The individual does not grow in height and becomes a dwarf. A similar condition in which the limbs are of normal length, but in which the vertebral column remains short, is called ***chondro-osteo-dystrophy***.
- Anomalous bone formation may be confined to membrane bones. One such condition is ***cleido-cranial dysostosis*** in which the clavicle is absent and there are deformities of the skull. On the other hand, anomalies like achondroplasia and exostoses are confined to cartilage bones.
- Generalised underdevelopment (***dwarfism***), or overdevelopment (***gigantism***) of bone may be present. Sometimes all bones of one half of the body are affected (***asymmetric development***). Overdevelopment or underdevelopment may be localised, e.g. to a digit, or to a limb.

FORMATION OF MUSCLE

Skeletal muscle may be derived from somites, from somitomeres and from lateral plate mesoderm. At these sites, there are cells that are precursors of muscle. These cells divide repeatedly and finally differentiate into myoblasts. Myoblasts synthesise the proteins actin and myosin. Several myoblasts fuse with each other to form multinucleated tube like elements that are called myotubes. Within these myotubes molecules of actin, myosin and other contractile proteins unite to form myofibrils. These fibrils are arranged in a definite orientation. Progressive aggregation of fibrils within the myotube pushes nuclei to the periphery. A muscle fibre is thus formed.

Satellite cells present around muscle fibres can help in growth of fibres.

Fate of Somites

We have seen that the paraxial mesoderm becomes segmented to form a number of somites, that lie on either side of the developing neural tube. A cross section through a somite shows that it is a triangular structure and has a cavity (Fig. 7.21A). The somite is divisible into three parts.

1. The ventromedial part is called the ***sclerotome***. The cells of the sclerotome migrate medially. They surround the neural tube and give rise to the vertebral column and ribs (Figs. 7.21B, C).
2. The lateral part is called the ***dermatome***. The cells of this part also migrate, and come to line the deep surface of the ectoderm covering the entire body. These cells give rise to the dermis of the skin and to subcutaneous tissue.

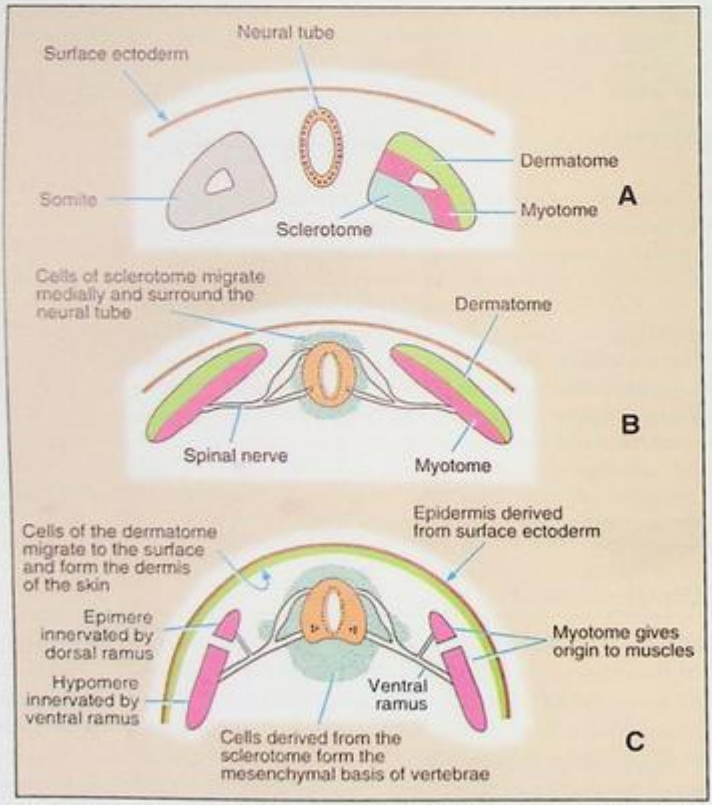

Fig. 7.21: (A) Somites lying on either side of the neural tube. Note subdivisions of somite. (B) The cells of the sclerotome have migrated medially and now surround the neural tube. The myotome is innervated by nerves growing out of the neural tube. (C) The cells of the dermatome have migrated to form the dermis of the skin.

Recently, it has been held that the dermatome only forms dermis on the back of the head and trunk, and that dermis elsewhere is derived from lateral plate mesoderm.

3. The intermediate part is the ***myotome***. It gives rise to striated muscle as described in the following section.

In the cervical, thoracic, lumbar and sacral regions one spinal nerve innervates each myotome. The number of somites formed in these regions, therefore, corresponds to the number of spinal nerves. In the coccygeal region, the somites exceed the number of spinal nerves but many of them subsequently degenerate.

The first cervical somite is ***not*** the most cranial somite to be formed. Cranial to it, there are:

- the ***occipital somites*** (four to five) which give rise to muscles of the tongue and are supplied by the hypoglossal nerve.
- the ***pre-occipital*** (or ***pre-otic***) ***somites*** (somitomeres), supplied by the third, fourth and sixth cranial nerves.

Development of Striated Muscle

Striated muscle is derived from somites and also from mesenchyme of the region.

We have seen that each myotome establishes contact with one segmental nerve. Hence, theoretically, the embryological derivation of a muscle should be indicated by its nerve supply. On this basis, it would be presumed that all the musculature of the body walls and limbs is derived from the myotomes and has subsequently migrated to these regions. Such migration of myotomes can be seen in embryos of some lower animals, but not in the human embryo. In man, the myotomes appear to give origin only to the musculature of the trunk, in whole or in part. The occipital myotomes are believed to give rise to the musculature of the tongue, while the extrinsic muscles of the eyeball are regarded as derivatives of the preoccipital myotomes.

Soon after its formation, each myotome, in the neck and trunk, separates into a dorsal part (***epimere***) which gives rise to the muscles supplied by the dorsal primary ramus of the spinal nerve, and a ventral part (***hypomere***), which gives origin to the muscles supplied by the ventral ramus (Fig. 7.21C). The epimeres give origin to the muscles of the back (extensors of the vertebral column), while the hypomeres give origin to the muscles of the body wall and limbs.

Some cells from the ventrolateral region of the dermo-myotomes migrate into the parietal layer of lateral plate mesoderm where they form muscles of limbs, and anterolateral muscles of the neck and abdomen.

Smooth Muscle

Almost all smooth muscle is formed from mesenchyme. Smooth muscle in the walls of viscera (e.g., the stomach) is formed from splanchnopleuric mesoderm in relation to them.

However, the muscles of the iris (sphincter and dilator pupillae) and myoepithelial cells of the sweat glands are derived from ectoderm.

Cardiac Muscle

This is derived from splanchnopleuric mesoderm in relation to the developing heart tubes and pericardium.

NERVOUS TISSUE

Nervous tissue consists of cells, fibres and blood vessels. Two different categories of cells are found in the nervous tissues i.e., neurons and neuroglial cells. The neurons are cells that generate and conduct nerve impulses, while the neuroglial cells are supporting structures. Neurons have many processes (axons and dendrites). These processes collect to form nerves. Blood vessels of the nervous tissue are not derived from the neural tube but enter it from surrounding mesoderm.

Formation of Neurons and Neuroglial Cells

The neurons and many neuroglial cells are formed in the neural tube.

The neural tube is at first lined by a single layer of cells, (Fig. 7.22A). These proliferate to form several layers (Fig. 7.22B). Nearest the lumen of the tube is the ***matrix cell layer*** (also called primitive ependymal or germinal layer). The cells of this layer give rise to nerve cells, to neuroglial cells, and also to more germinal cells. Next comes the ***mantle layer*** in which are seen the developing nerve cells, and neuroglial cells. The outermost layer, termed the ***marginal zone***, contains no nerve cells. It consists of a reticulum formed by protoplasmic

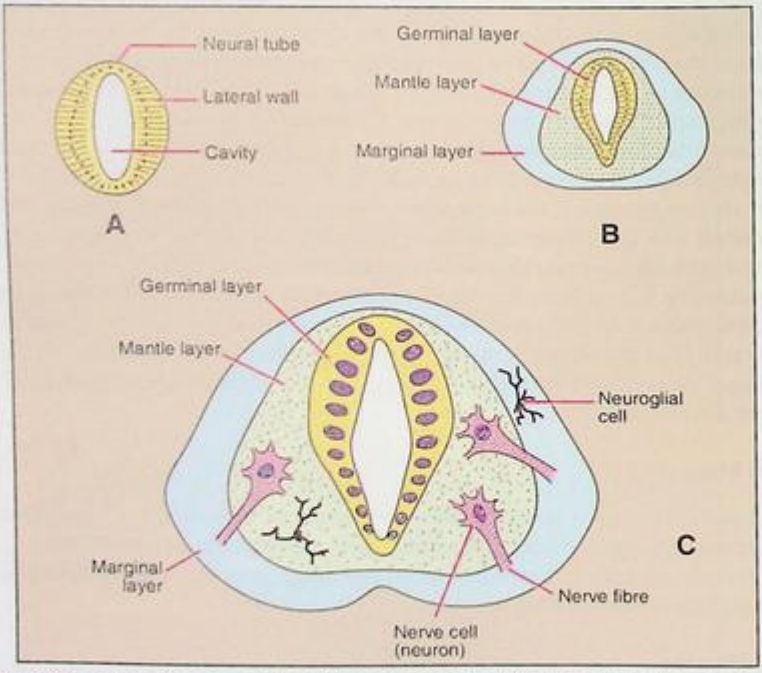

Fig. 7.22: Layers of the neural tube. Although the germinal (neuroepithelial) layer is shown as a simple epithelium, it is really pseudostratified.

processes of developing neuroglial cells (***spongioblasts***). It provides a framework into which the processes of nerve cells developing in the mantle layer can grow.

The stages in the formation of a nerve cell are as follows:

- One of the germinal cells passes from the germinal layer to the mantle layer and becomes an ***apolar neuroblast*** (Fig. 7.23A).
- Two processes develop and convert the apolar neuroblast to a ***bipolar neuroblast*** (Fig. 7.23B).
- One of the processes of the neuroblast disappears, and it can now be called an ***unipolar neuroblast*** (Fig. 7.23C).
- The process of the cell (which does not disappear) now elongates, and on the side opposite to it numerous smaller processes form. At this stage, the cell is called a ***multipolar neuroblast*** (Fig. 7.23D).
- The main process of the multipolar neuroblast now grows into the marginal layer, and becomes the ***axon*** of the nerve cell (Fig. 7.22B). The axon can grow to a considerable length. It may either remain within the central nervous system, or may grow out of it as an efferent nerve fibre of a peripheral nerve. At its destination, it establishes connections, either with the cell bodies and dendrites of other neurons, or with an effector organ (e.g. muscle).
- The smaller processes of the neuroblast are the ***dendrites***. These ramify and establish connections with other nerve cells.
- At first the cytoplasm of the nerve cell is homogeneous. Later ***Nissl's granules*** make their appearance. After their formation, neurons lose the ability to divide.

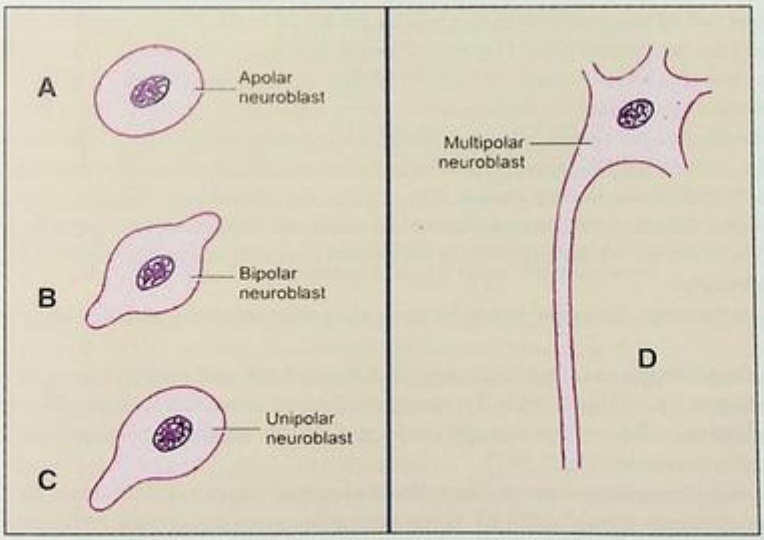

Fig. 7.23: Stages in formation of a typical neuroblast.

Derivation of Nerve Cells (neurons) and Neuroglial Cells		
From neural tube	**From neural crest**	**From mesenchymal cells**
Neurons	Schwann cells	Microglia
Fibrous astrocytes	Dorsal n. root ganglion cells	Oligodendroglia (?)
Protoplasmic astrocytes	Cells of other sensory ganglia	
Oligodendroglia (?)	Neurons in sympathetic ganglia	
Ependymal cells		

Fig. 7.24: Various types of cells are derived from neuroepithelium.

Neuroglial cells are also formed from germinal cells of the ependymal layer (Fig. 7.24). These cells (***glioblasts***) migrate to the mantle and marginal zones as ***medulloblasts*** (also called ***spongioblasts***), which differentiate either into ***astroblasts***, and subsequently into ***astrocytes***, or into ***oligodendroblasts*** and then into ***oligodendrocytes***. There is a third type of neuroglial cell called ***microglia***. This type does not develop from the cells of the neural tube, but migrates into it along with blood vessels. These cells are believed to be of mesodermal origin.

We have seen above that the ependymal (or neuroepithelial) cells give rise both to neuroblasts and to neuroglia. However, these two cell types are not formed simultaneously. The neuroblasts are formed first. Neuroglial cells are formed after the differentiation of neuroblasts is completed.

Formation of myelin sheath

Nerve fibres, which remain within the brain and spinal cord, receive support from, and are ensheathed by, neuroglial cells. However, the nerve fibres, which leave the central nervous system to become constituents of peripheral nerves, acquire a special sheath called the ***neurolemma***. This sheath is derived from some cells of the neural crest that are called ***Schwann cells***. At a later stage of development, a large number of nerve fibres, both inside and outside the central nervous system, develop another sheath between the neurolemma and the axon. This is called the ***myelin sheath***. The myelin sheaths of peripheral nerves are derived from the same Schwann cells that form the neurolemma. In the central nervous system itself, however, there are no Schwann cells and the myelin sheath is formed by neuroglial cells called ***oligodendrocytes***.

The relationship of an axon to a Schwann cell is illustrated in Fig. 7.25. Note the following points:

- Each axon invaginates the cytoplasm of a Schwann cell and thus comes to be completely surrounded by it (Figs. 7.25A, B). Along the line of invagination, the cell membrane of the Schwann cell becomes drawn in to form a double layered mesentery-like membrane called the ***mesaxon*** (Fig. 7.25C).
- In the case of myelinated nerve fibres, the mesaxon elongates and becomes spirally wound around the axon (Figs. 7.25D, E). Some fatty substances are deposited between adjacent layers of the mesaxon and, together with it, form the ***myelin sheath***.

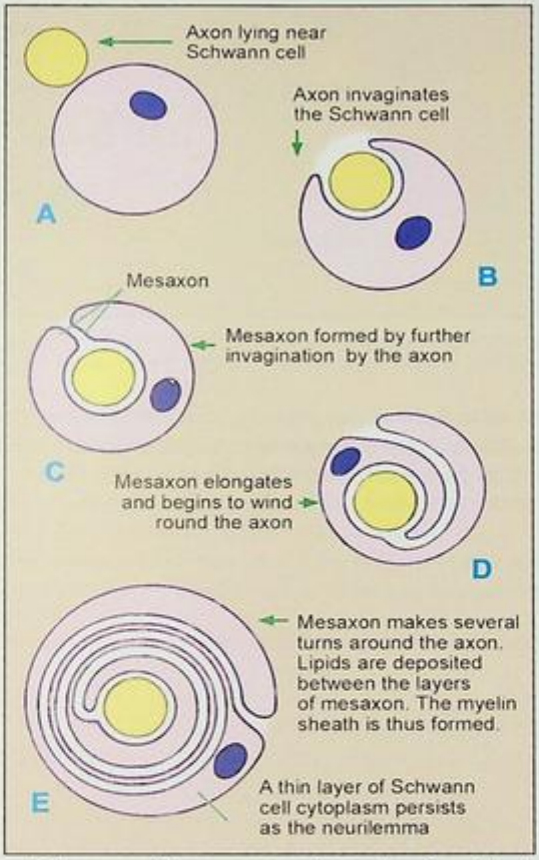

Fig. 7.25: Invagination of Schwann cell by an axon and formation of myelin sheath. (A) Axon lies near Schwann cell. (B) Axon invaginating Schwann cell. (C) Mesaxon formed (by two layers of cell membrane). (D) Mesaxon elongates. (E) Several layers of mesaxon spiral around the axon to form the basis of the myelin sheath. Lipids are deposited between layers of the mesaxon.

- In the case of unmyelinated fibres there is no elongation of the mesaxon. Several unmyelinated fibres may invaginate the same Schwann cell (Fig. 7.26).

Nerve fibres in different parts of the brain, and spinal cord, become myelinated at different stages of development. The process begins during the fourth month of intra-uterine life, but is not completed until the child is two to three years old. Nerve fibres become fully functional only after they have acquired their myelin sheaths.

The blood vessels of the brain, and their surrounding connective tissue, are not derived from the neural tube. These are mesodermal in origin and invade the developing brain and spinal cord from the surrounding mesoderm.

Chapter 8

The Skin and Its Appendages

HIGHLIGHTS

- The ***epidermis*** is derived from surface ectoderm.
- The ***dermis*** is formed by mesenchyme derived from dermatomes of somites.
- *Nails* develop from ectoderm at the tip of each digit. Later, this ectoderm migrates to the dorsal aspect.
- *Hair* are derived from surface ectoderm which is modified to form hair follicles.
- ***Sebaceous glands*** (ectoderm) arise as diverticula from hair follicles.
- ***Sweat glands*** develop as downgrowths from the epidermis that are later canalised.
- ***Mammary glands*** arise from surface ectoderm. They are formed along a milk line extending from axilla to the inguinal region.

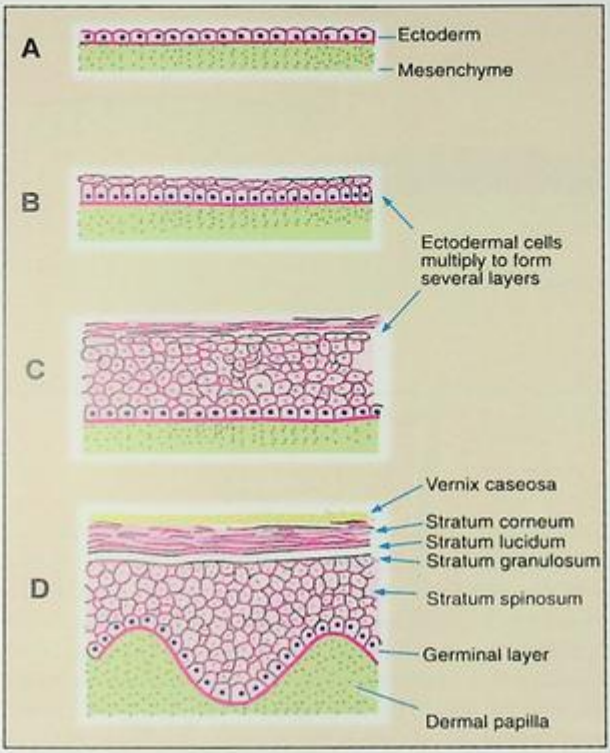

Fig. 8.2: Stages in the development of the epidermis.

NAILS

The nails develop from the surface ectoderm. The ectoderm at the tip of each digit becomes thickened to form a ***primary nail field***. Subsequently, this thickening migrates from the tip of the digit onto its dorsal aspect.

The cells in the most proximal part of the nail field proliferate to form the root of the nail. Here the cells of the germinal layer multiply to form a thick layer of cells called the ***germinal matrix***. As the cells in this matrix multiply, they are transformed into the nail substance which corresponds to the stratum lucidum of the skin (Fig. 8.3).

The migration of the primary nail fields from the tips of the digits to their dorsal aspect explains why the skin of the dorsal aspect of the terminal part of the digits is supplied by nerves of the ventral aspect.

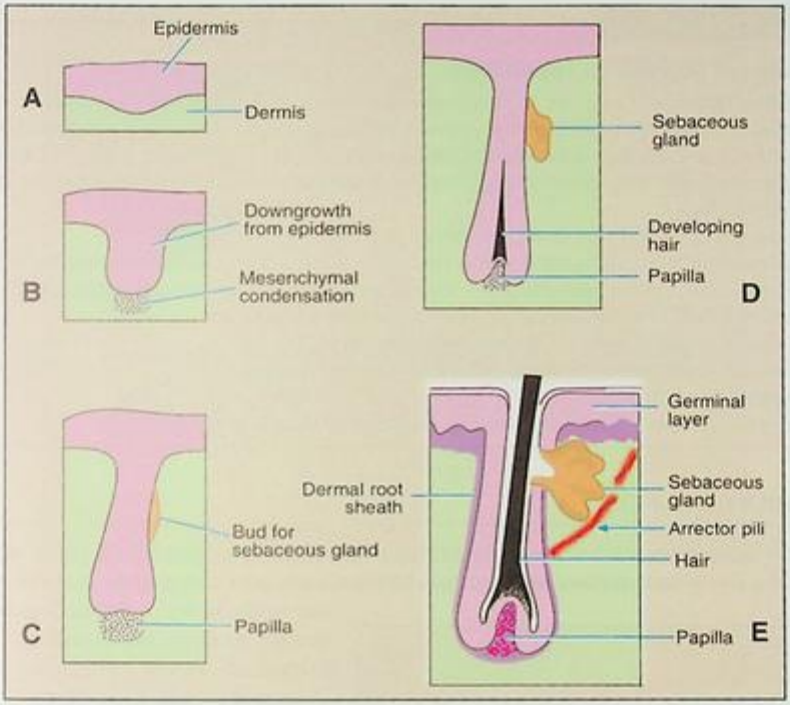

Fig. 8.4: Development of a hair follicle.

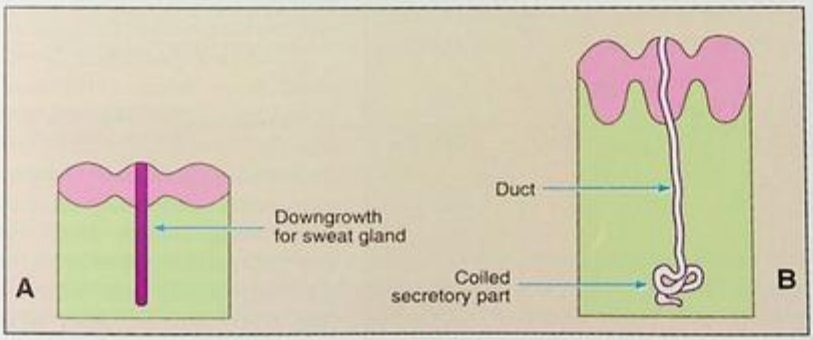

Fig. 8.5: Development of a sweat gland.

CLINICAL CORRELATION

Anomalies of Skin and its Appendages

- ***Albinism***: Absence of pigment in skin, hair and eyes occurs because melanocytes are unable to synthesize melanin. In this autosomal recessive genetic condition, skin is de-pigmented all over the body.This should be distinguished from ***vitiligo*** which is not congenital. In vitiligo the absence of pigment is patchy. In the affected areas, there is degeneration of already existing melanocytes. It is an auto-immune disease.
- ***Aplasia***: The skin may fail to develop in certain regions.
- ***Dysplasia***: The skin may be abnormal in structure. Numerous varieties of dysplasia are described. There may be congenital growths of the skin. Dysplasia may be part of maldevelopment of various ectodermal derivatives including hair, teeth, sweat glands and sebaceous glands.
- Hair may be absent over the scalp (***congenital alopecia***). The eyebrows and eyelashes may also be absent. Absence of hair in any part of the body is called ***atrichia***, while overgrowth of hair is called ***hypertrichosis***.
- ***Anonychia:*** Nails may be absent. Occasionally they may show over development.

MAMMARY GLANDS

In some animals (e.g. bitches), a series of mammary glands are present on either side of the midline, on the ventral surface of the trunk. These are situated along a line that extends from the axilla to the inguinal region. In the human embryo, the ectoderm becomes thickened along this line to form ***mammary ridges or lines*** (Fig. 8.6). Most of this line soon disappears. Each mammary gland develops from a part of this line that overlies the pectoral region.

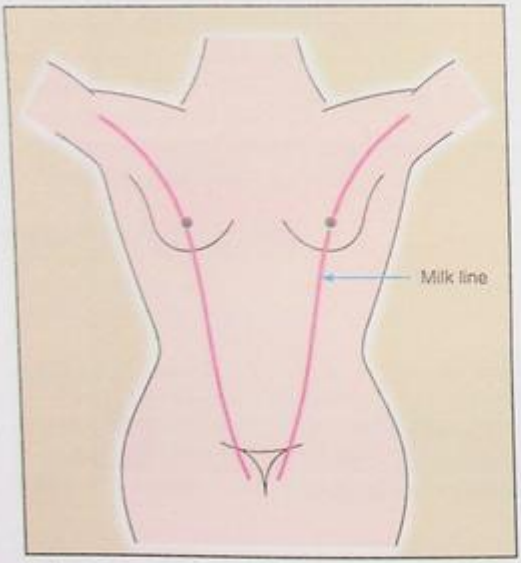

Fig. 8.6: The mammary line passing from the axilla to the inguinal region.

In the region where the mammary gland is to form, a thickened mass of epidermal cells is seen projecting into the dermis (Fig. 8.7A). From this thickened mass, sixteen to twenty solid outgrowths arise, and grow into the surrounding dermis (Figs. 8.7B, C). The thickened mass of epidermis (and the outgrowths), are now canalised (Fig. 8.7D). The ***secretory elements*** of the gland are formed by proliferation of the terminal parts of the outgrowths. The proximal end of each outgrowth forms one ***lactiferous duct***. The ducts at first open into a pit formed by cavitation of

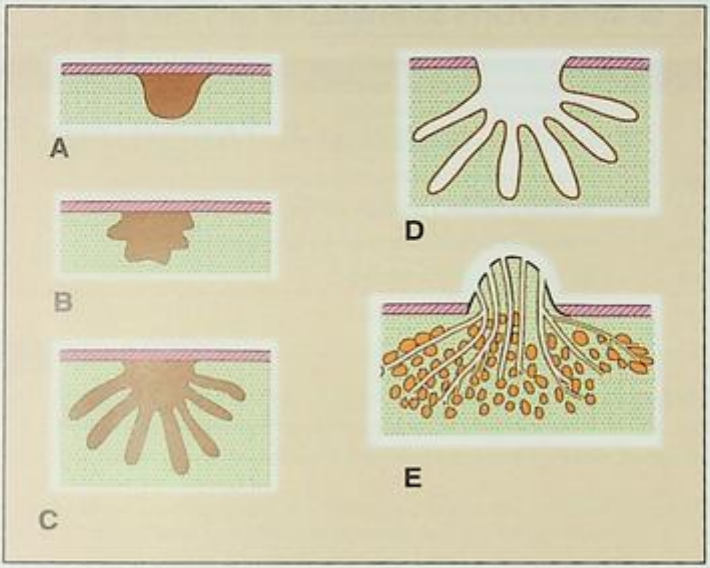

Fig. 8.7: Stages in the development of the mammary gland.

the original epithelial thickening. However, the growth of underlying mesoderm progressively pushes the wall of this pit outwards, until it becomes elevated above the surface and forms the ***nipple*** (Fig. 8.7E). The mammary gland remains rudimentary in the male. In females, the ducts and secretory elements undergo extensive development during puberty and pregnancy.

Clinical Correlation

Developmental Anomalies of the Mammary Glands

- ***Amastia***: The gland may be absent on one or both sides.
- ***Athelia***: The nipple may be absent.
- ***Polythelia*** and ***polymastia***: Supernumerary nipples may be present anywhere along the milk line. They may remain rudimentary (polythelia) or may form accessory mammary glands (polymastia).
- ***Accessory breasts*** may be found away from the milk line. They have been observed in the neck, cheeks, femoral triangle and vulva.
- ***Inverted or crater nipple***: The nipple may fail to form resulting in lactiferous ducts opening into a pit. This causes difficulty in suckling.
- The gland may be abnormally small (***micromastia***) or abnormally large (***macromastia***).
- ***Gynaecomastia***: The male breast may enlarge as in the normal female and may even secrete milk.

TIMETABLE OF SOME EVENTS MENTIONED IN THIS CHAPTER

Age	Developmental Events
7th week	Mammary line is established
8th week	Melanoblasts start appearing
1st to 3rd month	Cells of neural crest migrate to skin
2nd month	Surface ectoderm is single layered
2nd to 4th month	Surface ectoderm becomes multiple layered
3rd to 4th month	Dermal papillae are formed

Chapter 9

The Pharyngeal Arches

Highlights

- Pharyngeal arches are rod-like thickenings of mesoderm present in the wall of the foregut.
- At first there are six arches. The fifth arch disappears and only five remain.
- The ventral ends of the arches of the right and left sides meet in the middle line in the floor of the pharynx.
- In the interval between any two arches, the endoderm (lining the pharynx) is pushed outwards to form a series of pouches. These are called endodermal, or pharyngeal, pouches.
- Opposite each pouch the surface ectoderm dips inwards as an ectodermal cleft.
- Each pharyngeal arch contains a skeletal element (cartilage that may later form bone), striated muscle supplied by the nerve of the arch, and an arterial arch.
- The cartilage of the first arch (Meckel's cartilage) gives origin to the incus and malleus (of middle ear).
- The cartilage of the second arch forms the stapes, the styloid process and part of the hyoid bone.
- The cartilage of the third arch forms the greater part of the hyoid bone.
- The cartilages of the fourth and sixth arches give rise to the cartilages of the larynx.
- The nerves of the pharyngeal arches are as follows: First arch = mandibular; second arch = facial; third arch = glossopharyngeal; fourth arch = superior laryngeal; fifth arch = recurrent laryngeal. The muscles supplied by these nerves are derived from the mesoderm of the arch concerned.
- The external acoustic meatus develops from the first ectodermal cleft.
- The first endodermal pouch (and part of second) give off a diverticulum called the tubotympanic recess. The middle ear and the auditory tube develop from the tubotympanic recess.
- The palatine tonsil arises from the second pouch.
- The inferior parathyroid gland and the thymus are derived from the third pouch.
- The superior parathyroid gland is derived from the fourth pouch.
- The thyroid gland develops mainly from the thyroglossal duct. This duct is formed as a median diverticulum arising from the floor of the pharynx (at the foramen caecum).

INTRODUCTION

The formation of the foregut has been considered in Chapter 5. Reference to Fig. 5.14 will show that after the establishment of the head fold, the foregut is bounded ventrally by the pericardium, and dorsally by the developing brain. Cranially, it is at first separated from the stomatodaeum by the buccopharyngeal membrane. When this membrane breaks down, the foregut opens to the exterior through the stomatodaeum.

At this stage, the head is represented by the bulging caused by the developing brain (Fig. 5.14), while the pericardium may be considered as occupying the region of the future thorax. The two are separated by the stomatodaeum which is the future mouth. It is, thus, apparent that a neck is not yet present.

The neck is formed by the elongation of the region between the stomatodaeum and the pericardium. This is achieved, partly, by a 'descent' of the developing heart. However, this elongation is due mainly to the appearance of a series of mesodermal thickenings in the wall of the cranial-most part of the foregut. These are called the ***pharyngeal,*** or ***branchial, arches*** (see Fig. 9.1).

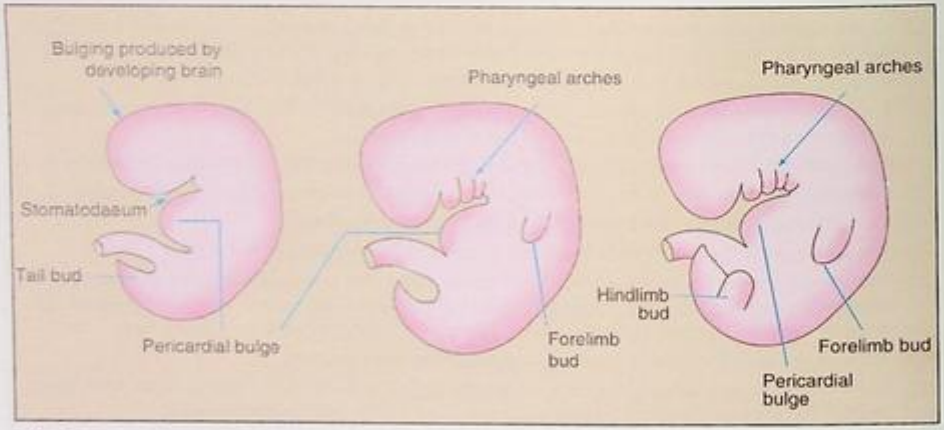

Fig. 9.1: Lateral views of embryos showing the formation of pharyngeal arches between stomatodaeum and the pericardial bulge.

A coronal section through the foregut (the part destined to form the pharynx), before the appearance of the pharyngeal arches, is shown in Fig. 9.2A. At this stage, the endodermal wall of the foregut is separated from the surface ectoderm by a layer of mesoderm. Soon, thereafter, the mesoderm comes to be arranged in the form of six bars that run dorso-ventrally in the side wall of the foregut. Each of these 'bars' grows ventrally in the floor of the developing pharynx and fuses with the corresponding 'bar' of the opposite side to form a ***pharyngeal or branchial arch***. In the interval between any two adjoining arches, the endoderm extends outwards in the form of a pouch (***endodermal or pharyngeal pouch***) to meet the ectoderm which dips into this interval as an ***ectodermal cleft*** (Fig. 9.2B).

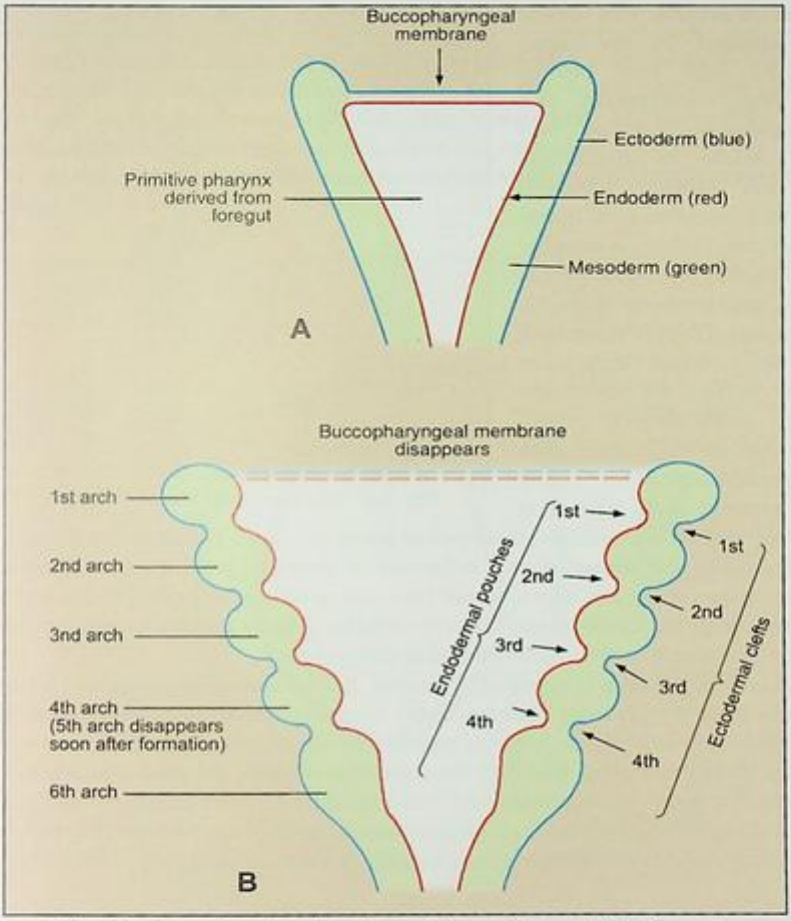

Fig. 9.2: Coronal sections through cranial part of foregut. (A) Before, and (B) After formation of pharyngeal arches.

The first arch is also called the ***mandibular arch***; and the second, the ***hyoid arch***. The third, fourth and sixth arches do not have special names. The fifth arch disappears soon after its formation, so that only five arches remain.

The following structures are formed in the mesoderm of each arch (Fig. 9.3):

- ***A skeletal element:*** This is cartilaginous to begin with. It may remain cartilaginous, may develop into bone, or may disappear.

- ***Striated muscle:*** This muscle is supplied by the nerve of the arch (see below). In later development, this musculature may, or may not, retain its attachment to the skeletal elements derived from the arch. It may subdivide to form a number of distinct muscles, which may migrate away from the pharyngeal region. When they do so, however, they carry their nerve with them and their embryological origin can thus be determined from their nerve supply.

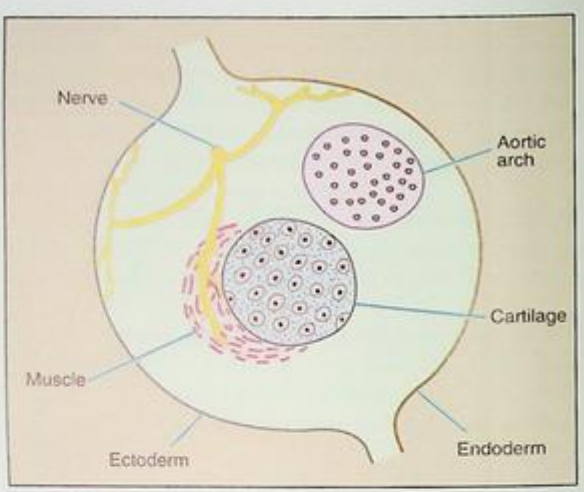

Fig. 9.3: Structures to be seen in a pharyngeal arch.

- ***An arterial arch:*** Ventral to the foregut, an artery called the ***ventral aorta*** develops. Dorsal to the foregut, another artery called the ***dorsal aorta***, is formed. A series of arterial arches (***aortic arches***) connect the ventral and dorsal aortae. One such arterial arch lies in each pharyngeal arch. In a subsequent development, the arrangement of these arteries is greatly modified. The fate of the arterial arches is considered in Chapter 15.

Each pharyngeal arch is supplied by a nerve. In addition to supplying the skeletal muscle of the arch, it supplies sensory branches to the overlying ectoderm, and endoderm (Fig. 9.3).

In some lower animals, each arch is supplied by two nerves (Fig. 9.4). The nerve of the arch itself runs along the cranial border of the arch. This is called the ***post-trematic nerve*** of the arch (trema = trench). Each arch also receives a branch from the nerve of the succeeding arch. This runs along the caudal border of the arch, and is called the ***pre-trematic nerve*** of the arch. In the human embryo, however, a double innervation is to be seen only in the first pharyngeal arch.

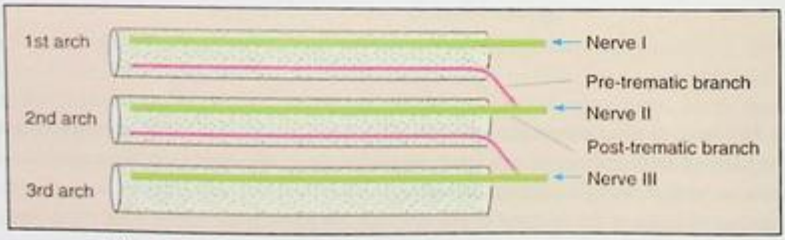

Fig. 9.4: Arrangement of nerves supplying the pharyngeal arches in some lower animals.

DERIVATIVES OF THE SKELETAL ELEMENTS

- The cartilage of the first arch is called ***Meckel's cartilage*** (Fig. 9.5). The ***incus*** and ***malleus*** (of the middle ear) are derived from its dorsal end. The ventral part of the cartilage is surrounded by the developing mandible, and is absorbed. The part of the cartilage extending from the region of the middle ear to the mandible disappears, but its sheath (perichondrium) forms the ***anterior ligament of the malleus*** and the ***sphenomandibular ligament***.

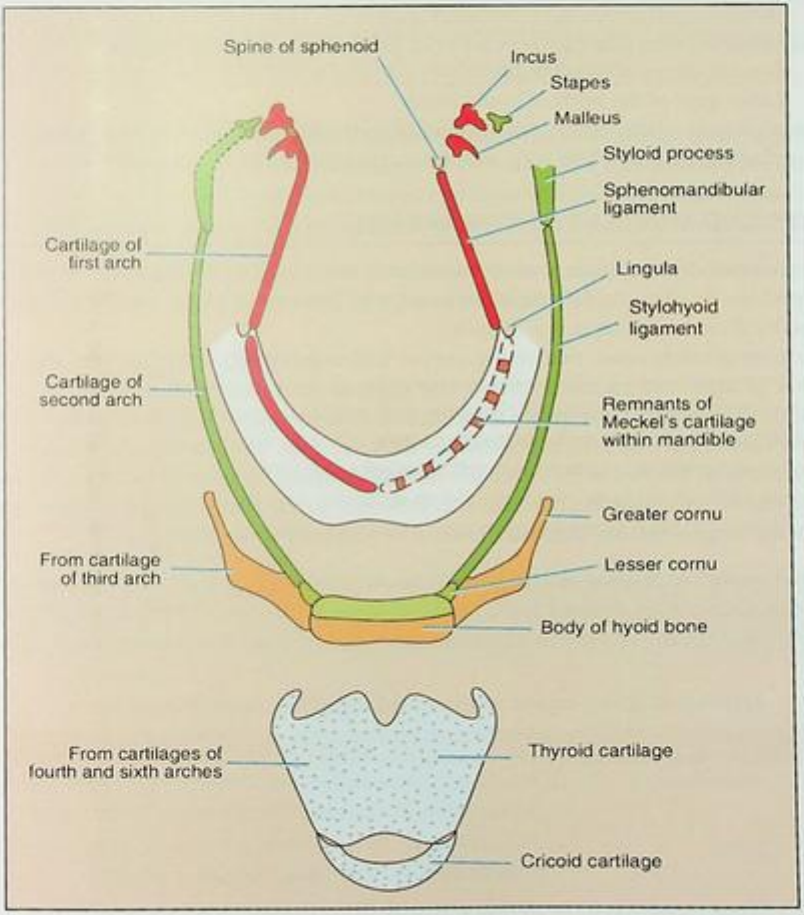

Fig. 9.5: Fate of the cartilages of the pharyngeal arches. The left half of the figure shows an earlier stage of development. The derivatives of the first arch are shown in red, second arch in green, third arch in orange, and fourth fifth and sixth arches in blue.

Mesenchyme of the first arch is also responsible for formation of bones of the face including the maxilla, the mandible, the zygomatic bone, the palatine bone and part of the temporal bone.

- The cartilage of the second arch forms the following:
  - Stapes.
  - Styloid process.
  - Stylohyoid ligament (from sheath).
  - Smaller (lesser) cornu of hyoid bone.
  - Superior part of body of hyoid bone.

  (Note that all structures listed start with 'S').
- The following structures are formed from the cartilage of the third arch:
  - Greater cornu of hyoid bone.
  - Lower part of the body of hyoid bone.
- The cartilages of the larynx are derived from the fourth and sixth arches with a possible contribution from the fifth arch, but their exact derivation is controversial.

NERVES AND MUSCLES OF THE ARCHES

All the muscles derived from a pharyngeal arch are supplied by the nerve of the arch and can, therefore, be identified by their nerve supply. The nerves of the arches and the muscles supplied by them are given in the Table 9.1.

We have already seen that these nerves not only supply muscles, but also innervate the parts of skin and mucous membrane derived from the arches. Some of the nerves (e.g. glossopharyngeal) have only a small motor component and are predominantly sensory. As stated above, the first arch has a double nerve supply. The mandibular nerve is the post-trematic nerve of the first arch, while the chorda tympani (branch of facial nerve) is the pre-trematic nerve. This double innervation is reflected in the nerve supply of the anterior two-thirds of the tongue that are derived from the ventral part of the first arch.

Some recent investigations suggest that mesenchyme giving rise to muscles of the pharyngeal arches is derived from paraxial mesoderm cranial to the occipital somites (i.e. from the region of the preoccipital somites); and that its organisation is influenced

Table 9.1: Nerves of pharyngeal arches and muscles supplied by them

Arch	Nerve of Arch	Muscles of Arch
First	Mandibular	Medial and lateral pterygoids, Masseter, Temporalis, Mylohyoid, Anterior belly of digastric, Tensor tympani, Tensor palati.
Second	Facial	Facial Muscles, Occipitofrontalis, Platysma, Stylohyoid, Posterior belly of digastric, Stapedius, Auricular muscles.
Third	Glosso-pharyngeal	Stylopharyngeus
Fourth	Superior laryngeal	Muscles of larynx and pharynx
Fifth	Recurrent laryngeal	

Table 9.2: Muscles derived from somitomeres and somites

Somitomere/Somites	Muscles Derived
Somitomere1 and 2	Muscles supplied by oculomotor nerve
Somitomere 3	Superior oblique muscle supplied by trochlear nerve
Somitomere 4	Muscles of first pharyngeal arch supplied by mandibular nerve
Somitomere 5	Lateral rectus muscle supplied by abducent nerve
Somitomere 6	Muscles of the second pharyngeal arch supplied by the facial nerve
Somitomere 7	Stylopharyngeus (from 3rd arch) supplied by glossopharyngeal nerve
Occipital somites1 and 2	Laryngeal muscles (from 4th to 6th arches) supplied by the vagus nerve
Occipital somites 3 to 5	Muscles of tongue supplied by hypoglossal nerve

by neural crest cells. Although paraxial mesoderm here does not form typical somites, it shows partial segmentation into seven masses of mesenchyme called ***somitomeres***. The structures derived from the seven somitomeres and from five occipital somites that follow them, have been described as given in Table 9.2.

If we accept this view of the origin of branchial musculature, there would be no significant reason to distinguish between it and muscle derived from somites.

FATE OF ECTODERMAL CLEFTS

After the formation of the pharyngeal arches, the region of the neck is marked on the outside by a series of grooves, or ectodermal clefts. The dorsal part of the first cleft (between the first and second arches) develops into the epithelial lining of the ***external acoustic meatus***. The ***pinna*** (or auricle) is formed from a series of swellings or hillocks, that arise on the first and second arches, where they adjoin the first cleft (for the development of pinna refer to Chapter 19). The ventral part of this cleft is obliterated.

The second arch grows much faster than the succeeding arches and comes to overhang them (Fig. 9.6). The space between the overhanging second arch and the third, fourth and sixth arches is called the ***cervical sinus***. Subsequently, the lower overhanging border of the second arch fuses with tissues

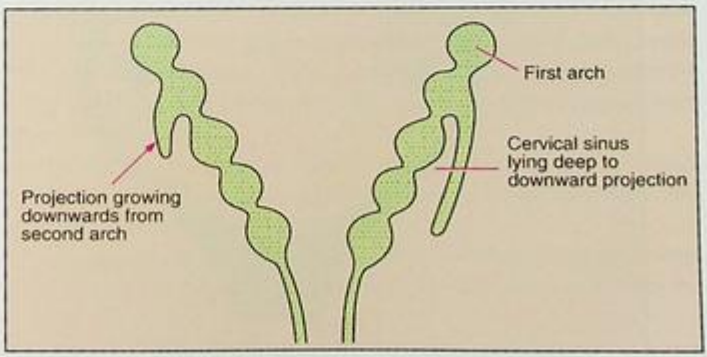

Fig. 9.6: Cervical sinus. The left half of the figure shows an earlier stage than the right half.

caudal to the arches. The side of the neck (which was thus far marked by the ectodermal clefts) now becomes smooth. The cavity of the cervical sinus (which is lined by ectoderm) normally gets obliterated. Part of it may persist and give rise to swellings that lie in the neck, along the anterior border of the sternocleidomastoid. These are called ***branchial cysts***, and are most commonly located just below the angle of the mandible. If such a cyst opens onto the surface, it becomes a ***branchial sinus***. Rarely, a cervical sinus may open into the lumen of the pharynx in the region of the tonsil.

FATE OF ENDODERMAL POUCHES

The endodermal pouches take part in the formation of several important organs (Fig. 9.7). These are listed below.

First Pouch

- Its ventral part is obliterated by formation of the ***tongue***.
- Its dorsal part receives a contribution from the dorsal part of the second pouch, and these two together form a diverticulum that grows towards the region of the developing ear.

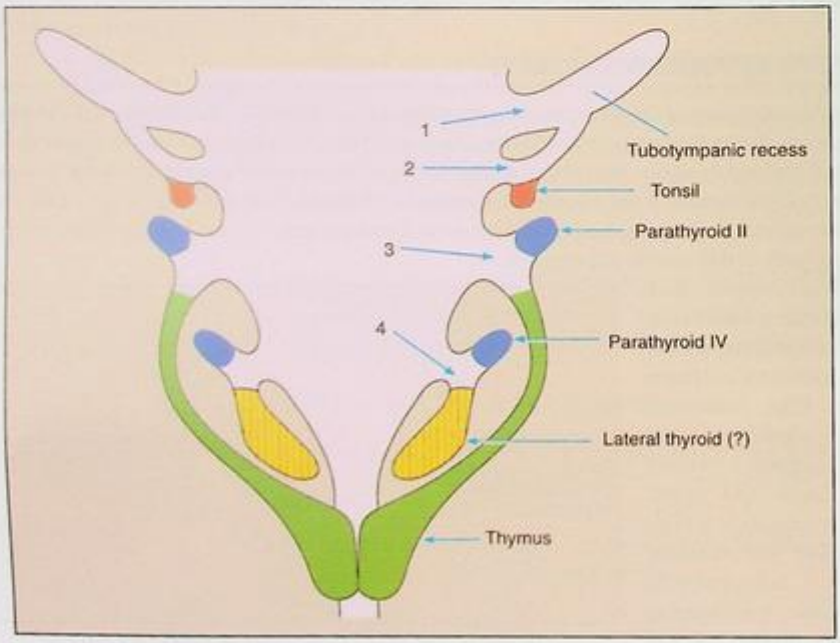

Fig. 9.7: Scheme to show the fate of the pharyngeal pouches (numbered 1 to 4).

This diverticulum is called the ***tubo-tympanic recess***. The proximal part of this recess gives rise to the ***auditory (pharyngotympanic) tube***, and the distal part to the ***middle ear cavity***, including the ***tympanic antrum***.

Second Pouch

- The epithelium of the ventral part of this pouch contributes to the formation of the ***tonsil***.
- The dorsal part takes part in the formation of the ***tubotympanic recess***.

Third Pouch

This gives rise to the ***inferior parathyroid glands***, and the ***thymus***.

Fourth Pouch

This gives origin to the ***superior parathyroid glands***, and may contribute to the ***thyroid gland***.

Fifth or Ultimobranchial Pouch

A fifth pouch is seen for a brief period during development. In some species it gives rise to the ***ultimobranchial body***. Its fate in man is controversial. It is generally believed to be incorporated into the fourth pouch, the two together forming the ***caudal pharyngeal complex***. The superior parathyroid glands arise from this complex. The complex probably also gives origin to the parafollicular cells of the thyroid gland.

DEVELOPMENT OF THE THYMUS

The thymus develops from the endoderm of the third pharyngeal pouch (which also gives rise to the inferior parathyroid glands).

Early in development, this pouch is cut off, both from the pharyngeal wall and from the surface ectoderm. After separation from the inferior parathyroid rudiment, each thymic rudiment has a thinner cranial part and a broader caudal part. The thinner portion forms the cervical part of the thymus. The broader parts, of the two sides, enter the thorax and become united to each other by connective tissue.

The endodermal cells of the thymus are invaded by vascular mesoderm which contains numerous lymphoblasts. This invading mesenchyme partially breaks up the thymic tissue into isolated masses, and thus gives the organ its lobulated appearance.

Fragmentation of the cervical part of the thymus may give rise to accessory thymic tissue. Such tissue, present in relation to the superior parathyroid glands, is believed to arise from the fourth pouch.

The thymus is relatively large at birth. It continues to increase in weight till puberty. Thereafter, it gradually undergoes atrophy.

DEVELOPMENT OF PARATHYROID GLANDS

Parathyroid glands are derived as follows:

- The ***inferior parathyroid glands*** develop from endoderm of the third pharyngeal pouch (parathyroid III).
- The ***superior parathyroid glands*** develop from endoderm of the fourth pharyngeal pouch (parathyroid IV).

As the third pouch also gives origin to the thymus, this organ is closely related to parathyroid III. When the thymus descends towards the thorax, parathyroid III is carried caudally along with it for some distance. Meanwhile, parathyroid IV is prevented from descending caudally, because of the close relationship of the fourth pouch to the developing thyroid gland. As a result, parathyroid III becomes caudal to parathyroid IV. Hence, the parathyroid glands derived from the fourth pouch become the superior parathyroid glands and those derived from the third pouch become the inferior parathyroid glands (Fig. 9.8).

In keeping with their developmental history, the superior parathyroid glands are relatively constant in position, but the inferior parathyroid glands may descend into the lower part of the neck or even into the anterior mediastinum. Alternatively, they may remain at their site of origin and are then seen near the bifurcation of the common carotid artery.

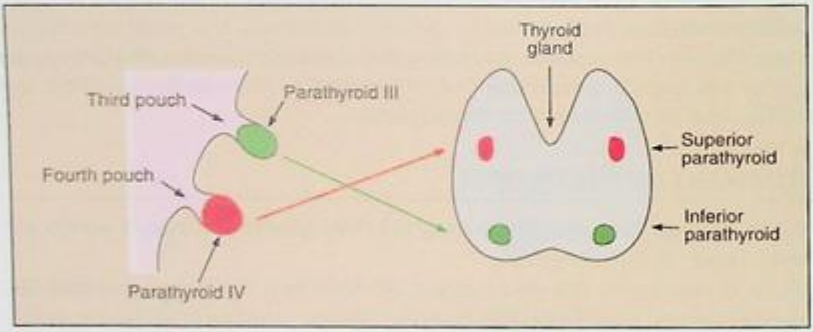

Fig. 9.8: Derivation of superior and inferior parathyroid glands. Note that the relative position of parathyroid III and IV is reversed during development.

DEVELOPMENT OF THE THYROID GLAND

The thyroid gland develops mainly from the thyroglossal duct. Parafollicular cells are derived from the caudal pharyngeal complex (derived from the fourth and fifth pharyngeal pouches).

After the formation of the pharyngeal arches, the floor of the pharynx has the appearance shown in Fig. 9.9. The medial ends of the two mandibular arches are separated by a midline swelling called the ***tuberculum impar***. Immediately behind the tuberculum, the epithelium of the floor of the pharynx shows a thickening in the middle line (Fig. 9.10A). This region is soon depressed below the surface to form a diverticulum called the ***thyroglossal duct*** (Fig. 9.10B).

The site of origin of the diverticulum is now seen as a depression called the ***foramen caecum***. The diverticulum grows down in the midline into the neck. Its tip soon bifurcates (Fig. 9.10C). Proliferation of the cells of this bifid end gives rise to the two lobes of the thyroid gland.

The developing thyroid comes into intimate relationship with the caudal pharyngeal complex and fuses with it (Fig. 9.10D). Cells arising from this complex are believed to give origin to the parafollicular cells of the thyroid which may represent the ultimobranchial body of lower animals.

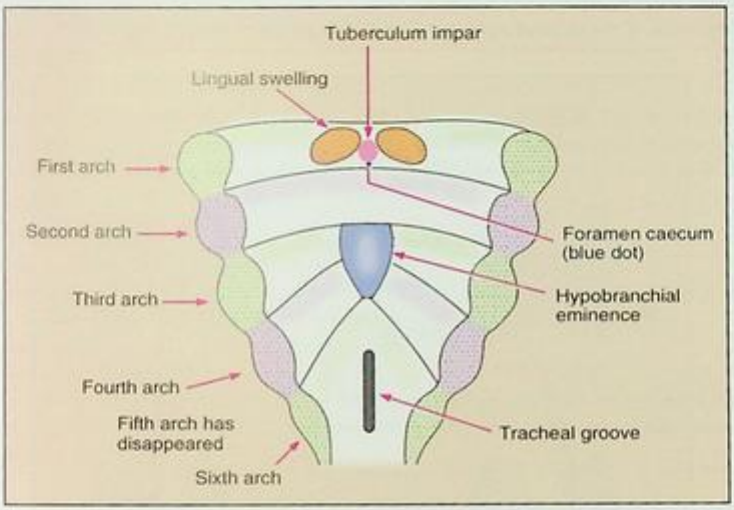

Fig. 9.9: Floor of the pharynx showing the foramen caecum from where the thyroglossal duct arises.

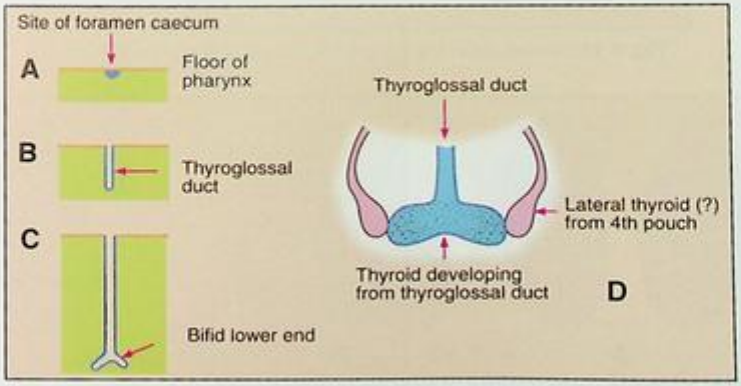

Fig. 9.10: Stages in the development of the thyroid gland.

Clinical Correlation

Anomalies of the Thyroid Gland

A. Anomalies of Shape

- The ***pyramidal lobe*** is present so often that it is regarded as a normal structure. It may arise from the isthmus (Fig. 9.11A) or from one of the lobes (Fig. 9.11B, C). It may have no connection with the rest of the thyroid, and may be divided into two or more parts (Fig. 9.11D). In extent, it may vary from a short stump (Fig. 9.11A) to a process reaching the hyoid bone (Fig. 9.11C).
- The isthmus may be, absent (Fig. 9.12A).
- One of the lobes of the gland may be very small (Fig. 9.12B), or absent (Fig. 9.12C).

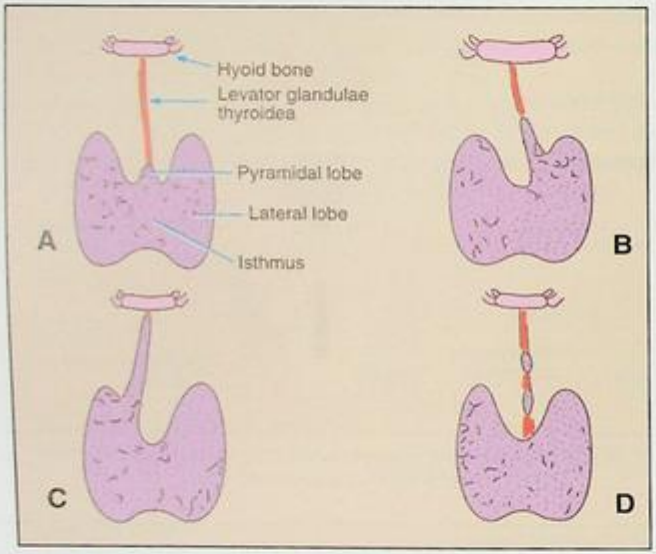

Fig. 9.11: Variations in the pyramidal process of the thyroid gland.

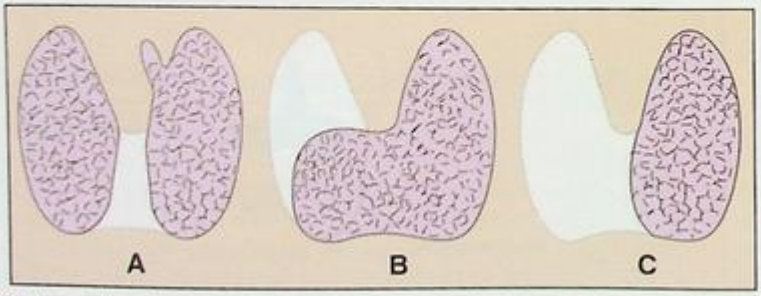

Fig. 9.12: Anomalies of the thyroid gland. The parts of the gland shown in dotted outline are missing.

Clinical Correlation *contd...*

B. Anomalies of Position (Fig. 9.13)

- ***Lingual thyroid:*** The thyroid may lie under the mucosa of the dorsum of the tongue and may form a swelling that may cause difficulty in swallowing.
- ***Intra-lingual thyroid:*** The thyroid may be embedded in the muscular substance of the tongue.
- ***Suprahyoid thyroid:*** The gland may lie in the midline of the neck, above the hyoid bone.
- ***Infrahyoid thyroid:*** The gland may lie below the hyoid bone, but above its normal position.
- ***Intrathoracic thyroid:*** The entire gland, or part of it, may lie in the thorax.

Note that when thyroid tissue is present in the anomalous positions described above, an additional thyroid may or may not be present at the normal site.

C. Ectopic Thyroid Tissue

Small masses of thyroid tissue may be present at abnormal sites.

Thyroid tissue has been observed in the larynx, trachea, oesophagus, pons, pleura, pericardium and ovaries. Masses of ectopic thyroid tissue have been described in relation to the deep cervical lymph nodes (*lateral aberrant thyroids*) but these are now believed to represent metastases in the lymph nodes from a carcinoma of the thyroid gland.

D. Remnants of the Thyroglossal Duct

These remnants may persist and lead to the formation of:

- ***Thyroglossal cysts***, that may occur anywhere along the course of the duct. They may acquire secondary openings on the surface of the neck to form fistulae.
- ***Thyroglossal fistula*** opening at the foramen caecum.
- ***Carcinoma*** of the thyroglossal duct.

In the surgical removal of thyroglossal cysts and fistulae, it is important to remove all remnants of the thyroglossal duct. In this connection, it has to be remembered that the duct is intimately related to the hyoid bone (Fig. 9.13).

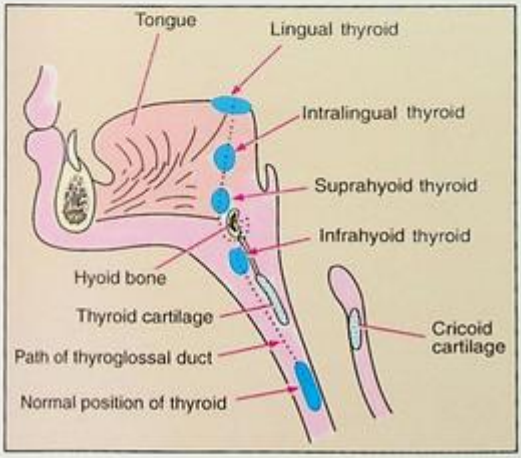

Fig. 9.13: Path of thyroglossal duct. Note that thyroid tissue may come to lie anywhere along the course of this duct.

TIMETABLE OF SOME EVENTS MENTIONED IN THIS CHAPTER

Age	Developmental Events
4th week (22nd day)	Appearance of 1st and 2nd arches
5th week (29th day)	Four arches are seen. Thyroid, parathyroid and thymus start forming
7th week	Thyroid gland reaches its definitive position.

Chapter 10

The Skeleton

HIGHLIGHTS

- The vertebral column is derived from the sclerotomes of somites. Each sclerotome divides into three parts: cranial, middle and caudal.
- A vertebra is formed by fusion of the caudal part of one sclerotome and the cranial part of the next sclerotome. It is, therefore, intersegmental in position.
- The middle part of the sclerotome forms an intervertebral disc, which is therefore segmental in position.
- The sternum is formed by fusion of right and left sternal bars.
- The skull develops from mesenchyme around the developing brain. Some skull bones are formed in membrane (e.g. parietal); some partly in membrane and partly in cartilage (e.g. sphenoid); and a few entirely in cartilage (e.g. ethmoid).
- The mandible is formed in membrane from the mesenchyme of the mandibular process.
- Limbs are first seen as outgrowths (limb buds) from the side wall of the embryo. Each bud grows and gets subdivided to form parts of the limb.
- Limb bones develop from mesenchyme of the limb buds. Joints are formed in intervals between bone ends.

The process of bone formation has been considered in Chapter 7. We have seen that all bone is of mesodermal origin, and that bones can be classified as cartilage bones or membrane bones, on the basis of their mode of ossification.

- Most bones of the axial skeleton are derived from sclerotomes of somites (paraxial mesoderm).
- Bones of the shoulder and hip girdle, and of the limbs, arise from lateral plate mesoderm.
- Some bones of the face and skull are derivatives of the neural crest.

THE VERTEBRAL COLUMN

The vertebral column is formed from the sclerotomes of the somites.

The cells of each sclerotome get converted into loose mesenchyme. This mesenchyme migrates medially and surrounds the notochord (Fig. 10.1). The mesenchyme then extends backwards on either side of the neural tube and surrounds it (Fig. 10.2). Extensions of this mesenchyme also take place laterally in the position to be subsequently occupied by the transverse processes, and ventrally in the body wall, in the position to be occupied by the ribs.

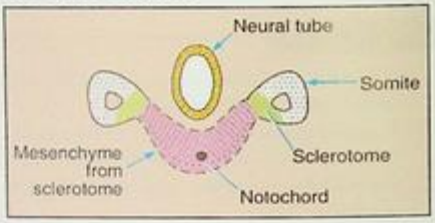

Fig. 10.1: Formation of mesenchymal basis of the body of a vertebra from a sclerotome.

For some time the mesenchyme derived from each somite can be seen as a distinct segment (Fig. 10.3A). The mesenchymal cells of each segment are at first uniformly distributed. However, the cells soon become condensed in a region that runs transversely across the middle of the segment. This condensed region is called the ***perichordal disc***. Above and below it there are less condensed parts (Fig. 10.3B). The mesenchymal basis of the ***body*** (or ***centrum***) of each vertebra is formed by fusion of the adjoining, less condensed parts of two segments (Fig. 10.3B). The perichordal disc becomes the ***intervertebral disc***.

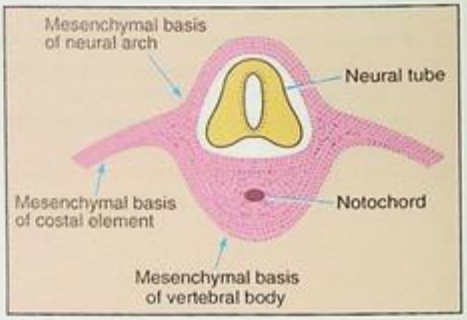

Fig. 10.2: Formation of mesenchymal basis of the neural arch and of the costal element.

The ***neural arch***, the ***transverse processes*** and the ***costal elements*** are formed in the same way as the body. The ***interspinous and intertransverse ligaments*** are formed in the same manner as the intervertebral disc.

The notochord disappears in the region of the vertebral bodies. In the region of the intervertebral discs, the notochord becomes expanded and forms the ***nucleus pulposus*** (Fig. 10.3C).

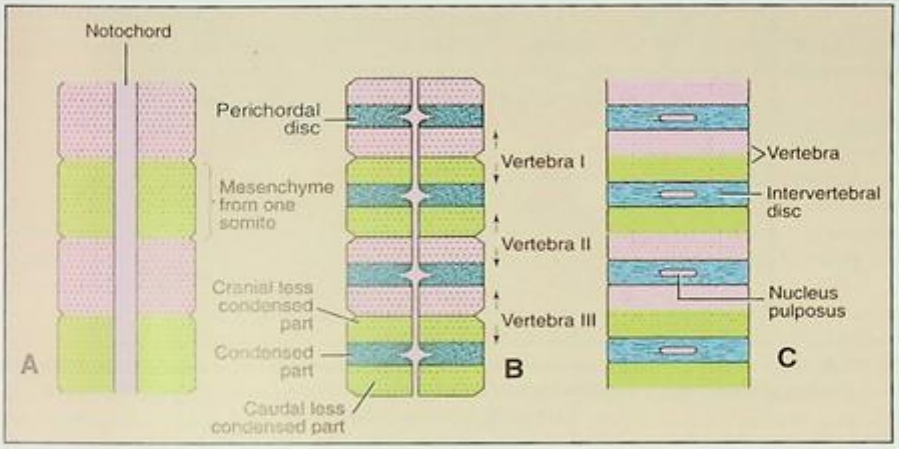

Fig. 10.3: (A) Mesenchyme derived from somites is seen in the form of segments. (B) Each segment has a central condensed part, and cranial and caudal less condensed parts. (C) A vertebra is formed by fusion of adjoining uncondensed parts of two somites. Hence it is an intersegmental structure. Each intervertebral disc is derived from the condensed part of one somite. Hence it is segmental in position.

From the above account we may note that:

- The vertebra is an ***intersegmental*** structure made up from portions of two somites. The intervertebral disc is formed at the centre of the somite.
- The transverse processes and ribs are also intersegmental. They separate the muscles derived from two adjoining myotomes.
- Spinal nerves are segmental structures. They, therefore, emerge from between the two adjacent vertebrae and lie between two adjacent ribs.
- The blood vessels supplying structures derived from the myotome (e.g. intercostal vessels) are intersegmental like the vertebrae. Therefore, the intercostal and lumbar arteries lie opposite the vertebral bodies.

The mesenchymal basis of the vertebra is converted into cartilage by the appearance of several centres of chondrification. Three primary centres of ossification appear in the cartilaginous model for each vertebra; one for each neural arch and one for the greater part of the body (centrum). At birth the centrum and the two halves of the neural arch are joined by cartilage (Fig. 10.4A). These are termed ***neurocentral joints***. Note that the posterolateral parts of the vertebral body are formed from the neural arch (Fig. 10.4B). After the centrum and neural arch have fused, the junction between the two is indicated by the ***neurocentral line***.

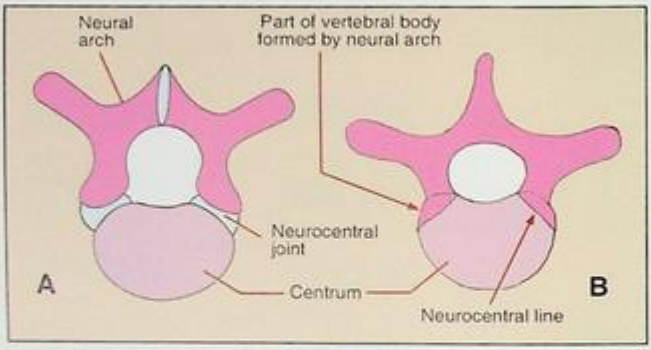

Fig. 10.4: (A) A vertebra at birth consisting of three separate pieces of bone: a centrum and two neural arches. (B) Diagram to show the neurocentral line which is the line along which body and neural arch have fused.

Fig. 10.5: Spina bifida produced by non-fusion of the two halves of the neural arch.

Clinical Correlation

Congenital Anomalies of Vertebral Column

- One or more vertebrae may be absent, the caudal vertebrae being more commonly affected. Absence of the coccyx alone, or of the sacrum and coccyx, may be seen.
- Additional vertebrae may be present. The sacrum may show six segments.
- Part of a vertebra may be missing. Various anomalies result, depending on the part that is absent.
  - The two halves of the neural arch may fail to fuse in the midline. This condition is called ***spina bifida*** (Fig. 10.5). The gap between the neural arches may not be obvious (***spina bifida occulta***), or may be large enough for meninges and neural elements to bulge out of it (see meningocoele and meningomyelocoele).

    Spina bifida in a fetus can be recognized by ultrasound examination. Examination of amniotic fluid shows increased levels of alpha-fetoproteins (AFP) in a case with spina bifida.

Clinical Correlation ***contd...***

- The vertebral body may ossify from two primary centres which soon fuse. One of these parts may fail to develop, resulting in only half of the body being present. This is called ***hemivertebra***. It is usually associated with absence of the corresponding rib.
- The two halves of the vertebral body may be formed normally but may fail to fuse. The vertebral body then consists of two hemivertebrae. Sometimes the gap between the two halves is large enough for meninges and nerves to bulge forward between them (***anterior spina bifida***).

- Two or more vertebrae that are normally separate may be fused to each other. Such fusion may occur in the cervical region (***Klippel-Feil syndrome***). The atlas vertebra may be fused to the occipital bone (***occipitalization of atlas***). The fifth lumbar vertebra may be partially or completely fused to the sacrum (***sacralisation of 5th lumbar vertebra***).
- Parts of the vertebral column that are normally fused to each other may be separate. The first sacral vertebra may be separate from the rest of the sacrum (***lumbarisation of the first sacral vertebra***). The odontoid process may be separate from the rest of the axis vertebra.
- The articular facets may be abnormal in orientation, or may be deficient. When there is deficiency of both the inferior articular processes of the fifth lubar vertebra, the body of the vertebra may slip forwards over the sacrum. This is called ***spondylolisthesis***.
- The vertebral canal may be divided into two lateral halves by a projecting shelf of bone, which splits the spinal cord longitudinally into two halves (***diastematomylia***).
- Ossification of the vertebral bodies may be defective thus reducing the total length of the spine. This can lead to the formation of dwarfs who have a short trunk but have limbs of normal length (***chondro-osteo-dystrophy***),
- A peculiar tumour arising from cells of the primitive knot may be seen attached to the lower end of the spine. Various tissues may be seen in it. Such a growth is called a ***sacrococcygeal teratoma***.

Anomalies of the vertebrae are of practical importance in that:

- They may cause deformities of the spine. The spine may be bent on itself (***congenital scoliosis***). Deformities of cervical vertebrae may lead to tilting of the head to one side and its rotation to the opposite side (***congenital torticolis***). This deformity may be secondary to a contracture of the sternocleidomastoid muscle.
- The spinal nerves, or even the spinal cord, may be implicated. They may be subjected to abnormal pressure leading to paralysis.
- They are frequently the cause of backache.

THE RIBS

The ribs are derived from ventral extensions of the sclerotomic mesenchyme that forms the vertebral arches. These extensions are present not only in the thoracic region but also in the cervical, lumbar and sacral regions. They lie ventral to the mesenchymal basis of the transverse processes with which they are continuous.

In the thoracic region, the entire extension (called the ***primitive costal arch***) undergoes chondrification, and subsequent ossification, to form the ribs. However, some mesenchyme between it and the developing transverse process does not undergo chondrification: it becomes loose and forms the ***costotransverse joint***. In the cervical, lumbar and sacral regions, chondrification and ossification of the costal arch is confined to the region in immediate relationship to the transverse process. The bone formed from the arch is fused to the transverse

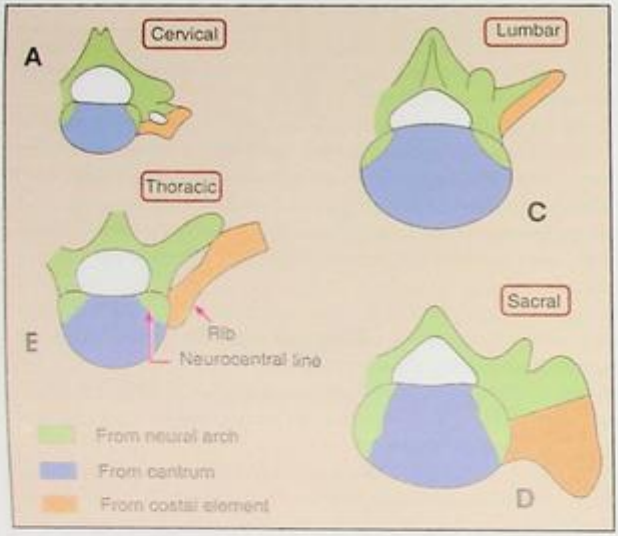

Fig. 10.6: Relative contribution to vertebrae by the centrum, the neural arch and the costal element in different regions. Note that a small part of the body of the vertebra is derived from the neural arch.

process and is referred to as the ***costal element*** of the process. The contributions made by the costal element to the cervical, lumbar and sacral vertebrae are shown in Fig. 10.6.

THE STERNUM

The sternum is formed by fusion of two ***sternal bars***, or ***plates***, that develop on either side of the midline. Mesenchymal condensations forming at these sites become cartilaginous in the seventh week of intrauterine life. Laterally, the sternal bars are continuous with ribs. The fusion of the two sternal bars first occurs at their cranial end (manubrium) and proceeds caudally (Figs.10.7B, C).

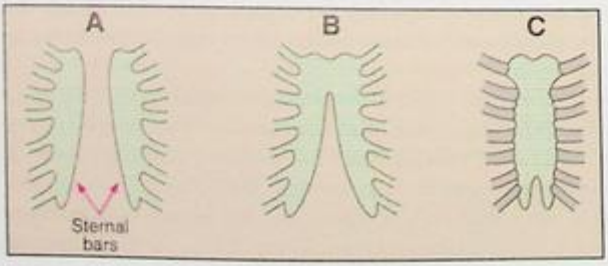

Fig. 10.7: Development of the sternum. (A) Sternal bars formed on each side of the middle line. (B) The sternal bars begin to fuse with each other at the cranial end. (C) Fusion progresses caudally.

The manubrium and the body of the sternum are ossified, separately. The xiphoid process ossifies only late in life.

Clinical Correlation

Anomalies of the Sternum and Ribs

- Some ribs that are normally present may be missing. Unilateral absence of a rib is often associated with hemivertebra.
- Accessory ribs may be present. Such a rib may be attached to the seventh cervical vertebra (***cervical rib***), or to the first lumbar vertebra (***lumbar rib***).
- When the fusion of the two sternal bars is faulty, the body of the sternum shows a partial or even a complete midline cleft. Minor degrees of non-fusion may result in a bifid xiphoid process or in midline foramina. Transverse clefts may also occur.
- In the condition called ***funnel chest***, the lower part of the sternum and the attached ribs are drawn inwards into the thorax. The primary defect is that the central tendon of the diaphragm is abnormally short.
- The upper part of the sternum (and related costal cartilages) may project forwards (***pigeon breast***).

THE SKULL

The skull is developed from mesenchyme surrounding the developing brain. This mesenchyme comes into close relationship with the following structures that also contribute to the development of the skull:

- Cranial to the first cervical somite there are four ***occipital somites***. The mesenchyme arising from the sclerotomes of these somites helps to form part of the base of the skull in the region of the occipital bone.
- The developing internal ear (otic vesicle), and the region of the developing nose, are surrounded by mesenchymal condensations called the ***otic, and nasal, capsules*** respectively. These capsules also take part in forming the mesenchymal basis of the skull.
- The first branchial arch is closely related to the developing skull. It soon shows two subdivisions, called the ***mandibular and maxillary processes***. Some bones of the skull are formed in the mesoderm of these processes.

Some bones of the skull are formed in membrane, some in cartilage, and some partly in membrane and partly in cartilage, as listed below.

Bones that are Completely Formed in Membrane

- The ***frontal and parietal bones*** are formed in relation to mesenchyme covering the developing brain.
- The ***maxilla*** (excluding the premaxilla), ***zygomatic*** and ***palatine*** bones, and part of the ***temporal*** bones, are formed by intramembranous ossification of the mesenchyme of the maxillary process.
- The ***nasal, lacrimal*** and ***vomer*** bones are ossified in the membrane covering the nasal capsule.

Bones that are Completely Formed in Cartilage

The ***ethmoid*** bone and the ***inferior nasal concha*** are derived from the cartilage of the nasal capsule. The septal and alar cartilages of the nose represent parts of the capsule that do not undergo ossification.

Bones that are Partly Formed in Cartilage and Partly in Membrane

- ***Occipital:*** The interparietal part (lying above the superior nuchal lines) is formed in membrane; the rest of the bone is formed by endochondral ossification.
- ***Sphenoid:*** The lateral part of the greater wing, and the pterygoid laminae, are formed in membrane; the rest is cartilage bone.
- ***Temporal:*** The squamous and tympanic parts are formed in membrane. The petrous and mastoid parts are formed by ossification of the cartilage of the otic capsule. The styloid process is derived from the cartilage of the second branchial arch.
- ***Mandible:*** Most of the bone is formed in membrane in the mesenchyme of the mandibular process. The ventral part of Meckel's cartilage gets embedded in the bone. The condylar and coronoid processes are ossified from secondary cartilages that appear in these situations. The development of the hyoid bone has been described in Chapter 9.

Clinical Correlation

Anomalies of the Skull

- The greater part of the vault of the skull is missing in cases of ***anencephaly***.
- The skull may show various types of deformity. In one syndrome, deformities of the skull are associated with absence of the clavicle (***cleidocranial dysostosis***). Premature union of the sagittal suture gives rise to a boat-shaped skull (***scaphocephaly***). Early union of the coronal suture results in a pointed skull (***acrocephaly***). Asymmetrical union of sutures results in a twisted skull (***plagiocephaly***). When the brain fails to grow the skull remains small (***microcephaly***).
- The bones of the vault of the skull may be widely separated by expansion of the cranial cavity in ***congenital hydrocephalus***.
- In a rare congenital condition called ***Hand-Schuller-Christian*** disease, large defects are seen in the skull bones. The primary defect is in the reticuloendothelial system; the changes in the bones are secondary.
- The occipital bone may be fused to the atlas vertebra.
- Several genetic disorders of cranio-facial development have been described. One syndrome caused by under development of the first branchial arch is ***mandibulo-facial dysostosis.***

FORMATION OF THE LIMBS

The bones of the limbs, including the bones of the shoulder and pelvic girdles, are formed from mesenchyme of the limb buds. With the exception of the clavicle (which is a membrane bone), they are all formed by endochondral ossification.

The ***limb buds*** are, paddle-shaped, outgrowths that arise from the side-wall of the embryo at the beginning of the second month of intrauterine life (Fig. 10.8). Each bud is a mass of mesenchyme covered by ectoderm.

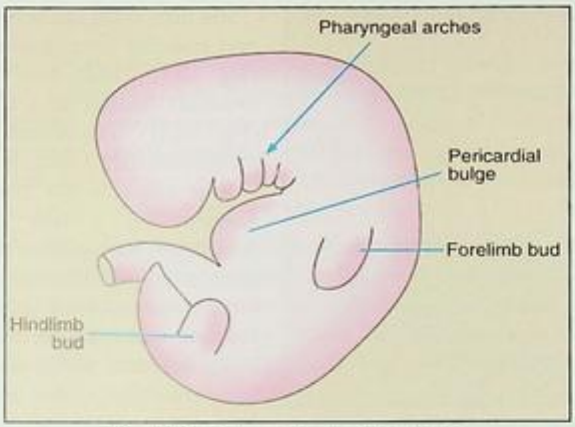

Fig. 10.8: Embryo showing limb buds.

The mesenchyme of limb buds is derived from (the parietal layer of) the lateral plate mesoderm. This mesenchyme gives rise to bones, connective tissue and some blood vessels. The muscles of the limbs are derived from myotomes of somites which migrate in to the limbs.

At the tip of each limb bud, the ectoderm is thickened to form the ***apical ectodermal ridge (AER)***. This ridge has an inducing effect on underlying mesenchyme causing it to remain undifferentiated and to proliferate. Areas away from the apical ridge undergo differentiation into cartilage, muscle, etc.

Sometimes two *AER* are formed on a limb bud. This results in formation of a supernumerary limb.

The ***forelimb buds*** appear a little earlier than the ***hindlimb buds***. As each forelimb bud grows, it becomes subdivided by constrictions into arm, forearm and hand. The hand itself soon shows outlines of the digits. The interdigital areas show cell death because of which the digits separate from each other (Fig. 10.9). Similar changes occur in the hindlimb.

While the limb buds are growing, the mesenchymal cells in the buds form cartilaginous models, which subsequently ossify to form the bones of the limb.

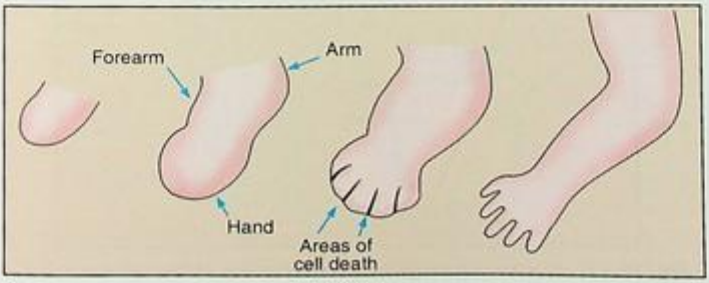

Fig. 10.9: Stages in differentiation of the forelimb bud.

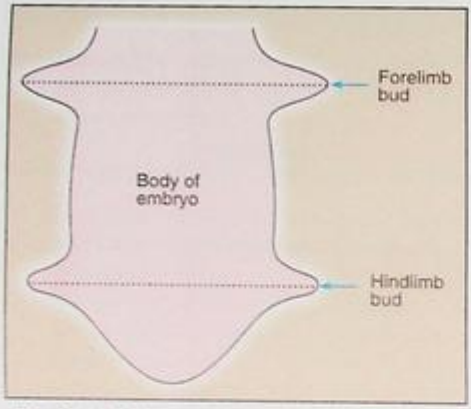

Fig. 10.10: Scheme to show that the longitudinal axis of the limb buds is transverse to the long axis of the embryonic body.

The limb buds are at first directed forward and laterally from the body of the embryo (Fig. 10.10). Each bud has a ***preaxial (or cranial) border*** and a ***postaxial border*** (Fig. 10.11). The thumb and great toe are formed on the preaxial border.

The radius is the preaxial bone of the forearm. In a later development, the forelimb is adducted to the side of the body (Fig. 10.11). The original ventral surface forms the anterior surface of the arm, forearm and hand. In the case of the lower limb, the tibia is the preaxial bone of the leg. Adduction of this limb is accompanied by medial rotation with the result that the great toe and tibia come to lie on the medial side. The original ventral surface of the limb is represented by the inguinal region, the medial side of the lower part of the thigh, the popliteal surface of the knee, the back of the leg and the sole of the foot.

The forelimb bud is derived from the part of the body wall belonging to segments C4, C5, C6, C7, C8, T1 and T2. It is, therefore, innervated by the corresponding spinal nerves. The hind limb bud is formed opposite the segments L2, L3, L4, L5, S1 and S2.

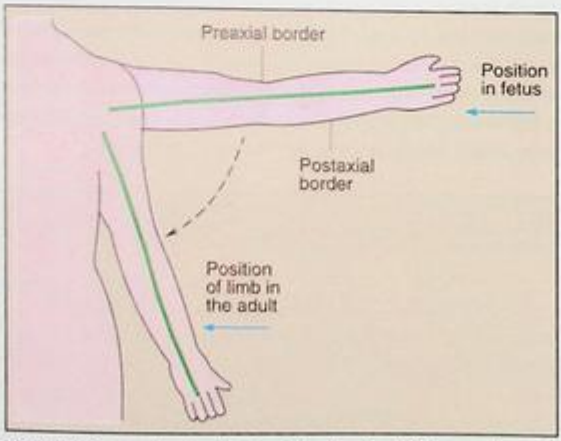

Fig. 10.11: Scheme showing that with 'adduction' of the embryonic limb, the preaxial border becomes the lateral border.

Joints

The tissues of joints are derived from mesenchyme intervening between developing bone ends. This mesenchyme may differentiate into fibrous tissue, forming a ***fibrous joint (syndesmosis),*** or into cartilage forming a ***cartilaginous joint.*** In the case of some cartilaginous joints ***(synchondrosis or primary cartilaginous joints)*** the cartilage connecting the bones is later ossified, with the result that the two bones become continuous. This is seen, typically, at the joints between the diaphyses and epiphyses of long bones.

At the site where a ***synovial joint*** is to be formed, the mesenchyme is usually seen in three layers. The two outer layers are continuous with the perichondrium covering the cartilaginous ends of the articulating bones. The middle layer becomes loose and a cavity is formed in it. The cavity comes to be lined by a mesothelium that forms the synovial membrane (Fig 10.12). The capsule, and other ligaments, are derived from the surrounding mesenchyme.

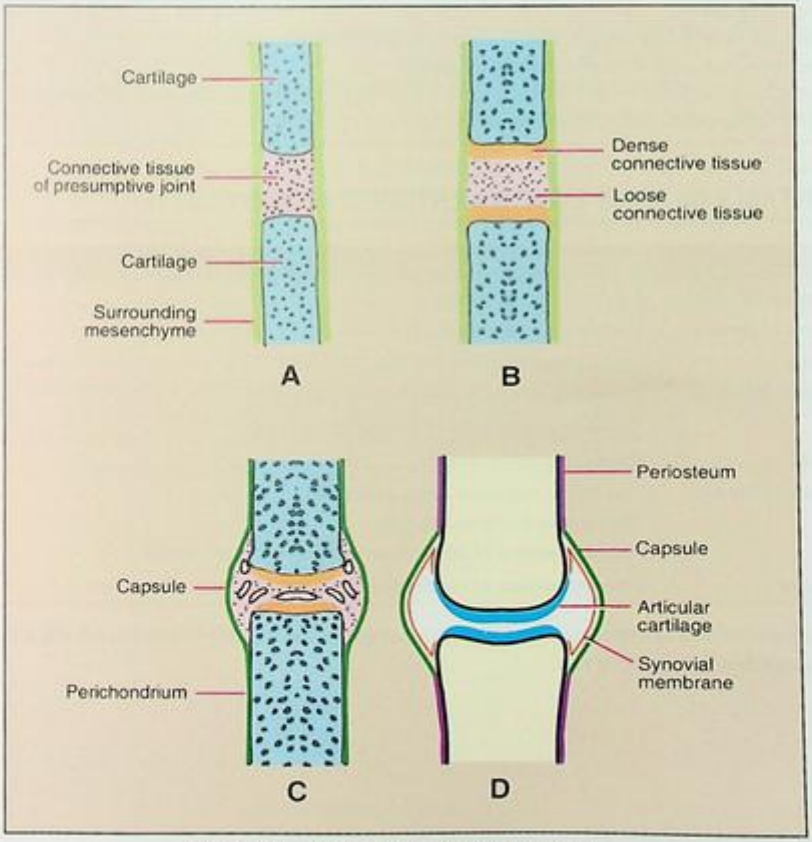

Fig. 10.12: Development of a synovial joint.

Clinical Correlation

Anomalies of Limbs

- One or more limbs of the body may be partially, or completely, absent ***(phocomelia, amelia)***. These conditions may be produced by ingestion of harmful drugs.
- Part of a limb may be deformed. ***Deformities*** are most frequently seen in the region of the ankle and foot, and are of various types. In the most common variety of deformity, the foot shows marked plantar flexion (equinus: like the horse), and inversion (varus). Hence this condition is called ***talipes equinovarus***, or ***club foot***.
- ***Congenital strictures, congenital amputations*** or ***congenital contractures*** may be present.
- There may be abnormal fusion (bony or fibrous) between different bones of the limb. Adjoining digits may be fused (***syndactyly***). The phalanges of a digit may be fused to one another (***synphalangia***).
- A digit may be abnormally large (***macrodactyly***), or abnormally short (***brachydactyly***). In ***arachnodactyly***, the fingers are long and thin (***spider fingers***).
- Supernumerary digits may be present (***polydactyly***). A digit (most commonly the thumb) may have an extra phalanx.
- The palm or sole may show a deep longitudinal ***cleft*** (***lobster claw***).
- The limbs may remain short in ***achondroplasia.***
- Sometimes the bone ends forming a joint are imperfectly formed (***congenital dysplasia***). This can lead to ***congenital dislocation***. The hip joint is most commonly affected.

TIMETABLE OF SOME EVENTS MENTIONED IN THIS CHAPTER

Age	Developmental Events
4th week (26th day)	Forelimb bud appears.
4th week (28th day)	Hindlimb bud appears.
5th week	Limbs become paddle shaped.
6th week (36th day)	Formation of future digits can be seen. Cartilaginous models of bone start forming.
7th week	Rotation of limbs occurs.
8th week (50th day)	The elbow and knee are established. The fingers and toes are free. Primary centers of ossification are seen in many bones.
12th week	Primary centers of ossification are seen in all the long bones.

The extremities are most susceptible to teratogens during the 4th to 7th weeks; and slightly less susceptible in the 8th week.

Chapter 11

Face, Nose and Palate

HIGHLIGHTS

- The *stomatodaeum* (future mouth) is a depression bounded cranially by a bulging produced by the brain, and caudally by a bulging produced by the pericardial cavity.
- Three prominences appear around the stomatodaeum. These are the ***frontonasal process*** (above), and the right and left ***mandibular arches*** (first pharyngeal arches) (Fig. 11.3A).
- The mandibular arch divides into a ***maxillary process*** and a ***mandibular process*** (Fig. 11.3B).
- The right and left mandibular processes meet in the midline and fuse (Fig. 11.4A). They form the *lower lip* and ***lower jaw***.
- The *upper* ***lip*** is formed by fusion of the frontonasal process with the right and left maxillary processes. Failure to fuse completely leads to various forms of ***harelip***.
- The *cheeks* are formed by fusion of (the posterior parts of) the maxillary and mandibular processes.
- The *nose* is derived from the frontonasal process.
- The *nasal* ***cavity*** is formed as follows. An ectodermal thickening, the nasal placode, appears over the frontonasal process (Fig. 11.4A). The placode gets depressed below the surface to form the nasal pit (Fig. 11.4B). The nasal pits enlarge to form the nasal cavity.
- ***Paranasal sinuses*** appear as outgrowths from the nasal cavity.
- The ***palate*** is formed by fusion of three components. These are the right and left palatal processes (arising from the maxillary process); and the primitive palate (derived from the frontonasal process) (Fig. 11.19). Deficiency in fusion leads to various forms of ***cleft palate*** (Fig. 11.20).

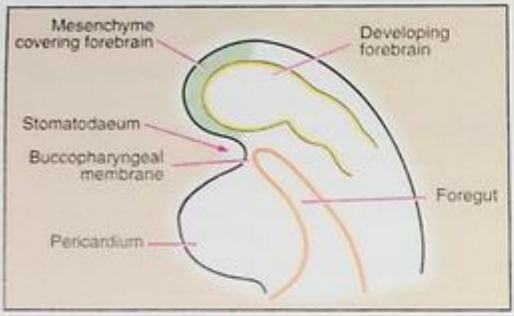

Fig. 11.1: Head end of an embryo just before formation of the frontonasal process.

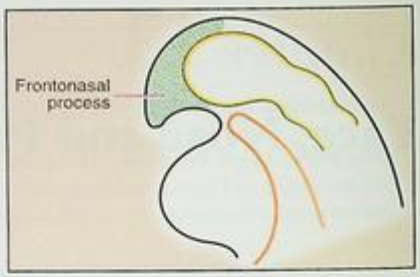

Fig. 11.2: Formation of frontonasal process.

INTRODUCTION

We have seen (Chapter 5) that, after the formation of the head fold, the developing brain and the pericardium form two prominent bulgings on the ventral aspect of the embryo (Fig. 5.16). These bulgings are separated by the stomatodaeum (Fig. 11.1). The floor of the stomatodaeum is formed by the buccopharyngeal membrane, which separates it from the foregut. Soon, mesoderm covering the developing forebrain proliferates, and forms a downward projection that overlaps the upper part of the stomatodaeum. This downward projection is called the ***frontonasal process*** (Fig. 11.2). We have also seen (Chapter 9) that the pharyngeal arches are laid down in the lateral and ventral walls of the most cranial part of the foregut (Fig. 9.1 B). These are also, therefore, in very close relationship to the stomatodaeum. It will now be readily appreciated that the face is derived from the following structures that lie around the stomatodaeum:

- the frontonasal process; and
- the first pharyngeal (or mandibular) arch of each side (Fig. 11.3A).

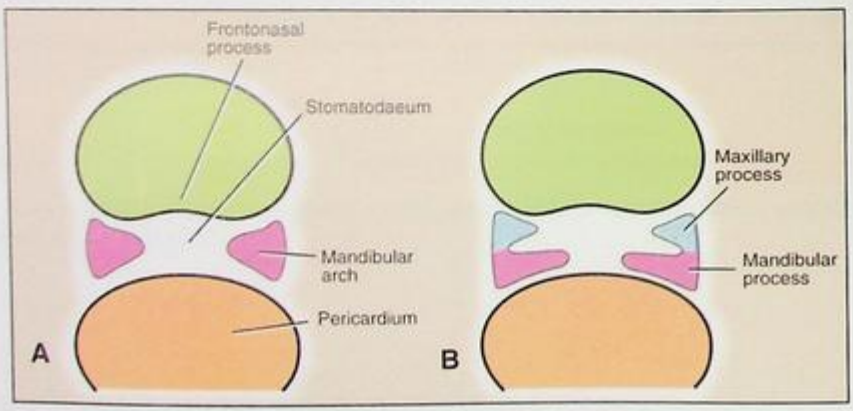

Fig. 11.3: Development of face: Formation of mandibular and maxillary processes.

At this stage each mandibular arch forms the lateral wall of the stomatodaeum (Fig. 11.3A). This arch gives off a bud from its dorsal end. This bud is called the ***maxillary process*** (Fig. 11.3B). It grows ventro-medially cranial to the main part of the arch which is now called the ***mandibular process***.

The ectoderm overlying the frontonasal process soon shows bilateral localised thickenings, that are situated a little above the stomatodaeum (Fig. 11.4A). These are called the ***nasal placodes***. The formation of these placodes is induced by the underlying forebrain. The placodes soon sink below the surface to form ***nasal pits*** (Fig. 11.4B). The pits are continuous with the stomatodaeum below. The edges of each pit are raised above the surface: the medial raised edge is called the ***medial nasal process*** and the lateral edge is called the ***lateral nasal process***.

DEVELOPMENT OF THE FACE

We are now in a position to study the formation of the various parts of the face.

Lower Lip

The mandibular processes of the two sides grow towards each other (Fig. 11.3B), and fuse in the midline (Fig. 11.4A). They now form the lower margin of the stomatodaeum. If it is remembered that the mouth develops from the stomatodaeum, it will be readily understood that the fused mandibular processes give rise to the lower lip, and to the lower jaw (Fig. 11.7).

Upper Lip

- Each maxillary process now grows medially and fuses, first with the lateral nasal process (Fig. 11.5), and then with the medial nasal process (Fig. 11.6). The medial and lateral nasal

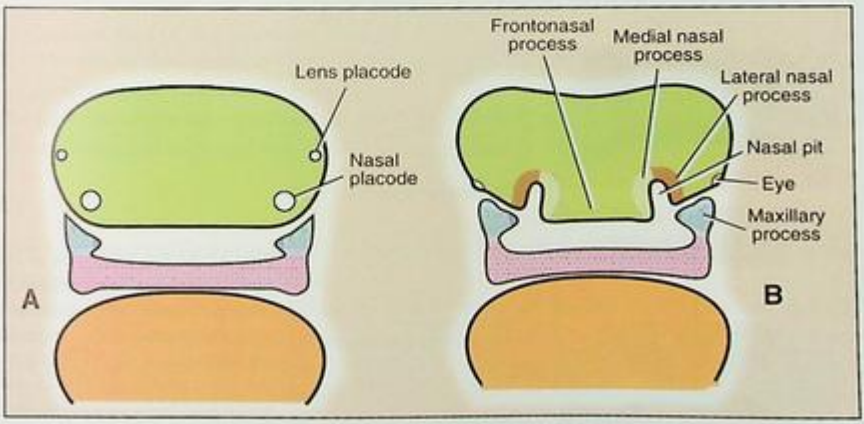

Fig. 11.4: Development of face (continued). (A) The right and left mandibular processes fuse and form the lower boundary of the future mouth. The nasal placodes appear over the frontonasal process. The lens placode appears. (B) The nasal placode is converted into the nasal pit. Elevations of the pit form the medial and lateral nasal processes.

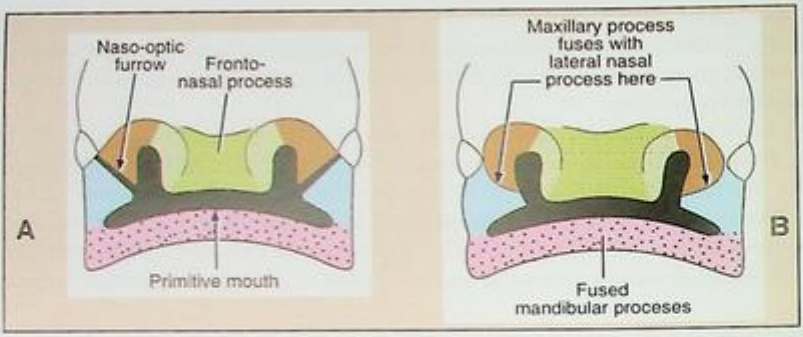

Fig. 11.5: Development of the face (continued). (A) The right and left nasal pits come close to each other. The lateral nasal process is separated from the maxillary process by the naso-optic furrow. (B) The maxillary process fuses with the lateral nasal process obliterating the naso-optic furrow.

processes also fuse with each other. In this way the nasal pits (now called ***external nares***) are cut off from the stomatodaeum.

- The maxillary processes undergo considerable growth (Fig. 11.6). At the same time the frontonasal process becomes much narrower from side to side, with the result that the two external nares come closer together.

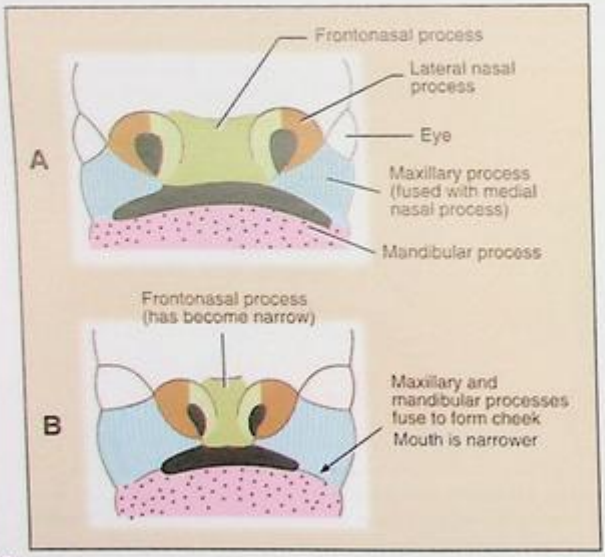

Fig. 11.6: Development of the face (continued). (A) The maxillary process extends below the nasal pit and fuses with the medial nasal process. In this way the nasal pit is separated from the stomatodaeum. (B) The maxillary and mandibular processes partly fuse to form the cheek. With growth of the maxillary processes the nasal pits come closer to each other.

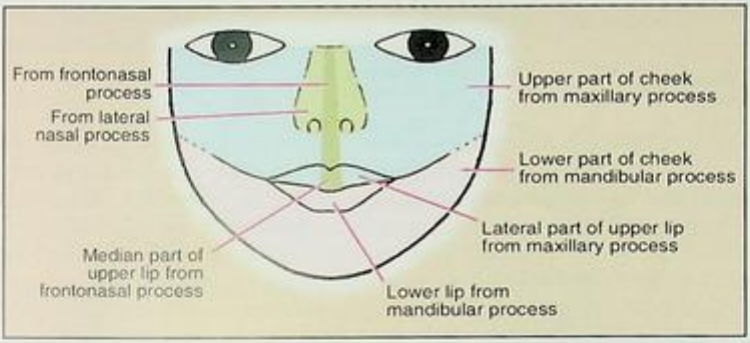

Fig. 11.7: Derivation of parts of the face.

- The stomatodaeum is now bounded above by the upper lip that is derived as follows (Figs. 11.7, 11.8).
  - The mesodermal basis of the lateral part of the lip is formed from the maxillary process. The overlying skin is derived from ectoderm covering this process.
  - The mesodermal basis of the median part of the lip (called ***philtrum***) is formed from the frontonasal process. The ectoderm of the maxillary process, however, overgrows this mesoderm to meet that of the opposite maxillary process in the midline (Fig. 11.8). As a result, the skin of the entire upper lip is innervated by the maxillary nerves.

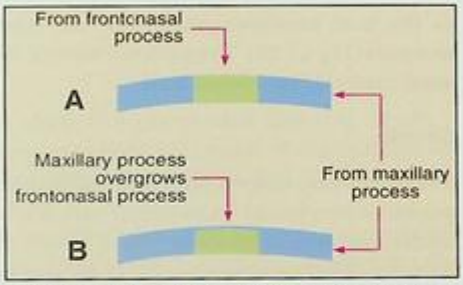

Fig. 11.8: Formation of upper lip: Scheme to show how the maxillary process 'overgrows' the frontonasal process.

- The muscles of the face (including those of the lips) are derived from mesoderm of the second branchial arch and are, therefore, supplied by the facial nerve.

Nose

The nose receives contributions from the frontonasal process, and from the medial and lateral nasal processes of the right and left sides.

We have seen that the external nares are formed when the nasal pits are cut off from the stomatodaeum by the fusion of the maxillary process with the medial nasal process. We have also noted that the external nares gradually approach each other. This is a result of the fact that the frontonasal process becomes progressively narrower and its deeper part ultimately forms the nasal septum. Mesoderm becomes heaped up in the median plane to form the prominence of the nose. Simultaneously, a groove appears between the region of the nose and the bulging forebrain (which may now be called the forehead) (Fig. 11.10).

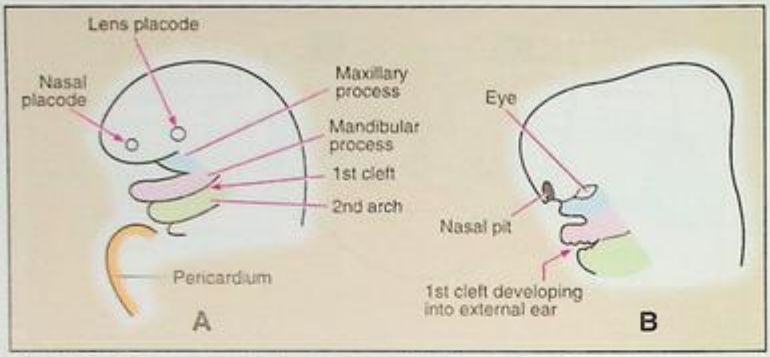

Fig. 11.9: Early stages in the development of the face as seen from the lateral aspect.

As the nose becomes prominent, the external nares come to open downwards instead of forwards (Fig. 11.10). The external form of the nose is thus established. The development of the nasal cavity is considered later.

Cheeks

After formation of the upper and lower lips, the stomatodaeum (which can now be called the mouth) is very broad. In its lateral part, it is bounded above by the maxillary process and below by the mandibular process. These processes undergo progressive fusion with each other to form the cheeks (compare Figs. 11.6A and B; also see Figs. 11.9 and 11.10).

We have already seen (while studying the formation of the upper lip) that the maxillary process fuses with the lateral nasal process. This fusion not only occurs in the region of the lip but also extends from the stomatodaeum to the medial angle of the developing eye (Figs. 11.6, 11.9B). For some time this line of fusion is marked by a groove called the ***naso-optic***

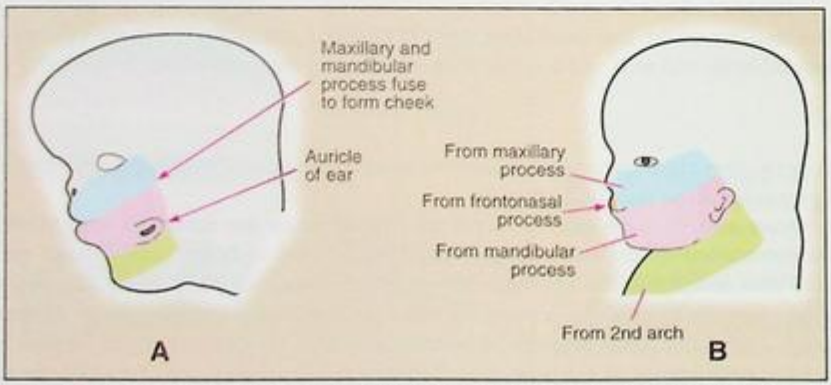

Fig. 11.10: Later stage in the development of the face as seen from the lateral aspect.

furrow or ***nasolacrimal sulcus*** (Fig. 11.5A). A strip of ectoderm becomes buried along this furrow and gives rise to the ***nasolacrimal duct*** (Chapter 19).

Eye

The development of the eye itself will be dealt with later (Chapter 19), but a brief reference to it is necessary to form a complete idea of the development of the face.

The region of the eye is first seen as an ectodermal thickening, the ***lens placode,*** which appears on the ventro-lateral side of the developing forebrain, lateral and cranial to the nasal placode (Fig. 11.4A). The lens placode sinks below the surface and is eventually cut off from the surface ectoderm. The developing eyeball produces a bulging in this situation (Fig. 11.5). The bulgings of the eyes are at first directed laterally (Figs. 11.5, 11.6), and lie in the angles between the maxillary processes and the lateral nasal processes. With the narrowing of the frontonasal process, they come to face forwards (Figs. 11.6, 11.7).

The eyelids are derived from folds of ectoderm that are formed above and below the eyes, and by mesoderm enclosed within the folds.

External Ear

The external ear is formed around the dorsal part of the first ectodermal cleft (Fig. 11.9B). A series of mesodermal thickenings (often called tubercles or hillocks) appear on the mandibular and hyoid arches where they adjoin this cleft. The pinna (or auricle) is formed by fusion of these thickenings (see Chapter 19, Fig. 19.25).

From a study of Figs. 11.9 and 11.10 it will be seen that when first formed, the pinna lies caudal to the developing jaw. It is pushed upwards and backwards to its definitive position due to the great enlargement of the mandibular process. If the mandibular process fails to enlarge, the ears remain low down. See mandibulofacial dysostosis below.

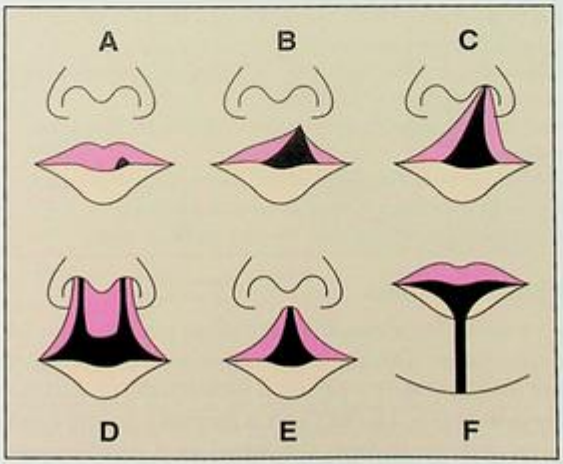

Fig. 11.11: Varieties of harelip. For explanation see text.

Clinical Correlation

Developmental Anomalies of the Face

It has been seen that the formation of various parts of the face involves fusion of diverse components. This fusion is occasionally incomplete and gives rise to various anomalies.

- ***Harelip:*** The upper lip of the hare normally has a cleft. Hence the term harelip is used for defects of the lips.
  - When one or both maxillary processes do not fuse with the medial nasal process, this gives rise to defects in the upper lip. These may vary in degree and may be unilateral (Figs. 11.11A-C), or bilateral (Fig. 11. 11D).
  - Defective development of the lowermost part of the frontonasal process may give rise to a midline defect of the upper lip (Fig. 11.11E).
  - When the two mandibular processes do not fuse with each other the lower lip shows a defect in the midline. The defect usually extends into the jaw (Fig. 11.11F).
- ***Oblique facial cleft:*** Non-fusion of the maxillary and lateral nasal process gives rise to a cleft running from the medial angle of the eye to the mouth (Fig. 11.12). The nasolacrimal duct is not formed.
- Inadequate fusion of the mandibular and maxillary processes with each other may lead to an abnormally wide mouth (***macrostomia***). Lack of fusion may be unilateral: this leads to formation of a ***lateral facial cleft***. Too much fusion may result in a small mouth (***microstomia***).
- The nose may be bifid. This may be associated with median cleft lip. Both these occur due to bifurcation of the frontonasal process. Occasionally one half of it may be absent. Very rarely the nose forms a cylindrical projection, or ***proboscis*** (Fig. 11.13) jutting out from just below the forehead. This anomaly may sometimes affect only one half of the nose and is usually associated with fusion of the two eyes (***cyclops***).
- The entire first arch may remain underdeveloped on one or both sides, affecting the lower eyelid (coloboma type defect), the maxilla, the mandible, and the external ear. The prominence of the cheek is absent and the ear may be displaced ventrally and caudally. There may be presence of cleft palate and of faulty dentition. This condition is called ***mandibulofacial dysostosis, Treacher Collins syndrome*** or ***first arch syndrome***. This is a genetic condition inherited as autosomal dominant.
- One half of the face may be underdeveloped or overdeveloped.
- The mandible may be small compared to the rest of the face resulting in a receding chin (***retrognathia***). In extreme cases it may fail to develop (**agnathia**).
- Congenital tumours may be present in relation to the face. These may represent attempts at duplication of some parts.
- The eyes may be widely separated (***hypertelorism***). The nasal bridge is broad. This condition results from the presence of excessive tissue in the frontonasal process.
- The lips may show congenital pits or fistulae. The lip may be double.

Development of Nasal Cavities

The nasal cavities are formed by extension of the nasal pits. We have seen that these pits are at first in open communication with the stomatodaeum (Fig. 11.14A). Soon the medial and lateral nasal processes fuse, and form a partition between the pit and the stomatodaeum. This is called the ***primitive palate*** (Fig. 11.14B), and is derived from the frontonasal process.

The nasal pits now deepen to form the ***nasal sacs*** which expand both dorsally and caudally (Fig. 11.14C). The dorsal part of this sac is, at first, separated from the stomatodaeum

Fig. 11.12: Oblique facial cleft.

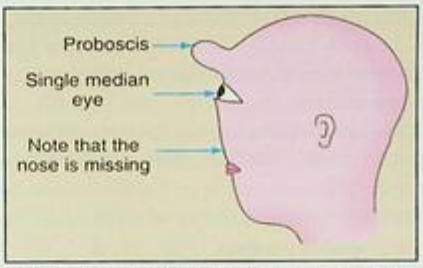

Fig. 11.13: Abnormal face showing single median eye (cyclops). A rod like projection is seen above the eye (proboscis). Also see Fig. 19.12.

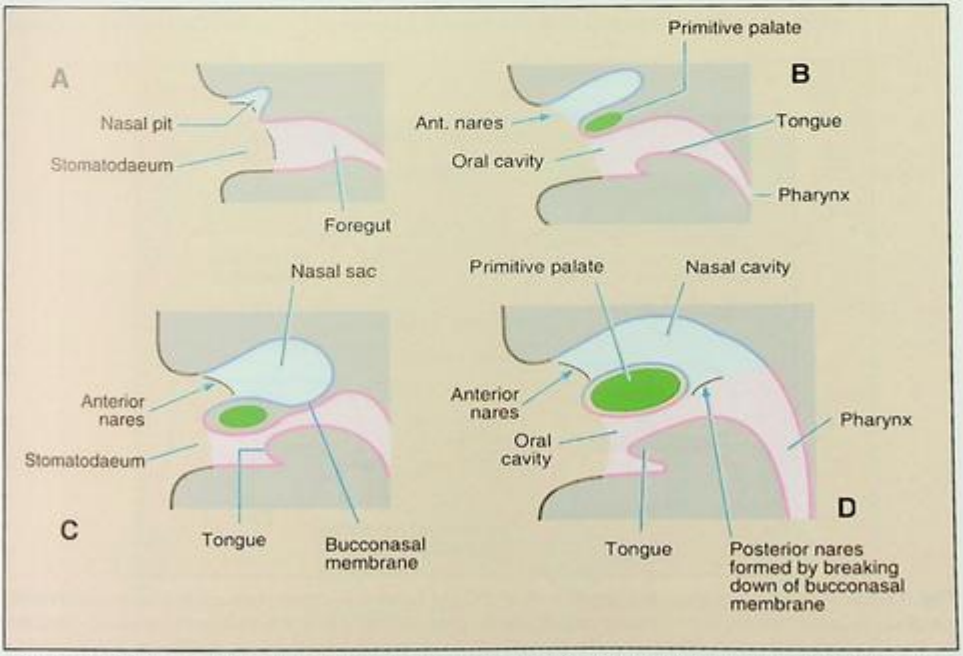

Fig. 11.14: (A) Parasagittal sections through developing nasal cavity. (A) Nasal pit formed. (B) Nasal pit deepens. It is separated from the stomatodaeum by the primitive palate. (C) The nasal pit enlarges to form the nasal sac. Posterior to the primitive palate the sac is separated from the oral cavity by the bucconasal membrane. (D) Bucconasal membrane breaks down.

by a thin membrane called the ***bucconasal membrane*** (or ***nasal fin***). This soon breaks down (Figs. 11.14D, 11.15B). The nasal sac now has a ventral orifice that opens on the face (***anterior or external nares***), and a dorsal orifice that opens into the stomatodaeum (***primitive posterior nasal aperture***).

The two nasal sacs are at first widely separated from one another by the frontonasal process (Figs. 11.15A, B). We have seen, however, that the frontonasal process becomes progressively narrower. This narrowing of the frontonasal process, and the enlargement of the nasal cavities themselves, brings them closer together. The intervening tissue becomes much thinned to from the ***nasal septum*** (Figs. 11.15 C, D). The ventral part of the nasal septum is attached below to the primitive palate (Fig. 11.15C). More posteriorly, the septum is at first attached to the bucconasal membrane (Fig. 11.15D), but on disappearance of this membrane it has a free lower edge. The nasal cavities are separated from the mouth by the development of the palate, as described below.

The ***lateral wall*** of the nose is derived, on each side, from the lateral nasal process. The ***nasal conchae*** appear as elevations on the lateral wall of each nasal cavity. The original olfactory placodes form the ***olfactory epithelium*** that lies in the roof, and adjoining parts of the walls, of the nasal cavity.

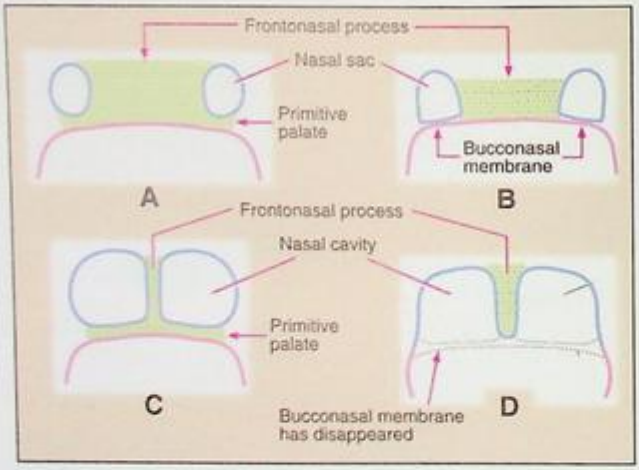

Fig. 11.15: Formation of the nasal septum. A and C are coronal sections through the anterior part of the nasal sac. B and D are sections through the posterior part. (A) Right and left nasal sacs are widely separated by the frontonasal process. Anterior part of nasal sac is separated from the stomatodaeum by the primitive palate. (B) Posterior part of nasal sac is separated from the stomatodaeum by the bucconasal membrane. (C) Nasal sacs enlarge and come close together. The frontonasal process is narrow and forms the nasal septum. The lower edge of the septum reaches the primitive palate. (D) Bucconasal membrane breaks down. As a result the posterior part of the nasal sac opens into the stomatodaeum.

Clinical Correlation

Anomalies of the Nasal Cavity

- There may be atresia of the cavity at the external nares, at the posterior nasal aperture, or in the cavity proper. This may be unilateral or bilateral. Very rarely, there may be total absence of the nasal passages.
- Congenital defects in the cribriform plate of the ethmoid bone may lead to a communication between the cranial cavity and the nose.
- The nasal septum may not be in the middle line, i.e. it may be deflected to one side. The septum may be absent.
- The nasal cavity may communicate with the mouth.

Paranasal Sinuses

The paranasal sinuses appear as diverticula from the nasal cavity. The diverticula gradually invade the bones after which they are named. The maxillary and sphenoidal sinuses begin to develop before birth. The other sinuses develop after birth.

Enlargement of paranasal sinuses is associated with overall enlargement of the facial skeleton, including the jaws. This provides space in the jaws for growth and eruption of teeth. Growth of the facial skeleton is responsible for the gradual change in looks of a baby.

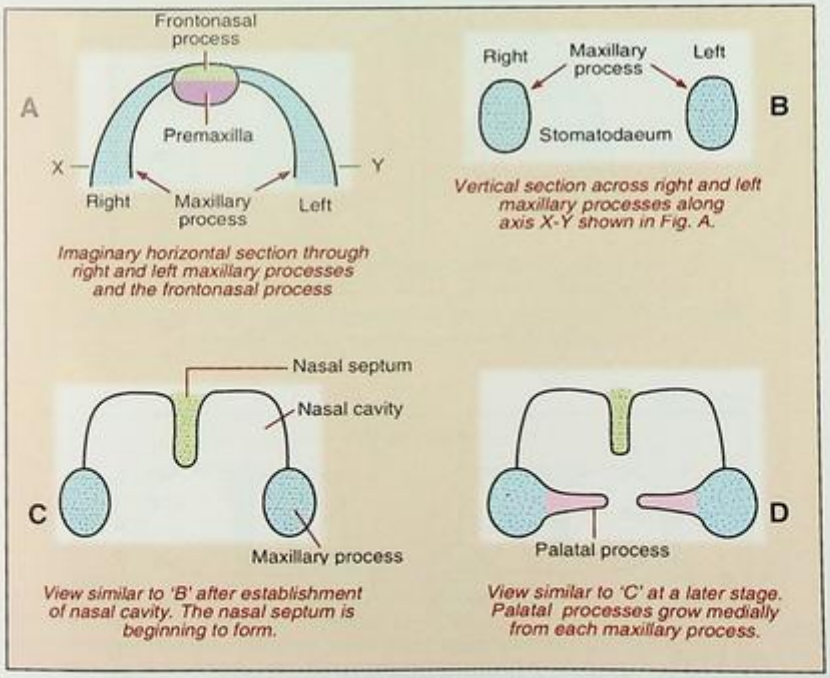

Fig. 11.16: Development of the palate.

DEVELOPMENT OF THE PALATE

To understand the development of the palate, let us have another look at the maxillary process. From Figs. 11.6 and 11.10 it will be seen that these processes not only form the upper lip but also extend backwards on either side of the stomatodaeum. They can, therefore, be diagrammatically illustrated as in Fig. 11.16A. If we cut a coronal section through the region (along the line XY in Fig. 11.16A) the maxillary processes will be seen as in Fig. 11.16B. Finally, if we now correlate Fig. 11.16B with Fig. 11.15D the relationship of the maxillary processes to the developing nasal cavity and mouth is easily understood (Fig. 11.16C).

From each maxillary process, a plate like shelf grows medially (Fig. 11.16D). This is called the ***palatal process***. We now have three components from which the palate will be formed. These are (Fig. 11.19):

- the two palatal processes; and
- the primitive palate formed from the frontonasal process.

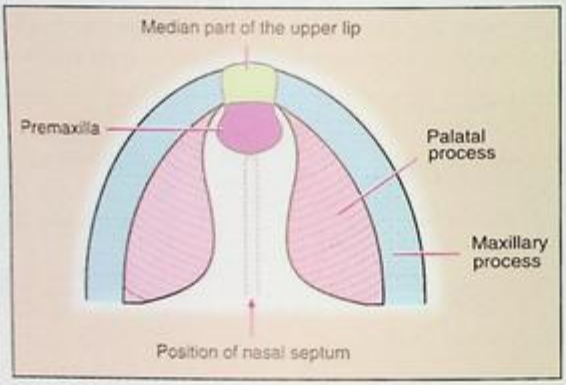

Fig. 11.17: Constituents of the developing palate as seen in a schematic horizontal section through the maxillary processes.

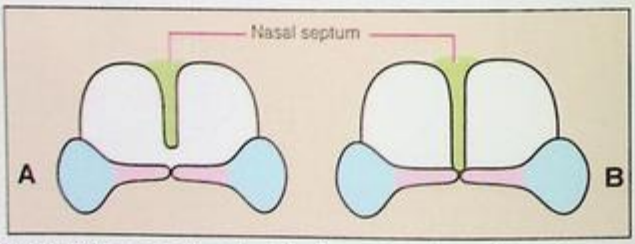

Fig. 11.18: Separation of nasal cavities from each other, and from the mouth. Compare with Fig. 11.16D.

The definitive palate is formed by the fusion of these three parts as follows:

1. Each palatal process fuses with the posterior margin of the primitive palate (Fig. 11.19).
2. The two palatal processes fuse with each other in the midline (Fig. 11.18A). Their fusion begins anteriorly and proceeds backwards.
3. The medial edges of the palatal processes fuse with the free lower edge of the nasal septum (Fig. 11.18B), thus separating the two nasal cavities from each other, and from the mouth.

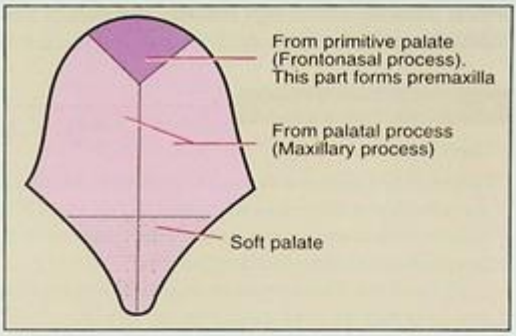

Fig. 11.19: Embryological subdivisions of the palate and the lines of fusion of these subdivisions.

At a later stage, the mesoderm in the palate undergoes intramembranous ossification to form the ***hard palate***. However, ossification does not extend into the most posterior portion,

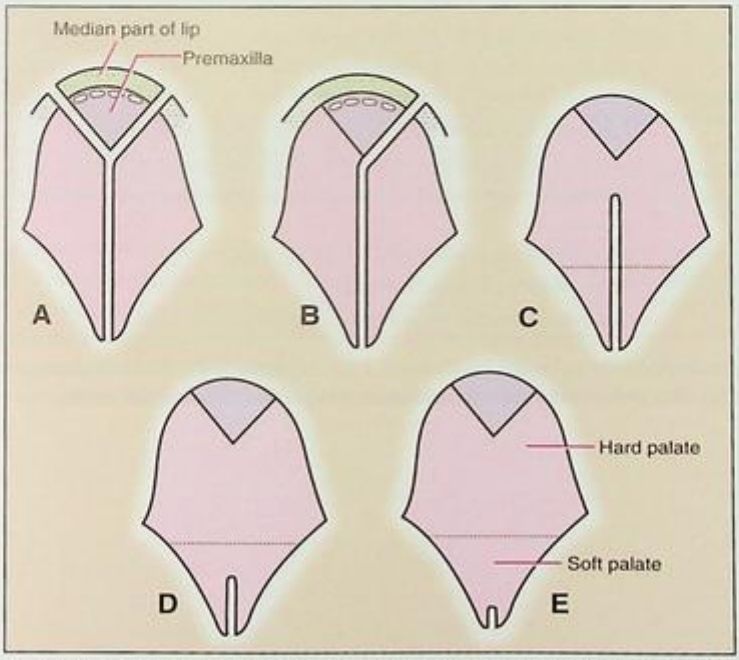

Fig. 11.20: Varieties of cleft palate. (A) Complete non-fusion, giving rise to a Y-shaped cleft, accompanied by bilateral harelip. (B) The left maxillary process has fused with the premaxilla, but not with the right maxillary process. The cleft is accompanied by unilateral harelip. (C) Midline cleft extending into the hard palate. (D) Cleft of soft palate. (E) Bifid uvula.

which remains as the ***soft palate***. The part of the palate derived from the frontonasal process forms the ***premaxilla***, which carries the incisor teeth.

Clinical Correlation

Cleft Palate

Defective fusion of the various components of the palate gives rise to clefts in the palate. These vary considerably in degree as illustrated in Fig. 11.20. Clefts of the palate that extend to its anterior end are associated with harelip, as both the upper lip and the palate are formed by fusion of the maxillary processes with the frontonasal process.

Clefts of the palate result in anomalous communications between the mouth and the nose. These may be unilateral, or bilateral (Figs. 11.20A, B).

TIMETABLE OF SOME EVENTS DESCRIBED IN THIS CHAPTER

Age	Developmental Events
4th week (28th day)	The frontonasal, maxillary and mandibular processes can be identified. The lens and nasal placodes are present.
5th week (31 to 35 days)	The nasal pits are established.
6th week	Tubercles for the development of pinna begins to be formed. On each side, palatal process arise from the maxillary process.
7th week	Eyelids are established. The maxillary process fuses with the medial nasal process.
8th week	Eyes shift from a lateral to a frontal position. Bucconasal membrane ruptures.
10th week	The palatal processes and nasal septum fuse with each other.

Teratogens are likely to cause lip defects if the embryo is exposed to them during the 5th and 6th weeks. The palate is most susceptible between the 7th and 8th weeks.

Chapter 12

Alimentary System—I: Mouth, Pharynx and Related Structures

HIGHLIGHTS

- The *oral* ***cavity*** is derived partly from the stomatodaeum (ectoderm), and partly from the foregut (endoderm). These two are separated by the buccopharyngeal membrane which later disappears (Fig. 12.1).
- *Teeth* are formed in relation to the dental lamina (Fig. 12.2). An enlargement of the lamina is formed for each tooth. It is called the ***enamel organ*** (Fig. 12.6).
- ***Ameloblasts*** (derived from ectoderm) form the ***enamel***. ***Odontoblasts*** (derived from mesoderm) form ***dentine***. The ***pulp*** is formed by mesenchyme that invaginates into the enamel organ (Fig. 12.6E).
- Three swellings appear in the floor of the pharynx, in relation to the first pharyngeal arch. These are the right and left ***lingual swellings***, and a median swelling the ***tuberculum impar*** (Fig. 12.11). Another median swelling is formed in relation to the third and fourth arches. This is the ***hypobranchial eminence***.
- The ***anterior two-third of the tongue*** is formed from the lingual swellings and the tuberculum impar.
- The ***posterior one-third of the tongue*** is formed by the cranial part of the hypobranchial eminence.
- ***Salivary glands*** develop as outgrowths of buccal epithelium.
- The ***palatine tonsil*** develops in relation to the second pharyngeal pouch.
- The ***pharynx*** is derived from the foregut.

MOUTH

The mouth is derived partly from the stomatodaeum and partly from the foregut. Hence its epithelial lining is partly ectodermal and partly endodermal. After disappearance of the buccopharyngeal membrane, the line of junction between the ectoderm and endoderm is difficult to define. The epithelium lining the inside of the lips and cheeks, and the palate, is most probably ectodermal. The teeth and gums are also of ectodermal origin. The epithelium of the tongue is, however, derived from endoderm (Fig. 12.1).

In the region of the floor of the mouth, the mandibular processes take part in the formation of three structures. These are:

1. the lower lip (and the lower part of cheeks);
2. the lower jaw; and
3. the tongue).

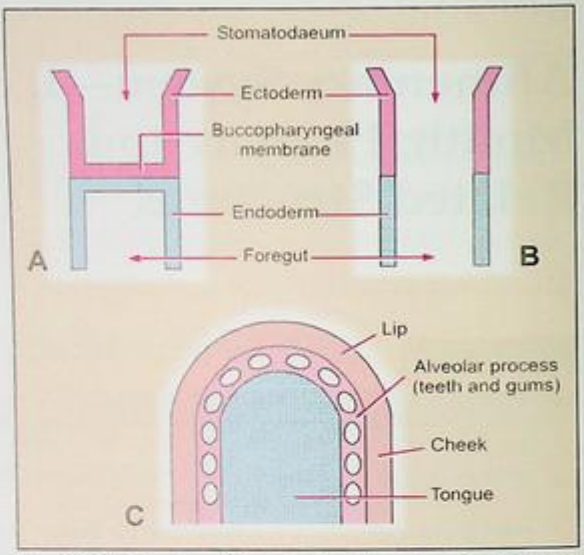

Fig. 12.1: Derivation of the ectodermal part, and endodermal part of the floor of the mouth. (A) Stomatodaeum separated from foregut by buccopharyngeal membrane. (B) Buccopharyngeal membrane disappears. (C) Lips, cheeks and gums lined by ectoderm, tongue by endoderm.

At first these regions are not demarcated from each other (Fig. 12.2A). Soon the tongue forms a recognisable swelling, which is separated laterally from the rest of the mandibular process by the ***linguo-gingival sulcus*** (Fig. 12.2B). Soon, thereafter, another more laterally placed sulcus makes its appearance. This is called the ***labio-gingival sulcus*** (Fig. 12.2C). This sulcus deepens rapidly and the tissues of the mandibular arch lateral to it form the lower lip (or cheek). With the deepening of these two sulci, the area lying between them becomes a raised ***alveolar process*** (Fig. 12.2D). This process forms the jaw, and the teeth develop in relation to it. The tongue, the alveolar process (or jaw) and the lips (or cheeks) are thus separated from one another (Fig. 12.3).

The roof of the mouth is formed by the palate. The development of the palate has already been considered. The alveolar process of the upper jaw is separated from the upper lip and cheek by appearance of a ***labio-gingival furrow***, just as in the lower jaw. The medial margin of the alveolus becomes defined when the palate becomes highly arched (Fig. 12.4).

Some anomalies in the region of the mouth are described in Chapter 11.

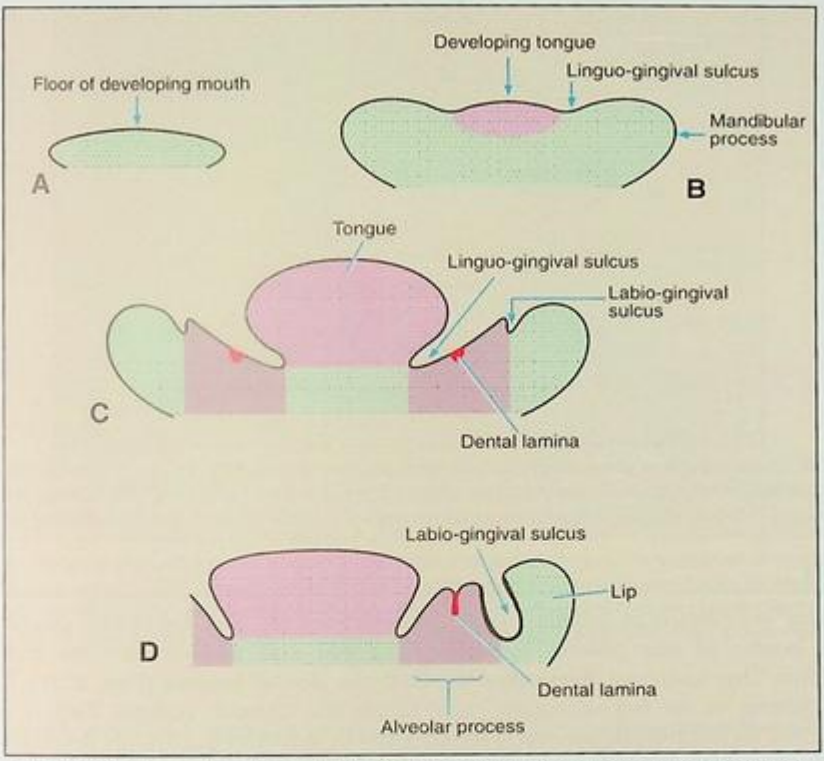

Fig. 12.2: (A) Floor of mouth formed by fused mandibular processes. (B) Linguo-gingival sulcus separates developing tongue from rest of mandibular processes. (C) Labio-gingival sulcus separates alveolar process from lip (or cheek). The dental lamina, seen in the alveolar process, gives origin to teeth. Also see Fig. 12.3.

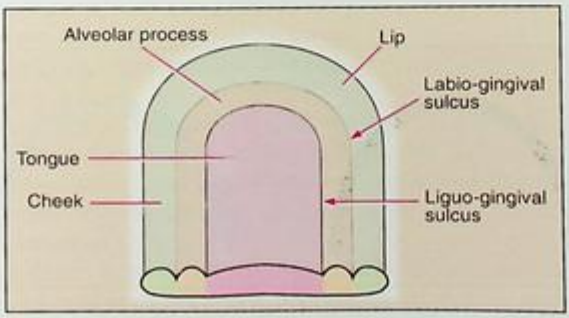

Fig. 12.3: Floor of mouth showing labio-gingival and linguo-gingival sulci.

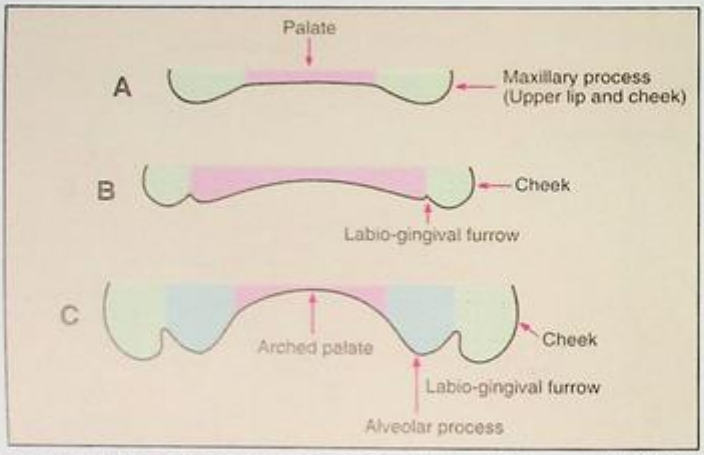

Fig. 12.4: Development of some structures seen in relation to the roof of the mouth. (A) Maxillary processes and palate. (B) Labio-gingival furrow separates upper lip (or upper part of cheek) from alveolar process (of upper jaw). (C) Medial margin of alveolar process becomes distinct because of upward arching of the palate.

TEETH

The teeth are formed in relation to the alveolar process. The epithelium overlying the convex border of this process becomes thickened and projects into the underlying mesoderm. This epithelial thickening is called the ***dental lamina*** (Figs. 12.2C, D). The dental lamina is, in fact, apparent even before the alveolar process itself is defined (Fig. 12.2C). As the alveolar process is semicircular in outline (Fig. 12.3) the dental lamina is similarly curved (Fig. 12.5A).

The dental lamina now shows a series of local thickenings, each of which is destined to form one milk tooth. These thickenings are called ***enamel organs***. There are ten such enamel organs (five on each side) in each alveolar process (Fig. 12.5B). The stages in the formation of an enamel organ and the development of a tooth are as follows:

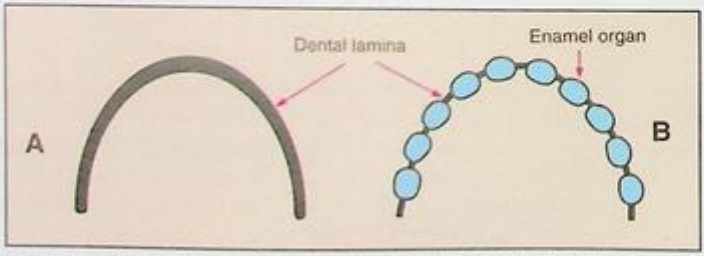

Fig. 12.5: Formation of enamel organs from dental lamina. (A) Dental lamina following the curve of the alveolar process. (Compare with Fig. 12.3). (B) Enamel organs formed in relation to the dental lamina.

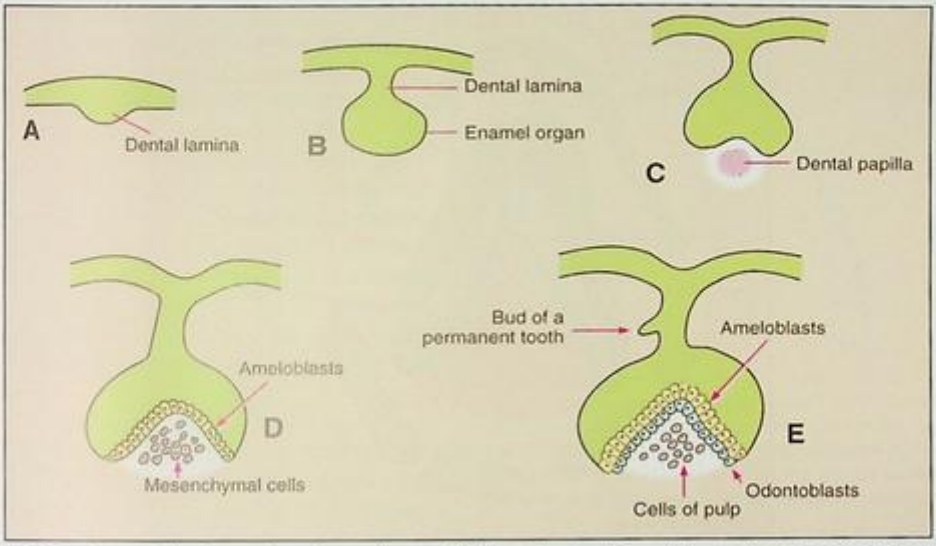

Fig. 12.6: Stages in the formation of a tooth germ. (A) Dental lamina formed by proliferation of ectoderm lining the alveolar process. (B) Deeper part of dental lamina enlarges to form enamel organ. (C) Mesodermal cells invaginate the enamel organ to form the papilla. (D) Layer of ameloblasts (ectoderm) formed from deepest cells of enamel organ. (E) Odontoblasts, derived from mesodermal cells, form a layer next to the ameloblasts.

- As already stated each enamel organ is formed by localised proliferation of the cells of the dental lamina (Figs. 12.6A, B).
- As the enamel organ grows downwards into the mesenchyme (of the alveolar process) its lower end assumes a cup-shaped appearance (Fig. 12.6C). The cup comes to be occupied by a mass of mesenchyme called the ***dental papilla***. (According to some authorities, this mesenchyme is of neural crest origin). The enamel organ and the dental papilla together constitute the ***tooth germ***. At this stage the developing tooth looks like a cap: it is, therefore, described as the ***cap stage*** of tooth development.
- The cells of the enamel organ that line the papilla become columnar. These are called ***ameloblasts*** (Fig. 12.6D).
- Mesodermal cells of the papilla that are adjacent to the ameloblasts arrange themselves as a continuous epithelium-like layer. The cells of this layer are called ***odontoblasts*** (Fig. 12.6E). The ameloblasts and odontoblasts are separated by a basement membrane. The remaining cells of the papilla from the pulp of the tooth. The developing tooth now looks like a bell (***bell stage***).
- Ameloblasts lay down enamel on the superficial (outer) surface of the basement membrane. The odontoblasts lay down dentine on its deeper surface. The process of laying down of enamel and of dentine is similar to that of formation of bone by osteoblasts.

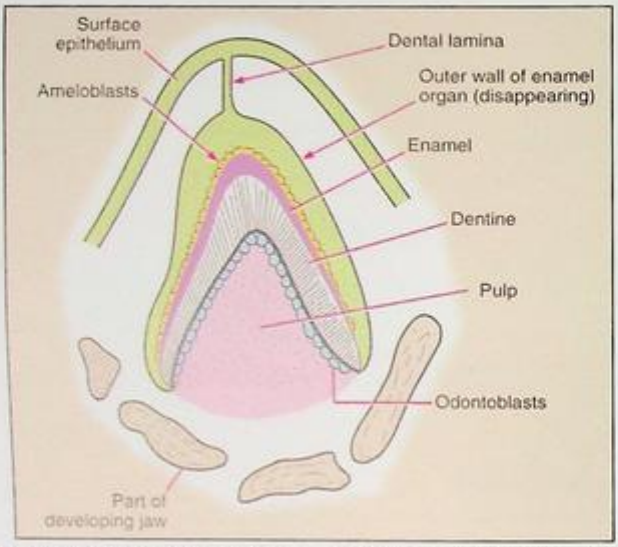

Fig. 12.7: Parts of a developing tooth. Ameloblasts lay down enamel. Odontoblasts lay down dentine. Ossification in relation to mesenchymal cells surrounding the developing tooth forms the jaw.

As layer after layer of enamel and dentine are laid down, the layer of ameloblasts and the layer of odontoblasts move away from each other (Fig. 12.7).

- After the enamel is fully formed the ameloblasts disappear leaving a thin membrane, the ***dental cuticle***, over the enamel. The odontoblasts, however, continue to separate the dentine from the pulp throughout the life of the tooth.

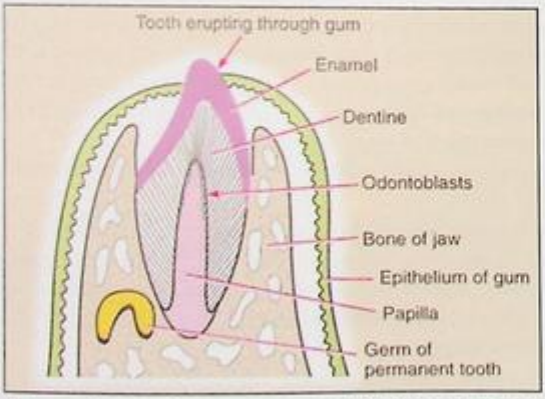

Fig. 12.8: Diagram of an erupting temporary tooth. Note its relationship to the jaw. Also observe germ of permanent tooth.

- The alveolar parts of the maxillae and mandible are formed by ossification in the corresponding alveolar process. As ossification progresses, the roots of the teeth are surrounded by bone.

The root of the tooth is established by continued growth into underlying mesenchyme. Odontoblasts in this region lay down dentine. As layers of dentine are deposited, the pulp space becomes progressively narrower and is gradually converted into a canal through which nerves and blood vessels pass into the tooth.

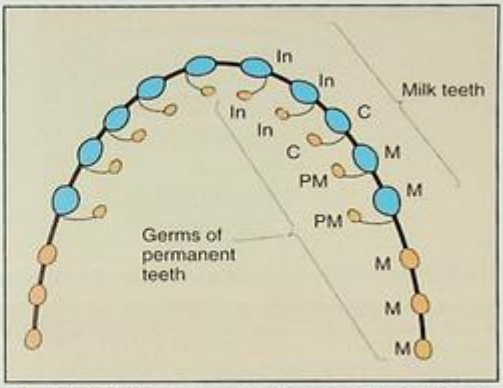

Fig. 12.9: Origin of germs of permanent teeth. Germs of permanent incisors, canines, and premolars are formed in relation to temporary teeth (as seen in Fig. 12.8). Permanent molars arise from the dental lamina behind the part that gives rise to temporary teeth.

In the region of the root there are no ameloblasts. The dentine is covered by mesenchymal cells that differentiate into ***cementoblasts***. These cells lay down a layer of dense bone called the ***cementum***. Still further to the outside, mesenchymal cells form the ***periodontal ligament*** which connects the root to the socket in the jaw bone.

The permanent teeth are formed as follows:

- The dental lamina gives off a series of buds, one of which lies on the medial side of each developing milk tooth (Fig. 12.9). These buds form enamel organs exactly as described above. They give rise to the permanent incisors, canines and premolars.
- The permanent molars are formed from buds that arise from the dental lamina posterior to the region of the last milk tooth.

The dental lamina is established in the 6th week of intrauterine life. At birth the germs of all the temporary teeth, and of the permanent incisors, canines and first molars, show considerable development. The germs of the permanent premolars and of the second molars are rudimentary. The germ of the third molar is formed after birth. The developing tooth germs undergo calcification. All the temporary teeth and the permanent lower first molar begin to calcify before birth; the other permanent teeth begin to calcify at varying ages after birth.

The eruption of a tooth is preceded by a major development of its root. The ages at which teeth erupt vary considerably. The average age of eruption is as follows:

a. *Temporary or Milk Teeth*

Lower central incisor	6–9 months
Upper incisors	8–10 months
Lower lateral incisors	12–20 months
First molar	12–20 months
Canines	16–20 months
Second molars	20–39 months

b. *Permanent Teeth*

First molar	6–7 years
Central incisors	6–8 years
Lateral incisors	7–9 years
Premolars	10–12 years
Canines	10–12 years
Second molars	11–13 years
Third molars	17–21 years

Table 12.1: Summary of the derivatives of parts of a tooth

Summary of Derivation of Parts of Tooth	
Ectoderm	Ameloblasts → ENAMEL
Mesoderm (of neural crest origin ?)	Odontoblasts → DENTINE
Mesenchyme around tooth	CEMENTUM PERIODONTAL LIGAMENT

CLINICAL CORRELATION

Anomalies of Teeth

- One or more teeth may be absent. Complete absence is called ***anodentia***.
- Supernumerary teeth may be present.
- Individual teeth may be abnormal. They may be too large or too small. They may have supernumerary cusps or roots. Alternatively, cusps or roots may be less than normal.
- Two (or more) teeth may be fused to each other (***gemination***).
- The alignment of the upper and lower teeth may be incorrect (***malocclusion***). This may be caused by one or more of the above anomalies or by defects of the jaws.
- Eruption of teeth may be precocious (i.e. too early). Lower incisors may be present at birth.
- Eruption of teeth may be delayed. The third molar frequently fails to erupt.
- Teeth may form in abnormal situations, e.g. in the ovary or in the hypophysis cerebri.
- There may be improper formation of the enamel or dentine of the tooth.

TONGUE

The tongue develops in relation to the pharyngeal arches in the floor of the developing mouth. We have seen that each pharyngeal arch arises as a mesodermal thickening in the lateral wall of the foregut and that it grows ventrally to become continuous with the corresponding arch of the opposite side (Fig. 12.10). The medial-most parts of the mandibular arches proliferate to form two ***lingual swellings*** (Fig. 12.11). The lingual swellings are partially separated from each other by another swelling that appears in the midline. This median swelling is called the ***tuberculum impar***. Immediately behind the tuberculum impar, the epithelium proliferates to form a downgrowth (***thyroglossal duct***) from which the thyroid gland develops. The site of this downgrowth is subsequently marked by a depression called the ***foramen caecum.***

Another, midline swelling is seen in relation to the medial ends of the second, third and fourth arches. This swelling is called the ***hypobranchial eminence*** (Fig. 12.11). The eminence soon shows a subdivision into a cranial part related to the second and third arches (called the ***copula***) and a caudal part related to the 4th arch (Fig. 12.12A). The caudal part forms the epiglottis.

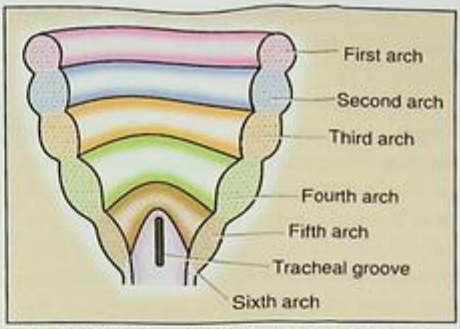

Fig. 12.10: Floor of primitive pharynx: Stage 1. Note that the right and left pharyngeal arches meet in the midline to form the floor of the pharynx.

The ***anterior two-third of the tongue*** is formed by fusion of:

a. the tuberculum impar, and

b. the two lingual swellings.

The anterior two-third of the tongue is thus derived from the mandibular arch (Figs. 12.12B, C). According to some, the tuberculum impar does not make a significant contribution to the tongue.

The ***posterior one-third of the tongue*** is formed from the cranial part of the hypobranchial eminence (copula) (Fig. 12.12). In this situation, the second arch mesoderm gets buried below the surface. The third arch mesoderm grows over it to fuse with the mesoderm of the first arch (Fig. 12.13). The posterior one-third of the tongue is thus formed by third arch mesoderm.

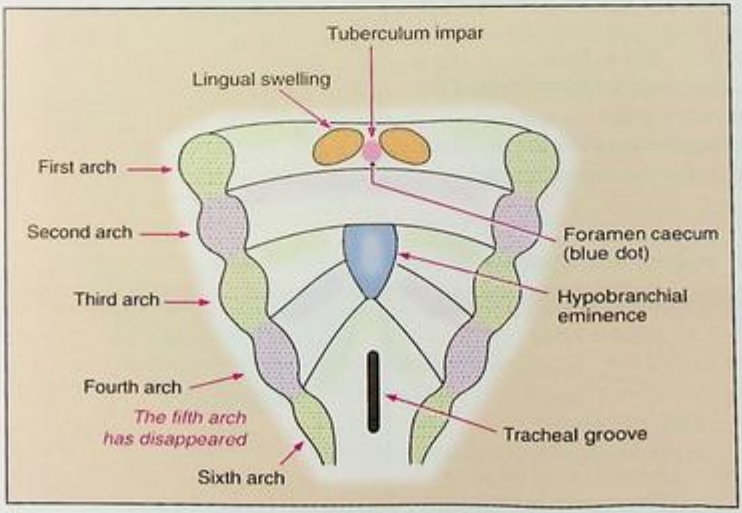

Fig. 12.11: Floor of primitive pharynx: Stage 2. The fifth pharyngeal arch has disappeared. Note the right and left lingual swellings, and the tuberculum impar formed in relation to the first arch; and the hypobranchial eminence formed in relation to the medial ends of the third and fourth arches.

The ***posterior-most part of the tongue*** is derived from the fourth arch (Fig. 12.13).

In keeping with its embryological origin, the anterior two-third of the tongue is supplied by the lingual branch of the mandibular nerve, which is the post-trematic nerve of the first arch, and by the chorda tympani which is the pre-trematic nerve of this arch. The posterior one-third of the tongue is supplied by the glossopharyngeal nerve, which is the nerve of the third arch. The most posterior part of the tongue is supplied by the superior laryngeal nerve, which is the nerve of the fourth arch.

The musculature of the tongue is derived from the occipital myotomes. This explains its nerve supply by the hypoglossal nerve, which is the nerve of these myotomes.

The ***epithelium*** of the tongue is at first made up of a single layer of cells. Later it becomes stratified and papillae become evident. ***Taste buds*** are formed in relation to the terminal branches of the innervating nerve fibres.

The development of the tongue starts in the 4th month of intrauterine life.

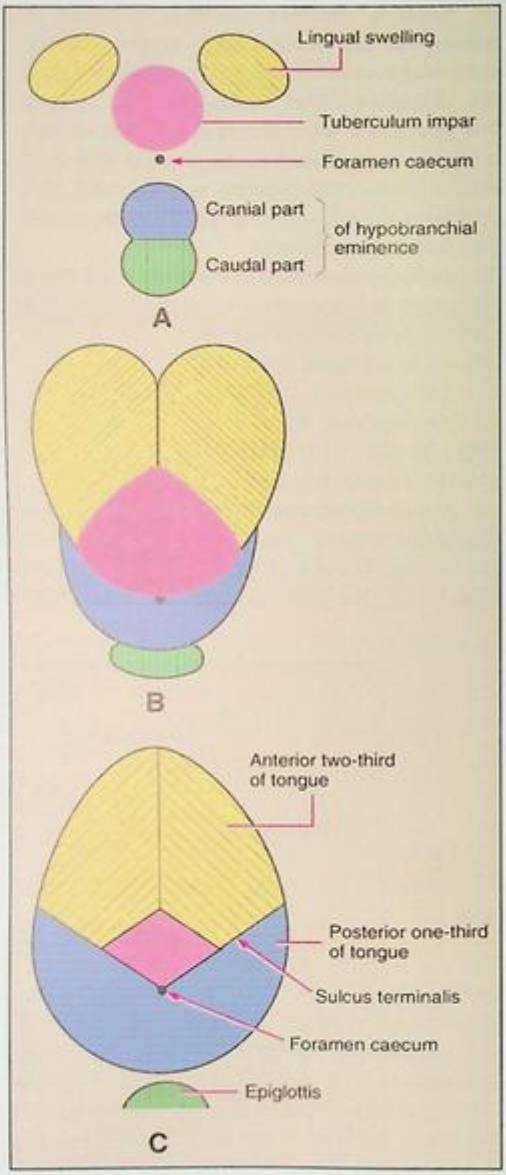

Fig. 12.12: Scheme to show the origin of different parts of the tongue.

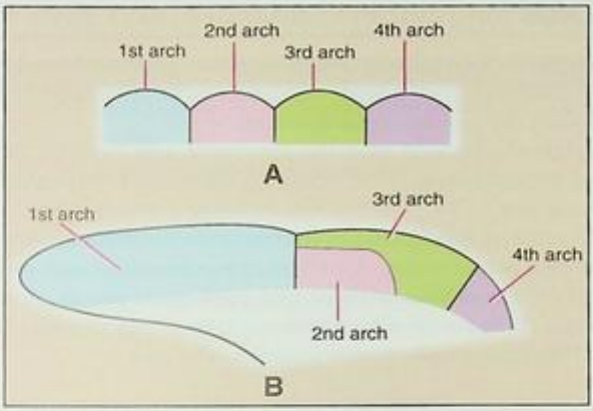

Fig. 12.13: Scheme to show how the second arch is buried by overgrowth of the third arch, during development of the tongue.

Clinical Correlation

Anomalies of the Tongue

- The tongue may be too large (***macroglossia***) or too small (***microglossia***). Very rarely the tongue may be absent (***aglossia***).
- The tongue may be bifid because of non-fusion of the two lingual swellings.
- The apical part of the tongue may be anchored to the floor of the mouth by an overdeveloped frenulum. This condition is called ***ankyloglossia*** or tongue-tie. It interferes with speech. Occasionally, the tongue may be adherent, to the palate (***ankyloglossia superior***).
- A red, rhomboid-shaped smooth zone may be present on the tongue in front of the foramen caecum. It is considered to be the result of persistence of the tuberculum impar.
- Thyroid tissue may be present in the tongue either under the mucosa or within the muscles.
- Remnants of the thyroglossal duct may form cysts at the base of the tongue.
- The surface of the tongue may show fissures.

Table 12.2: Summary of the derivation of the components of the tongue.

Summary of Derivation of Components of the Tongue				
Part of tongue	Embryonic part from which derived	General sensation	Nerve supply Taste	Motor
Epithelium over anterior two-thirds	First arch	Mandibular (lingual br.)	Facial (Chorda tympani)	
Epithelium over posterior two-thirds	Third arch	Glossopharyngeal	Glossopharyngeal	
Epithelium over posterior-most part	Fourth arch	Superior laryngeal br. of vagus	Superior laryngeal br. of vagus	
MUSCLE	Occipital myotomes			Hypoglossal

SALIVARY GLANDS

The salivary glands develop as outgrowths of the buccal epithelium. The outgrowths are at first solid and are later canalised. They branch repeatedly to form the duct system. The terminal parts of the duct system develop into secretory acini.

As the salivary glands develop near the junctional area between the ectoderm of the stomatodaeum and the endoderm of the foregut, it is difficult to determine whether they are ectodermal or endodermal.

The outgrowth for the ***parotid gland*** arises in relation to the line along which the maxillary and mandibular processes fuse to form the cheek. It is generally considered to be ectodermal.

The outgrowths for the ***submandibular*** and ***sublingual*** glands arise in relation to the linguo-gingival sulcus. They are usually considered to be of endodermal origin.

One or more of the salivary glands may sometimes be absent.

TONSILS

The ***palatine tonsil*** develops (on each side) in relation to the lateral part of the second pharyngeal pouch. The endoderm lining the pouch undergoes considerable proliferation. It invades the underlying mesoderm of second arch, which forms the tonsillar stroma. As a result, most of the pouch is obliterated. Lymphocytes collect in relation to the tonsillar stroma beneath the epithelium. It is not certain whether these lymphocytes differentiate in situ or are derived from blood (possibly, they come to the tonsil from the liver as lymphoblasts). The ***intratonsillar cleft*** or ***tonsillar fossa*** is believed to represent a persisting part of the second pharyngeal pouch.

Similar epithelial proliferations and aggregations of lymphoid tissue give rise to the ***tubal tonsils***, the ***lingual tonsil*** and the ***pharyngeal tonsils***.

PHARYNX

The pharynx is derived from the cranial-most part of the foregut. We have already seen that the endodermal pouches are formed in relation to the lateral wall of this part of the foregut. In addition, the floor of the foregut gives rise to a midline diverticulum (Fig. 14.20) from which the entire respiratory system is developed (Chapter 14).

Most of the endodermal pouches lose contact with the pharyngeal wall. The opening of the pharyngo-tympanic tube represents the site of origin of the tubotympanic recess. The site of the midline respiratory diverticulum is represented by the inlet of the larynx.

With the establishment of the palate and mouth, the pharynx shows a subdivision into nasopharynx, oropharynx and laryngopharynx.

The muscles forming the wall of the pharynx are derived from the 3rd and subsequent pharyngeal arches.

TIMETABLE OF SOME EVENTS DESCRIBED IN THIS CHAPTER

Age	Developmental Events
4 weeks	Tongue starts forming i.e., two lateral lingual swelling and tuberculum impar become visible.
5 weeks	Hypobranchial eminence becomes visible.
6 weeks	Dental laminae of upper and lower jaws are established.
7 weeks	Salivary glands starts developing.
8 weeks	Enamel organs are formed.
10 weeks	Enamel organ becomes cup-shaped.
3 months	Formation of tonsil begins.
5 months	The tonsil is infiltrated by lymphatic tissue.
6 months	Enamel and dentine have formed considerably. Formation of tongue is almost complete.
Just before birth	Cementum is formed.
After birth	Periodontal ligaments are formed before eruption of teeth.

Chapter 13

Alimentary System—II: Gastrointestinal Tract

HIGHLIGHTS

- ***Endoderm***, which is at first in the form of a flat sheet, is converted into a tube by formation of head, tail and lateral folds of the embryonic disc. This tube is the ***gut***.
- The gut consists of ***foregut***, ***midgut*** and ***hindgut***. The midgut is at first in wide communication with the yolk sac (Fig. 13.1). Later it becomes tubular. Part of it forms a loop that is divisible into ***prearterial*** and ***postarterial*** segments (Fig. 13.2).
- The most caudal part of the hindgut is the cloaca. It is partitioned to form the ***primitive rectum*** (dorsal) and the ***primitive urogenital sinus*** (Fig. 13.4).
- The ***oesophagus*** is derived from the foregut.
- The ***stomach*** is derived from the foregut (Fig. 13.12).
- ***Duodenum***: The superior part and the upper half of the descending part, is derived from the foregut. The rest of the duodenum develops from the midgut.
- The ***jejunum*** and ***ileum*** are derived from the prearterial segment of the midgut loop.
- The postarterial segment of the midgut loop gives off a caecal bud. The ***caecum*** and ***appendix*** are formed by enlargement of this bud.
- The ***ascending colon*** develops from the postarterial segment of the midgut loop.
- After its formation the gut undergoes ***rotation***. As a result the caecum and ascending colon come to lie on the right side; and the jejunum and ileum lie mainly in the left half of the abdominal cavity.

INTRODUCTION

The epithelial lining of the various parts of the gastrointestinal tract is of endodermal origin. In the region of the mouth and the anal canal, however, some of the epithelium is derived from the ectoderm of the stomatodaeum and of the proctodaeum respectively.

We have seen that as a result of the establishment of the head and tail folds, part of the cavity of the yolk sac is enclosed within the embryo to form the primitive gut (Fig. 5.15). The primitive gut is in free communication with the rest of the yolk sac. The part of the gut cranial to this communication is the ***foregut***, the part caudal to the communication is the ***hindgut***, while the intervening part is the ***midgut*** (Fig. 13.1). Cranially, the foregut is separated from the stomatodaeum by the buccopharyngeal membrane. Caudally, the hindgut is separated from the proctodaeum by the cloacal membrane. At a later stage of development, these membranes disappear, and the gut opens to the exterior at its two ends.

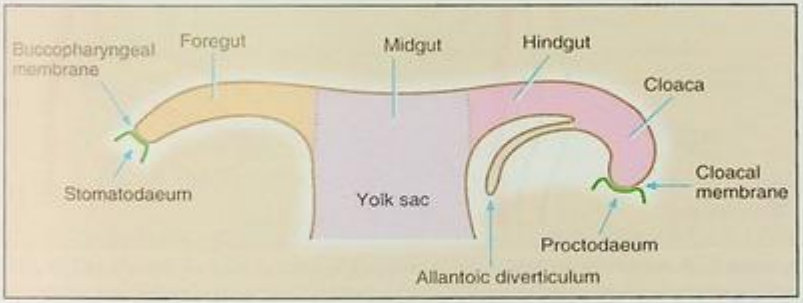

Fig. 13.1: Parts of the primitive gut. Compare with Fig. 5.11.

While the gut is being formed, the circulatory system of the embryo undergoes considerable development. A midline artery, the dorsal aorta, is established and comes to lie just dorsal to the gut (Fig. 13.2). It gives off a series of branches to the gut. Those in the region of the midgut, initially, run right up to the yolk sac and are, therefore, called ***vitelline arteries***. Subsequently, most of these ventral branches of the dorsal aorta disappear and only three of them remain; one for the foregut, one for the midgut and one for the hindgut. The artery of the abdominal part of the foregut is the ***coeliac***, that of the midgut is the superior mesenteric and that of the hindgut is the ***inferior mesenteric***.

The wide communication between the yolk sac and the midgut is gradually narrowed down (Fig. 13.2B) with the result that the midgut becomes tubular. Thereafter, the midgut assumes the form of a loop (Fig. 13.2C). The superior mesenteric artery now runs in the mesentery of this loop to its apex. The loop can, therefore, be said to have a ***proximal***, or ***pre-arterial, segment*** and a ***distal***, or ***postarterial, segment***. A bud (called ***caecal bud***) soon arises from the post-arterial segment very near the apex of the loop (Fig. 13.2D).

For a number of weeks, the midgut loop comes to lie outside the abdominal cavity of the embryo. It passes through the umbilical opening into a part of the extra-embryonic coelom that persists in relation to the most proximal part of the umbilical cord. The loop is subsequently withdrawn into the abdominal cavity.

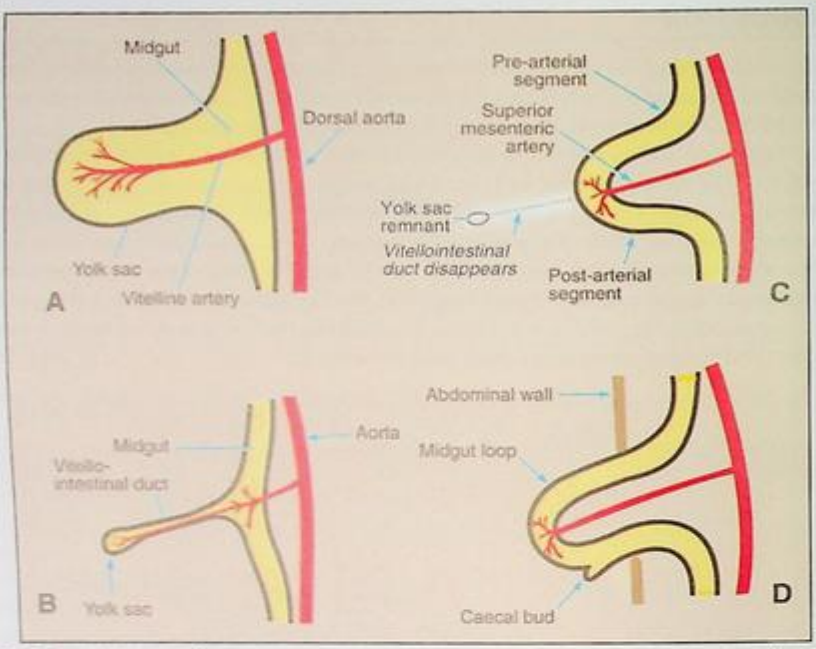

Fig. 13.2: Establishment of the midgut loop. (A) Midgut in wide communication with the yolk sac. Note vitelline artery passing from dorsal aorta to the yolk sac. (B) Yolk sac much smaller, and attached to midgut through a narrow vitello-intestinal duct. The original vitelline artery gives branches to the midgut. (C) The midgut increases in length and forms a loop. The loop has a prearterial segment and a postarterial segment. (D) Midgut loop passes out of abdominal cavity. The caecal bud arises from the postarterial segment.

While considering the formation of the allantoic diverticulum, it was seen that the diverticulum opens into the ventral aspect of the hindgut (Figs. 5.14, 13.1). The part of the hindgut caudal to the attachment of the allantoic diverticulum is called the ***cloaca***. The cloaca soon shows a subdivision into a broad ventral part and a narrow dorsal part (Fig. 13.3). These two parts are separated from each other by the formation of the ***urorectal septum***, which

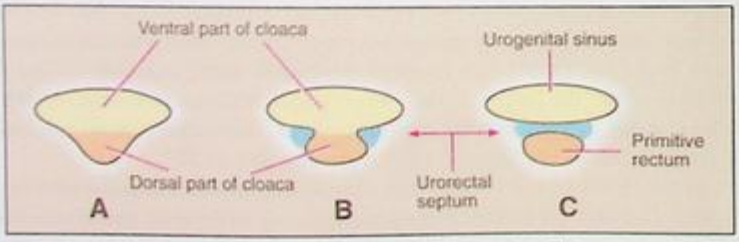

Fig. 13.3: Formation of urorectal septum as seen in transverse sections. This septum divides the cloaca into the primitive urogenital sinus and the primitive rectum.

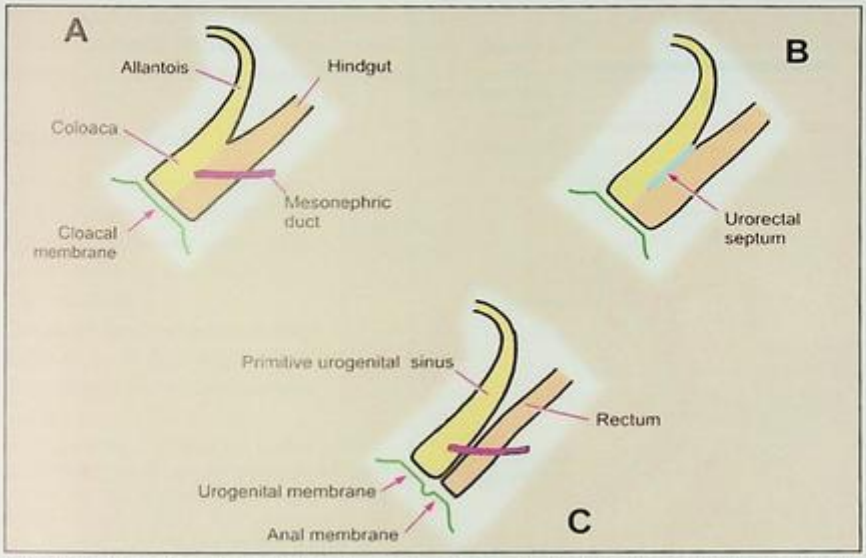

Fig. 13.4: Formation of urorectal septum as seen in longitudinal sections through the cloaca.

is first formed in the angle between the allantois and the cloaca (Figs. 13.4A, B). The ventral subdivision of the cloaca is now called the ***primitive urogenital sinus***, and gives origin to some parts of the urogenital system. The dorsal part is called the ***primitive rectum***. It forms the rectum, and part of the anal canal. The urorectal septum grows towards the cloacal membrane and eventually fuses with it (Fig. 13.4C). The cloacal membrane is now divided into a ventral ***urogenital membrane***, related to the urogenital sinus, and a dorsal ***anal membrane*** related to the rectum. Mesoderm around the anal membrane becomes heaped up with the result that the anal membrane comes to lie at the bottom of a pit called the anal pit, or proctodaeum. The anal pit contributes to the formation of the anal canal.

Derivatives of Foregut

- Part of the floor of the mouth, including the tongue.
- Pharynx.
- Various derivatives of the pharyngeal pouches, and the thyroid.
- Oesophagus.
- Stomach.
- Duodenum: Whole of the superior (first) part and upper half of the descending (second) part (up to the major duodenal papilla).
- Liver and extra-hepatic biliary system.
- Pancreas.
- Respiratory system.

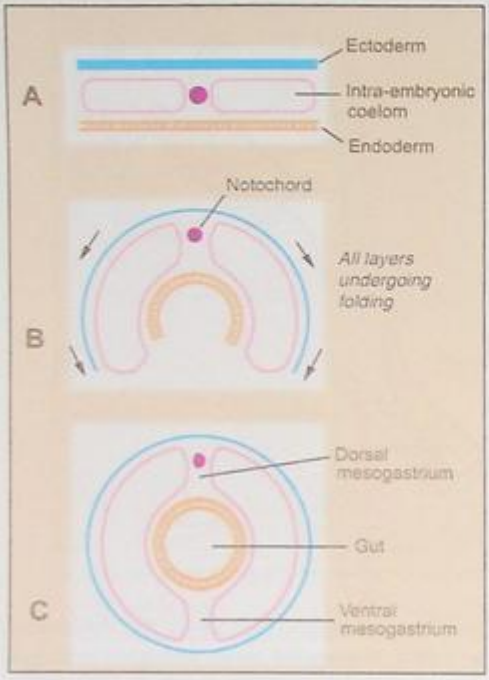

Fig. 13.5: Scheme to show how the gut is formed by lateral folding of the embryonic disc. (A) Embryonic disc before lateral folding. (B) The lateral edges of the disc grow in a ventral direction. (C) The edges pass medially to meet in the middle line. In this way, the layer of endoderm is converted into a tube which is the future gut. The ectoderm also meets in the midline and cuts off the coelom from the exterior.

Derivatives of Midgut

- Duodenum: Descending (second) part distal to the major papilla; horizontal (third) and ascending (fourth) parts.
- Jejunum.
- Ileum.
- Caecum and appendix.
- Ascending colon.
- Right two-thirds of transverse colon.

Derivatives of Hindgut

- Left one-third of transverse colon.
- Descending and pelvic colon.
- Rectum.
- Upper part of anal canal.
- Parts of the urogenital system derived from the primitive urogenital sinus.

At this stage, it may be noted that endoderm of the foregut, midgut and hindgut gives rise only to the epithelial lining of the intestinal tract. The smooth muscle, connective tissue and peritoneum are derived from splanchnopleuric mesoderm (Fig. 13.6).

Arteries of the Gut

- The ***coeliac artery*** is the artery of the foregut. It supplies the gut from the lower part of the oesophagus to the middle of the duodenum.
- The ***superior mesenteric artery*** is the artery of the midgut.
- The ***inferior mesenteric artery*** is the artery of the hindgut.

At this stage, it might be noted that the endoderm of the foregut, midgut and hindgut gives rise only to the epithelial lining of the intestinal tract. Smooth muscle, connective tissue and peritoneum are derived from splanchnic mesoderm (Fig. 13.6).

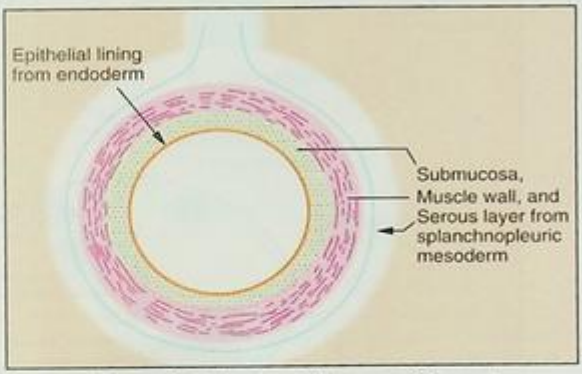

Fig. 13.6: Derivation of the coats of the gut.

DERIVATION OF INDIVIDUAL PARTS OF ALIMENTARY TRACT

Oesophagus

The oesophagus is developed from the part of the foregut between the pharynx and the stomach. It is at first short but elongates with the formation of the neck, with the descent of the diaphragm, and with the enlargement of the pleural cavities.

The musculature of the oesophagus is derived from mesenchyme surrounding the foregut. Around the upper two-thirds of the oesophagus, the mesenchyme forms striated muscle. Around the lower one-third, the muscle formed is smooth (as over the rest of the gut).

Stomach

The stomach is first seen as a fusiform dilatation of the foregut just distal to the oesophagus. Its dorsal border is attached to the posterior abdominal wall by a fold of peritoneum called the ***dorsal mesogastrium***. Its ventral border is attached to the septum transversum by another fold of peritoneum called the ***ventral mesogastrium*** (Figs. 13.7A, B).

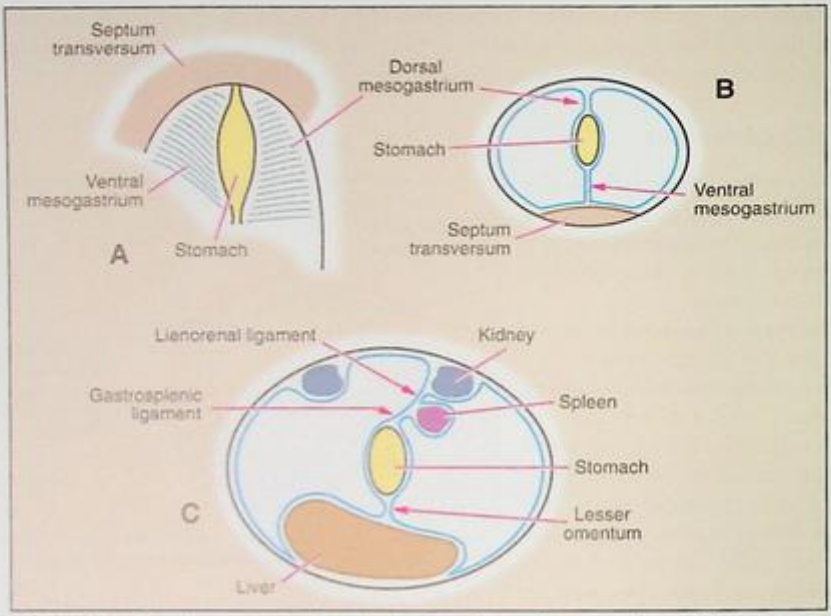

Fig. 13.7: (A) Side view of stomach showing the dorsal and ventral mesogastriums. (B) Transverse section through 'A' showing that the ventral mesogastrium connects the stomach to the septum transversum. (C) The most important remnant of the ventral mesogastrium is the lesser omentum. It passes from the stomach to the liver (which develops in the septum transversum). The spleen is formed in relation to the dorsal mesogastrium. Its formation divides this part of the dorsal mesogastrium into the gastrosplenic ligament and the lienorenal ligament.

Subsequently, the liver and the diaphragm are formed in the substance of the septum transversum. The ventral mesogastrium now passes from the stomach to the liver, and from the liver to the diaphragm and anterior abdominal wall (Fig. 13.7C). The part of the ventral mesogastrium between the liver and the stomach becomes the ***lesser omentum***, while the part between the liver and the diaphragm (and anterior abdominal wall) gives rise to the ***coronary***, and ***falciform*** ligaments.

Similarly, the dorsal mesogastrium is divided by the development of the spleen into a part between stomach and spleen (***gastrosplenic ligament***) and a part between spleen and posterior abdominal wall called the ***lienorenal ligament*** (Fig. 13.7C).

The stomach undergoes differential growth resulting in considerable alteration in its shape and orientation. The original ventral border comes to face upward and to the left and becomes the ***lesser curvature***. The dorsal border now points downwards and to the right and becomes the ***greater curvature***. The original left surface becomes its anterior surface and the original right surface becomes the posterior surface.

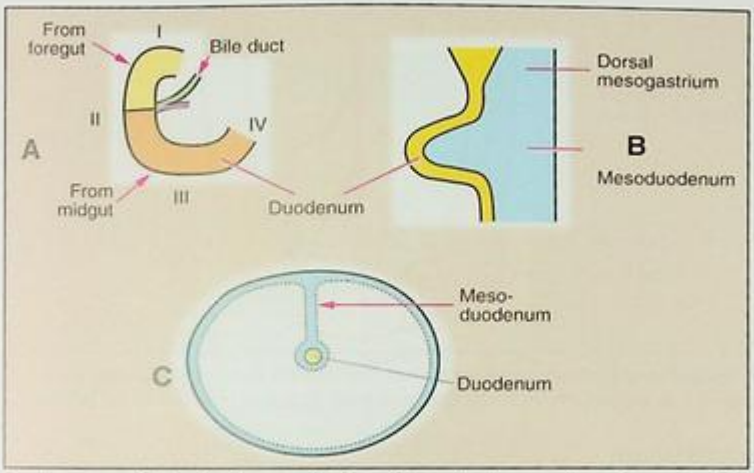

Fig. 13.8: Development of the duodenum. (A) Part of the duodenum above the entry of the bile duct is derived from the foregut; and the part below this level is derived from the midgut. (B) & (C) At first the duodenum has a mesentery called the mesoduodenum. As seen in 'B' this is continuous, cranially, with the dorsal mesogastrium. The mesoduodenum later disappears (Fig. 13.9).

Duodenum

The superior (or first) part, and the upper half of the descending (or second) part of the duodenum are derived from the foregut. The rest of the duodenum develops from the most proximal part of the midgut (Fig. 13.8A). The part of the gut that gives rise to the duodenum forms a loop attached to the posterior abdominal wall by a mesentery (***mesoduodenum***) (Figs. 13.8B, C). Later, this loop falls to the right. The mesoduodenum then fuses with the peritoneum of the posterior abdominal wall with the result that most of the duodenum becomes retroperitoneal (Fig. 13.9). The mesoduodenum persists in relation to a small part of the duodenum adjacent to the pylorus. This is the part seen in radiographs as the duodenal cap.

In keeping with its development, the proximal part of the duodenum is supplied by branches of the coeliac artery, and the distal part by branches of the superior mesenteric.

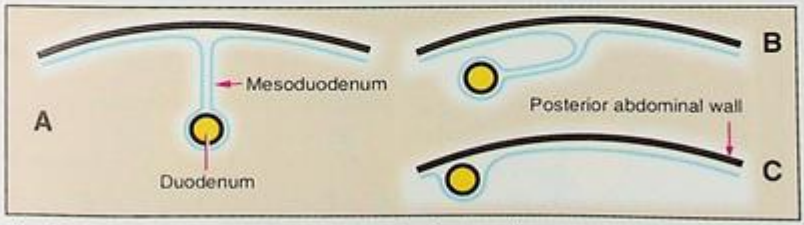

Fig. 13.9: Scheme to show how the mesoduodenum disappears. The duodenum then becomes retroperitoneal.

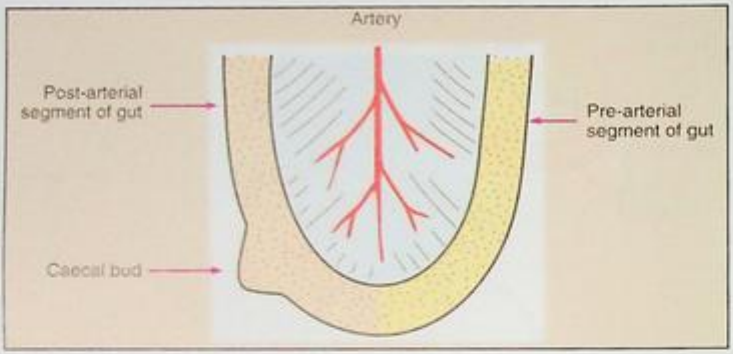

Fig. 13.10: Midgut loop. In this figure the loop has been drawn to correspond with the orientation of the ileocaecal region in postnatal life. (Actually, the prearterial segment is cranial to the postarterial segment).

Jejunum and Ileum

The jejunum and most of the ileum are derived from the pre-arterial segment of the midgut loop. The terminal portion of the ileum is derived from the postarterial segment proximal to the caecal bud (Fig. 13.12).

Caecum and Appendix

We have seen that the caecal bud is a diverticulum that arises from the post-arterial segment of the midgut loop (Fig. 13.10). The caecum and appendix are formed by enlargement of this bud. The proximal part of the bud grows rapidly to form the caecum. Its distal part remains narrow and forms the appendix (Fig. 13.11).

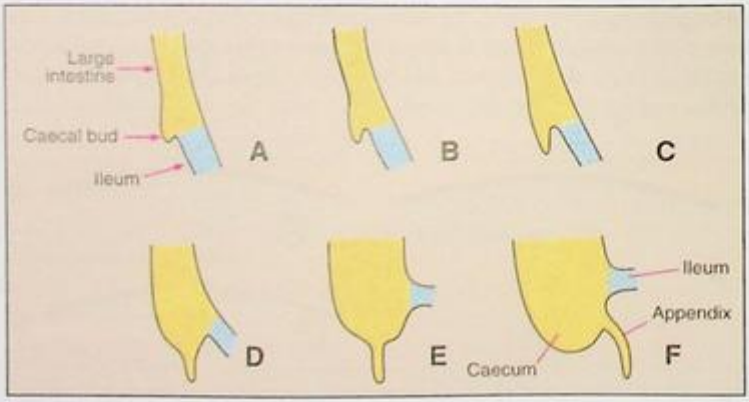

Fig. 13.11: Development of caecum and appendix. The orientation is as in Fig. 13.10.

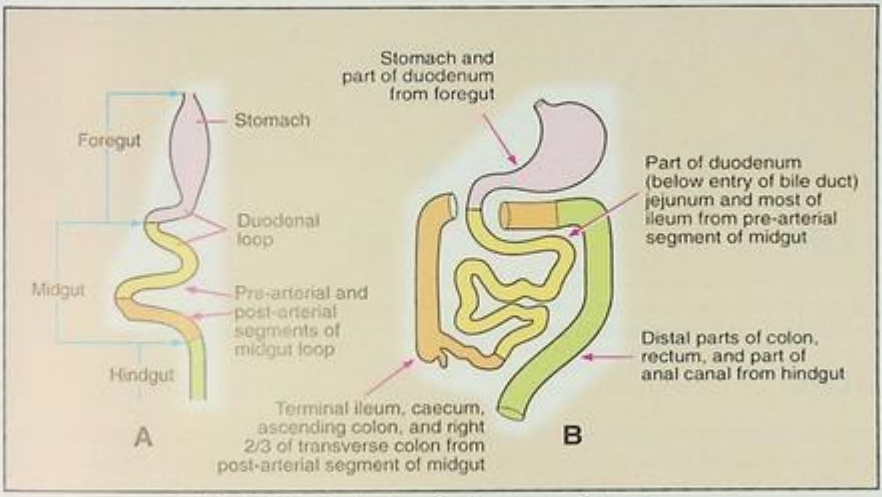

Fig. 13.12: Derivation of various parts of the gut.

During the greater part of fetal life, the appendix arises from the apex of the caecum (Fig. 13.11). Subsequently, the lateral (or right) wall of the caecum grows much more rapidly than the medial (or left) wall with the result that the point of attachment of the appendix comes to lie on the medial side (Fig. 13.11).

Ascending Colon

It develops from the post-arterial segment of the midgut loop (Fig. 13.12) distal to the caecal bud.

Transverse Colon

The right two-thirds of the transverse colon develop from the post-arterial segment of the midgut loop. The left one-third arises from the hindgut. This mode of origin is reflected in its arterial supply; the right two-thirds are supplied by the superior mesenteric artery and the left one-third by the inferior mesenteric.

Descending Colon

The descending colon develops from the hindgut.

Rectum

The rectum is derived from the primitive rectum, i.e. the dorsal subdivision of the cloaca. According to some authorities, the upper part of the rectum is derived from the hindgut proximal to the cloaca.

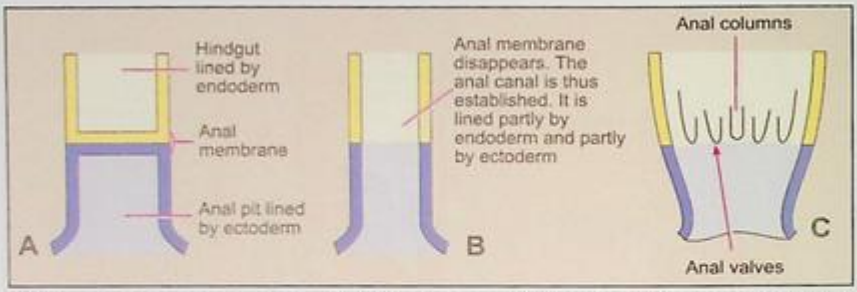

Fig. 13.13: (A) Anal membrane separates hindgut from anal pit. (B) Anal membrane disappears. (C) Scheme to show the parts of the anal canal in which the lining epithelium is derived from ectoderm or endoderm.

Anal Canal

The anal canal is formed partly from the endoderm of the primitive rectum and partly from the ectoderm of the anal pit or proctodaeum (Fig. 13.13). The line of junction of the endodermal and ectodermal parts is represented by the anal valves (pectinate line).

ROTATION OF THE GUT

We have seen that after its formation, the midgut loop lies outside the abdominal cavity of the embryo, in a part of the extra-embryonic coelom that persists near the umbilicus. The loop has a pre-arterial, or proximal, segment and a post-arterial, or distal, segment (Fig. 13.2C). Initially, the loop lies in the sagittal plane, its proximal segment being cranial and ventral to the distal segment (Fig. 13.14A). The midgut loop now undergoes rotation. This rotation plays a very important part in establishing the definitive relationships of the various parts of the intestine. The steps of the rotation must, therefore, be clearly understood.

- Viewed from the ventral side the loop undergoes an anticlockwise rotation by 90°, with the result that it now lies in the horizontal plane. The pre-arterial segment comes to lie on the right side and the post-arterial segment on the left (Compare Figs. 13.14A and B).
- The pre-arterial segment now undergoes great increase in length to form the coils of the jejunum and ileum. These loops still lie outside the abdominal cavity, to the right side of the distal limb (Fig. 13.14C).
- The coils of jejunum and ileum (pre-arterial segment) now return to the abdominal cavity. As they do so, the midgut loop undergoes a further anticlockwise rotation.

As a result, the coils of jejunum and ileum pass behind the superior mesenteric artery into the left half of the abdominal cavity (Fig. 13.14D). The duodenum, therefore, comes to lie behind the artery and the coils of jejunum and ileum occupy the posterior and left part of the abdominal cavity.

- Finally, the post-arterial segment of the midgut loop returns to the abdominal cavity. As it does so, it also rotates in an anticlockwise direction (Fig. 13.14E) with the result that the

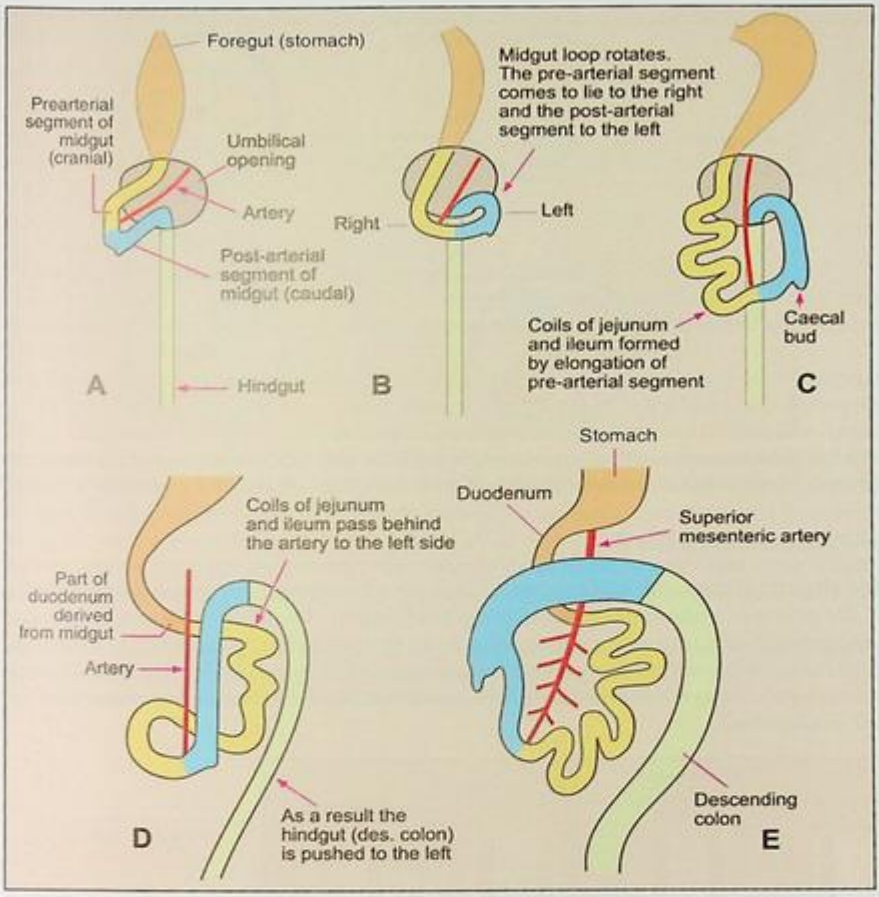

Fig. 13.14: Stages in rotation of the gut. Study these figures carefully along with the corresponding description in the text. In (E), note that the caecum moves to the right, and the transverse colon now lies in front of the superior mesenteric artery.

transverse colon lies anterior to the superior mesenteric artery, and the caecum comes to lie on the right side. Note that all rotation has taken place in an anticlockwise direction (Fig. 13.15).

- At this stage the caecum lies just below the liver, and an ascending colon cannot be demarcated. Gradually, the caecum descends to the iliac fossa, and the ascending, transverse and descending parts of the colon become distinct.

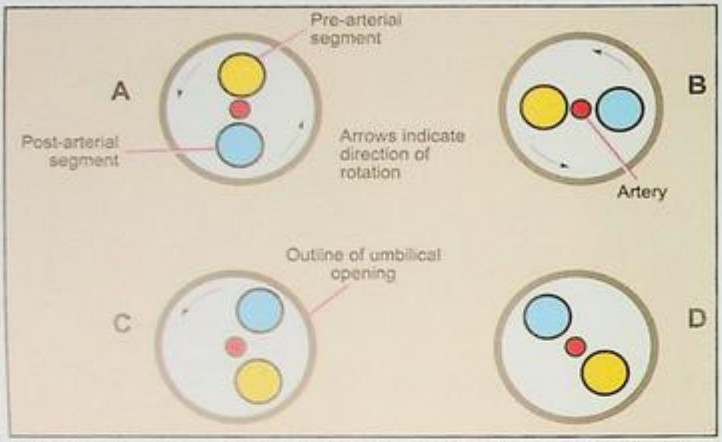

Fig. 13.15: Scheme to show the orientation of the proximal and distal ends of the midgut loop at different phases of the rotation of the gut. Arrows indicate the direction of rotation. Compare with Fig. 13.14.

FIXATION OF THE GUT

At first all parts of the small and large intestines have a mesentery by which they are suspended from the posterior abdominal wall. After the completion of rotation of the gut, the duodenum, the ascending colon, the descending colon and the rectum become retroperitoneal by fusion of their mesenteries with the posterior abdominal wall (as indicated in Fig. 13.9). The original mesentery persists as the ***mesentery of the small intestine***, the ***transverse mesocolon*** and the ***pelvic mesocolon***).

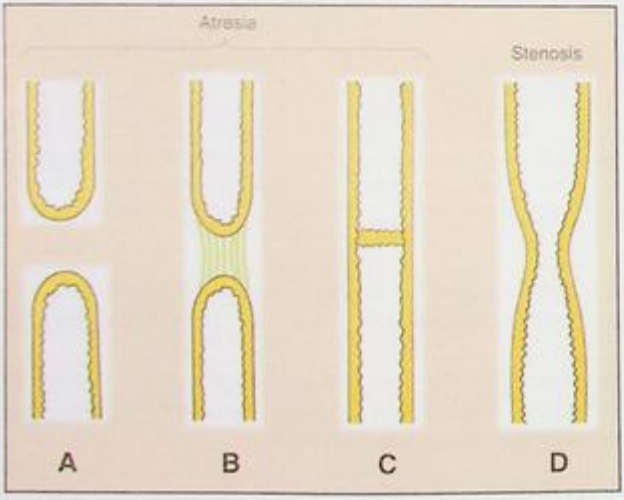

Fig. 13.16: Varieties of atresia and stenosis of the gut.

Clinical Correlation

Developmental Anomalies of the Gut

Congenital Obstruction

This may be due to a variety of causes.

- ***Atresia:*** The continuity of the lumen of the gut is interfered with as follows:
  - A segment of the gut may be missing (Fig. 13.16A).
  - A segment of the gut may be replaced by fibrous tissue (Fig. 13.16B).
  - A septum may block the lumen (Fig. 13.16C).
- ***Stenosis:*** The lumen may be abnormally narrow (Fig. 13.16D).
  (As a normal developmental process, there is epithelial occlusion of the lumen of gut in early stages of development. The gut later gets recanalised. Some cases of atresia, duplication and stenosis of gut may be due to abnormal recanalisation).
- ***Non-development of nerve plexuses*** in the wall of a part of the intestinal tract may result in difficulty in the passage of intestinal contents through the part. Such a defect in the lower part of the colon gives rise to a condition in which the colon proximal to the defective segment becomes greatly distended with its contents. This condition is called ***megacolon*** or ***Hirschsprung's disease*** (Fig. 13.17).
- ***Abnormal thickening of muscular wall:*** This is seen typically at the pyloric end of the stomach (***Congenital pyloric stenosis***) (Fig. 13.18). The thickened muscle bulges into the lumen and narrows it. According to some authorities, the primary cause of this defect is the same as in megacolon.
- ***External pressure*** by abnormal peritoneal bands or abnormal blood vessels. Such bands are often seen in relation to the duodenum (Fig. 13.19). The duodenum may also be compressed by an annular pancreas (Fig. 13.20).
- ***Imperforate anus:*** This is caused by stenosis or atresia of the lower part of the rectum or the anal canal. Some varieties of this condition are shows in Figs, 13.21 and 13.23.

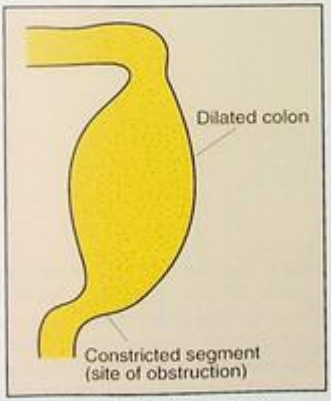

Fig. 13.17: Megacolon.

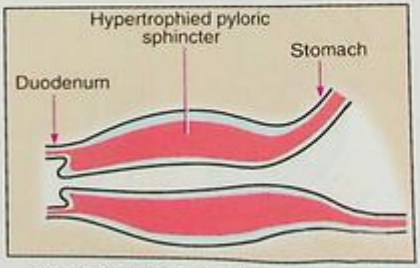

Fig. 13.18: Congenital pyloric stenosis.

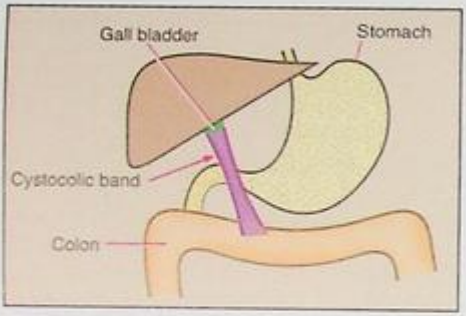

Fig. 13.19: Obstruction of duodenum by a cystocolic band passing from the gall bladder to the transverse colon.

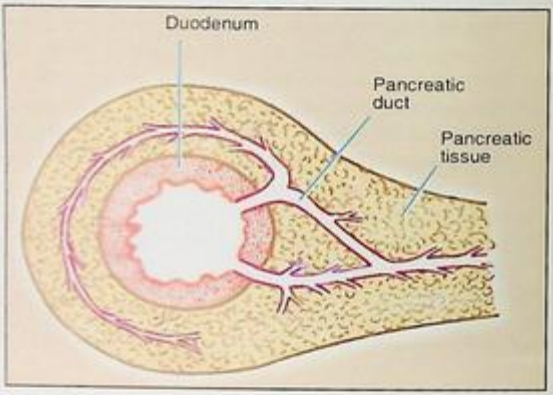

Fig. 13.20: Annular pancreas surrounding the duodenum.

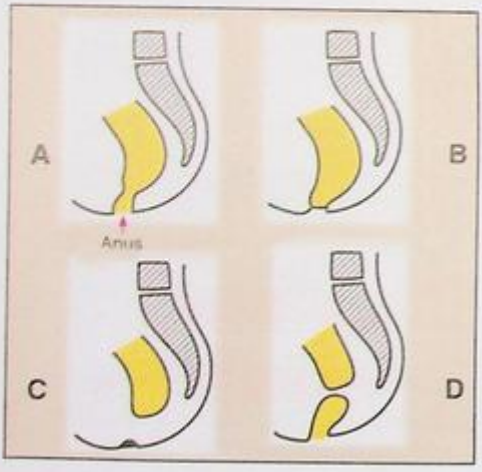

Fig. 13.21: Various types of imperforate anus. (A) Stenosis of anal canal. (B) Persistent anal membrane. (C) The proctodaeum is represented by a solid mass of ectodermal cells and there is a big gap between it and the hindgut (rectum). (D) Upper and lower parts of rectum separated by a gap.

Clinical Correlation

Abnormal Communications or Fistulae

Parts of the gut may have abnormal communications with other cavities or with the surface of the body. These are most frequently seen in relation to the oesophagus and the rectum, and are usually associated with atresia of the normal passage.

- ***Tracheo-oesophageal fistula***: Atresia of the oesophagus is often accompanied by abnormal communications between the oesophagus and trachea as illustrated in Fig. 13.22.
- Incomplete ***septation of the cloaca***: The rectum may communicate with the urinary bladder, urethra, or vagina (Figs. 13.23A to C, E, F), or may open onto the perineum at an abnormal site (Figs. 13.23D, G). These conditions are associated with imperforate anus.

Duplication

Varying lengths of the intestinal tract may be duplicated. The duplicate part may form only a small cyst, or may be of considerable length. It may or may not communicate with the rest of the intestine (Fig. 13.24).

Diverticula

These may arise from any part of the gut. They are most common near the duodenum (Fig. 13.25).

Persistence of a part of the vitello-intestinal duct may give rise to the presence of a diverticulum attached to the terminal part of the ileum. This is called ***Meckel's diverticulum*** or ***diverticulum ilei***. It is of surgical importance as it may undergo inflammation giving rise to symptoms similar to those of appendicitis. Meckel's diverticulum is also of interest as pancreatic tissue or a gastric type of mucosa may be present in its wall. (In such cases ulceration and perforation can occur in the diverticulum). Occasionally the whole of the vitello-intestinal duct, or its distal part alone, may be patent. The former conditions lead to a fecal fistula at the umbilicus. The latter condition leads to formation of an umbilical sinus. The vitello-intestinal duct may be represented by cysts (enterocystoma, or vitelline cyst), or by fibrous cords (Fig. 13.26). Fibrous cords constitute a danger in later life as coils of intestine may get twisted round them leading to strangulation. Remnants of the vitello-intestinal duct may also give rise to growths.

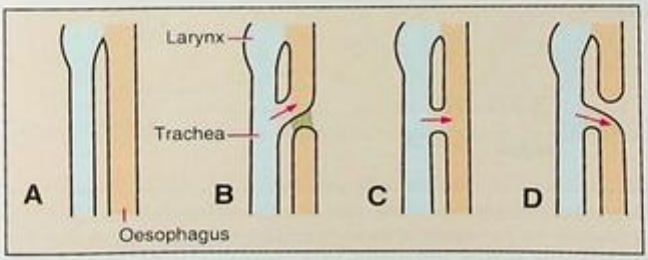

Fig. 13.22: (A) Normal arrangement of trachea and oesophagus. (B), (C), (D) Various forms of tracheo-oesophageal fistulae.

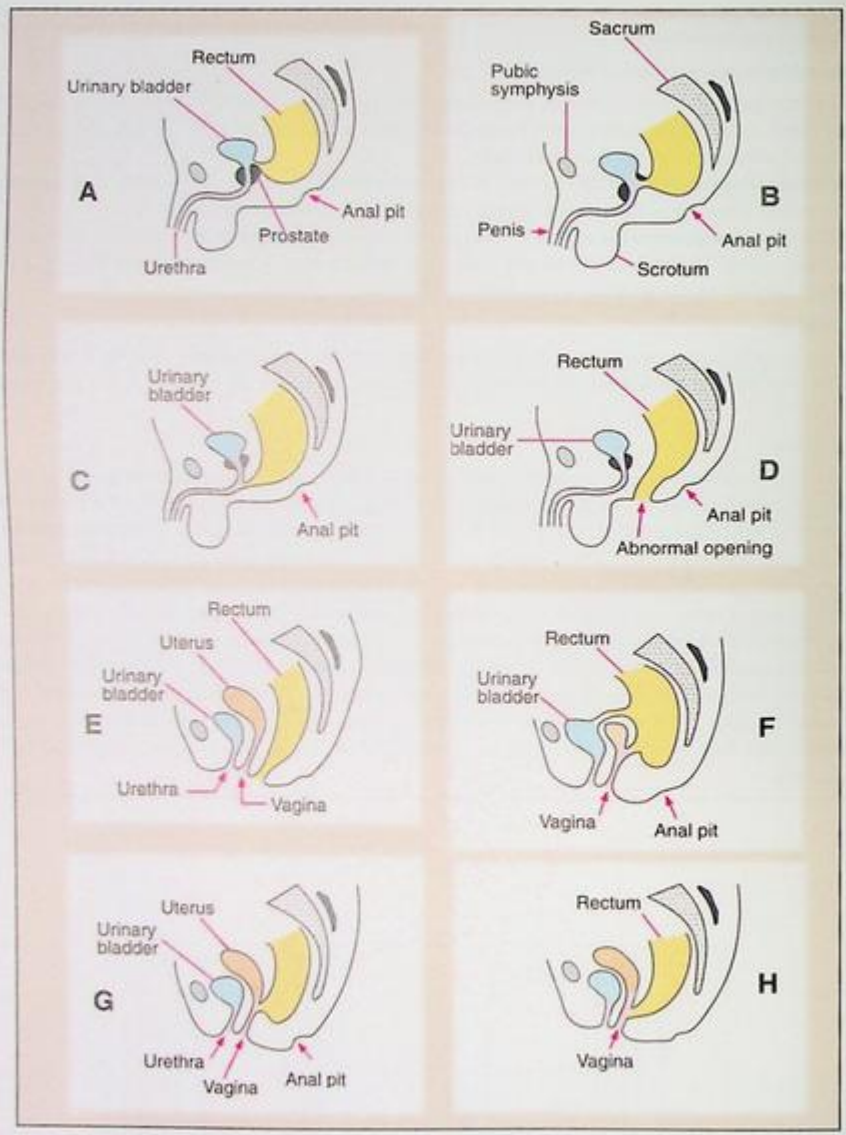

Fig. 13.23: Various types of rectal fistulae in the male (A to D) and female (E to H). The fistula may be between rectum and urinary bladder (i.e. rectovesical) as in (A) and (F), between rectum and urethra (rectourethral) as in (B) and (C), and between rectum and vagina (rectovaginal) as in (G), (H) and (F). More than one type may be present at the same time (F). The rectum may open on to the perineum at an abnormal site (D), (E). In these cases the anal pit is formed at the normal site.

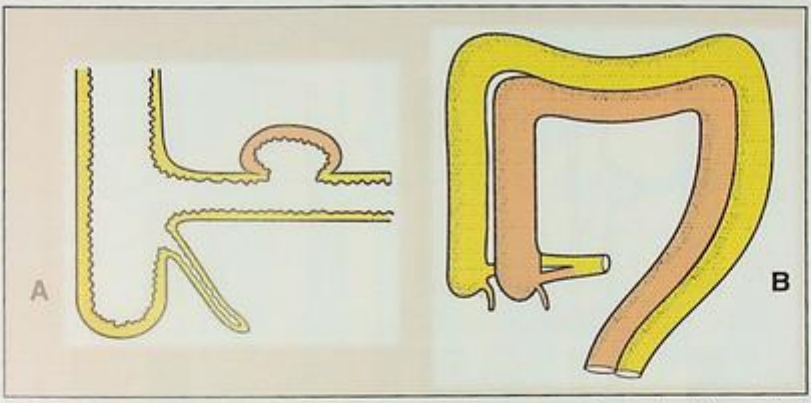

Fig. 13.24: Degrees of duplication of the gut represented by a cyst on the terminal ileum as in (A), and by duplication of the entire colon and terminal ileum as in (B).

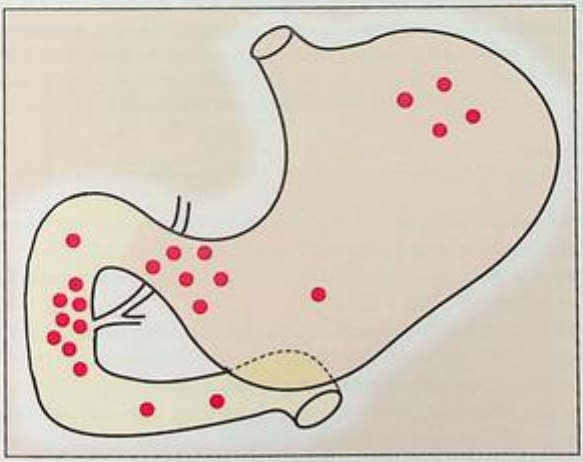

Fig. 13.25: Sites at which congenital diverticula may arise from stomach and duodenum.

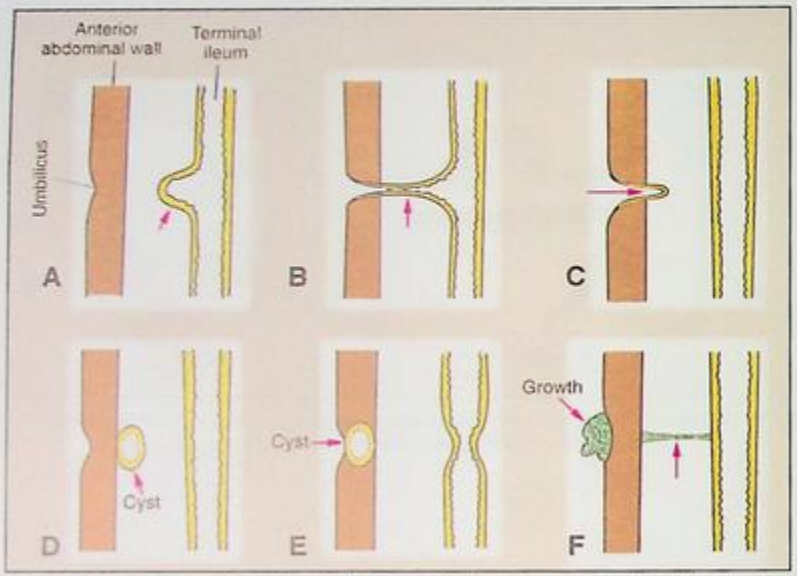

Fig. 13.26: Anomalies in relation to the vitello-intestinal duct (See arrows). (A) Meckel's diverticulum. (B) Patent vitello-intestinal duct. (C) Umbilical sinus. (D) Cyst attached to the abdominal wall. A cyst may also be seen attached to the gut, or embedded in the abdominal wall as shown in 'E'. (E) Stenosis of gut at the site of attachment of duct. (F) Vitello-intestinal duct represented by a fibrous cord. An umbilical growth arising from remnants of the duct is also shown.

Clinical Correlation *contd...*

Errors of Rotation

- ***Non-rotation of the midgut loop***: In this condition the small intestine lies towards the right side of the abdominal cavity, and the large intestine towards the left (Fig. 13.27A).
- ***Reversed rotation***: The transverse colon crosses behind the superior mesenteric artery, and the duodenum crosses in front of it (Fig. 13.27B).
- ***Non-return of umbilical hernia***: Sometimes, the coils of intestine that develop from the midgut loop remain outside the abdominal cavity. The child is born with loops of intestine hanging out of the umbilicus. This condition is called ***exomphalos*** or ***omphalocoele*** (Fig. 13.28).

Loops of intestine, and other abdominal contents may also be seen outside the abdominal cavity for an entirely different reason. In ***congenital umbilical hernia*** the muscle layer and skin are absent in the region of the umbilicus, creating a defect in the abdominal wall through which abdominal contents can pass. Such contents are covered with peritoneum, but in exomphalos they are covered only by amnion.

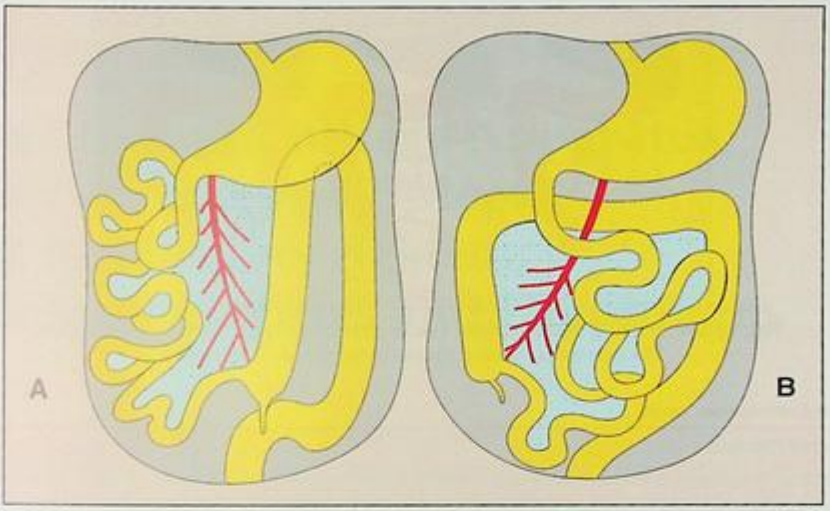

Fig. 13.27: Errors of rotation. (A) Non-rotation. Coils of small intestine lie in the right half of the abdomen, and colon in the left half. (B) Reversed rotation. The duodenum lies anterior to the superior mesenteric artery, and the colon crosses behind it.

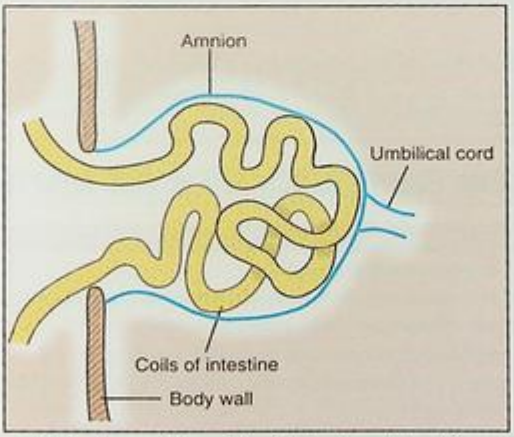

Fig. 13.28: Exomphalos. Coils of intestine derived from the midgut loop fail to return into the abdominal cavity.

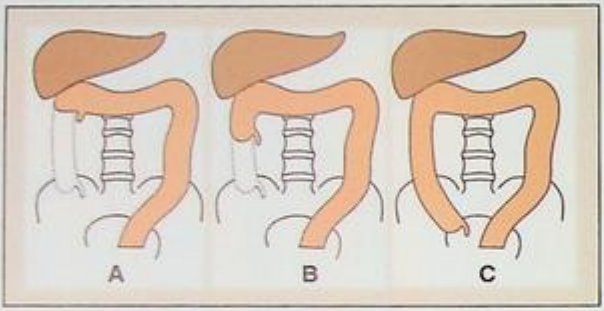

Fig. 13.29: Errors in descent of the caecum. (A) Sub-hepatic. (B) Lumbar. (C) Pelvic. The normal position is shown in dotted line in (A) and (B).

Clinical Correlation *contd...*

Errors of Fixation

- Parts of the intestine that are normally retroperitoneal may have a mesentery. Abnormal mobility of this part of the intestine may result in its twisting. This condition is called volvulus. Twisting of blood vessels to the loop can lead to obstruction of its blood supply.
- Parts of the intestines, that normally have a mesentery, may be fixed by abnormal adhesions of peritoneum.
- The caecum may remain sub-hepatic, or may descend only to the lumbar region. Alternatively, it may descend into the pelvis (Fig. 13.29).

Situs Inversus

In this condition all abdominal and thoracic viscera are laterally transposed, i.e. all parts normally on the right side are seen on the left side, and vice versa. For example, the appendix and duodenum lie on the left side, and the stomach on the right side.

TIMETABLE OF SOME EVENTS DESCRIBED IN THIS CHAPTER

Age	Developmental Events
16 days	Allontoic diverticulum starts appearing.
3 weeks	Gut begins to acquire tubular form because of head and tail foldings. At the end of third week the buccopharyngeal membrane ruptures.
4 weeks	The fusiform shape of the stomach becomes visible.
5 weeks	Stomach rotates and dilates. Intestinal loop begins to form. Caecal bud can be identified.
6 weeks	Intestinal loop is well formed.
	Urorectal septum starts dividing the cloaca.
	Allantois and appendix become clearly visible. Stomach completes its rotation.
7 weeks	Septation of cloaca into rectum and urogenital sinus is completed.
	Intestinal loop herniates out of the abdominal cavity.
8 week	Intestinal loop rotates counter clockwise.
9 weeks	Anal membrane breaks down.
3 months	Head and tail foldings are completed.
	Herniated coils of intestine return to the abdominal cavity.

Chapter 14

The Liver and Biliary Apparatus, The Pancreas and Spleen; The Respiratory System; The Body Cavities and Diaphragm

HIGHLIGHTS

- The *liver and biliary passages* (endoderm) are derived from the ***hepatic bud***. This bud arises from the gut at the junction of foregut and midgut.
- The *pancreas* (endoderm) develops from two buds, dorsal and ventral, that arise from the gut near the junction of foregut and midgut. Most of the pancreas is formed from the dorsal bud. The ventral bud forms part of the head of the pancreas.
- The *spleen* (mesoderm) develops in the dorsal mesogastrium.
- The ***respiratory system*** develops from a median diverticulum of the foregut (endoderm). At its caudal end the diverticulum divides into right and left ***lung buds***.
- The *larynx* and ***trachea*** develop from the part of the respiratory diverticulum cranial to its division.
- The lung buds undergo repeated division to establish the bronchial tree and alveoli of the ***lungs***.
- The peritoneal, pericardial and pleural cavities develop from the intra-embryonic coelom. This coelom at first consists of right and left halves that are connected, across the middle line, cranial to the prochordal plate.
- The ***pericardial cavity*** is derived from the median midline part of the intra-embryonic coelom. After formation of the head fold this cavity comes to lie ventral to the foregut.
- The ***peritoneal cavity*** is derived from the right and left limbs of the intra-embryonic coelom. The two limbs unite to form a single cavity after formation of lateral folds of the embryonic disc.
- The ***pleural cavities*** are formed from right and left pericardio-peritoneal canals that connect the pericardial and peritoneal cavities. Each canal is invaginated by the corresponding lung bud. Enlargement of the bud leads to great enlargement of the canal, and formation of the pleural cavity.
- The ***diaphragm*** develops in relation to the septum transversum. It receives contributions from the pleuro-peritoneal membranes, the body wall and the mesenteries of the oesophagus.

THE LIVER AND BILIARY APPARATUS

THE LIVER

The liver develops from an endodermal bud that arises from the ventral aspect of the gut, at the point of junction between foregut and midgut (Fig. 14.1A). This bud grows into the ventral mesogastrium and passes through it into the septum transversum (Fig. 14.1B). It enlarges, and soon shows a division into a larger cranial part called the ***pars hepatica***, and a smaller caudal portion called the ***pars cystica*** (Fig. 14.1C). The pars hepatica divides into right and left parts, each of which forms one lobe of the liver (Figs. 14.1D, E).

As the right and left divisions of the pars hepatica enlarge and extend into the septum transversum, the cells arising from them are broken up into interlacing columns called ***hepatic trabeculae***. In this process, the umbilical and vitelline veins that lie in the septum transversum, are broken up to form the sinusoids of the liver. Sinusoids are also formed from the mesenchyme of the septum transversum.

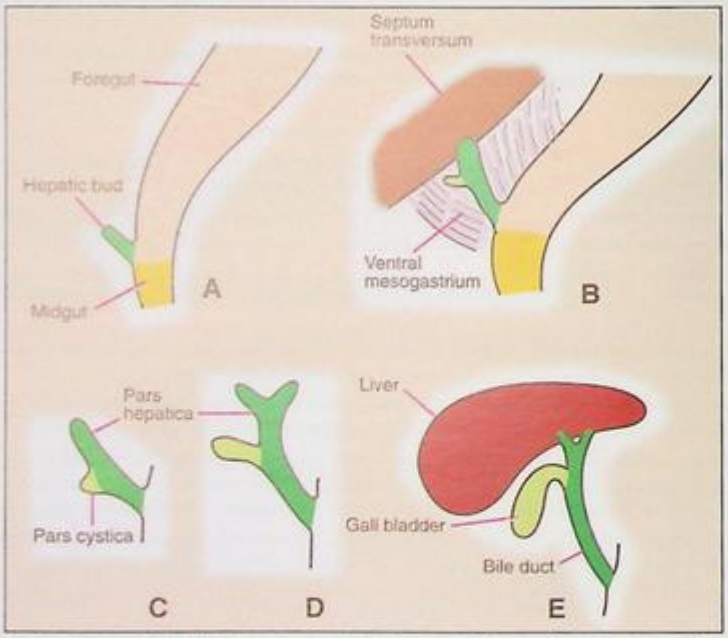

Fig. 14.1: Development of the biliary apparatus. (A) Hepatic bud arises from the gut at the junction of foregut and midgut. (B) It grows towards the septum transversum through the ventral mesogastrium. (C) The bud divides into the pars hepatica (that forms the liver) and the pars cystica (that forms the gall bladder). The part of the hepatic bud proximal to its division forms the bile duct.

The endodermal cells of the hepatic bud give rise to the ***parenchyma of the liver*** and to ***bile capillaries***. The mesoderm of the septum transversum forms the ***capsule*** and fibrous tissue basis of the liver.

The fetal liver is an important centre of blood formation (haemopoiesis). Large aggregations of blood forming cells are present between hepatic cells and blood vessels.

Bile formation begins when the fetus is about three months old. The bile is responsible for the black colour of the first stools (***meconium***) passed by the new born.

Clinical Correlation

Anomalies of the Liver

Anomalies of the liver are rare. Some of them are illustrated in Fig. 14.2.

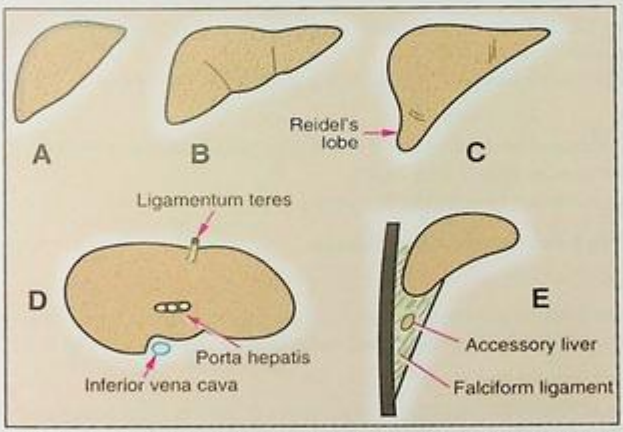

Fig. 14.2: Anomalies of the liver. (A) Rudimentary left lobe. (B) Anomalous lobation. (C) Reidel's lobe. (D) Absence of quadrate lobe associated with absence of gall bladder. (E) Accessory liver in falciform ligament.

GALL BLADDER AND BILIARY PASSAGES

The pars cystica of the hepatic bud gives origin to the ***gall bladder*** and to the ***cystic duct*** (Fig. 14.1). The part of the hepatic bud proximal to the pars cystica forms the ***bile duct***. The bile duct at first opens on the ventral aspect of the developing duodenum. As a result of differential growth of the duodenal wall, and as a result of the rotation of the duodenal loop, it comes to open on the dorsomedial aspect of the duodenum along with the ventral pancreatic bud (see below).

Clinical Correlation

Anomalies of the Gall Bladder

Anomalies of Shape

- The fundus may be folded on itself, to form a cap-like structure called the ***Phrygian cap*** (Fig. 14.3D).
- The wall of the infundibulum may project downwards as a pouch (***Hartmann's pouch***), which may be adherent to the cystic duct or even to the bile duct (Fig. 14.3E).

Anomalies of Position

- The organ may lie transversely on the undersurface of the right lobe of the liver, or may lie under the left lobe (Fig. 14.3G).
- The gall bladder may be lined by peritoneum on all sides. It may be attached to the liver by a fold of peritoneum or may be completely free (***floating gall bladder***) (Fig. 14.3I).
- It may be embedded in the substance of the liver (Fig. 14.3H).

Duplication

- The lumen may be, partially, or completely subdivided by a septum, which may, or may not, extend into the cystic duct (Figs. 14.3A, B).
- The gall bladder may be partially, or completely, duplicated (Figs. 14.3B, C).

Other Anomalies

- The gall bladder may open directly into the bile duct (***sessile bladder***) (Fig. 14.3F).
- The gall bladder may be absent (Fig. 14.4D).
- Diverticula may arise from any part of the organ.

Anomalies of the Extrahepatic Duct System

Abnormal Length

There is considerable variation in the level at which various ducts join each other, with the result that occasionally some of them may become abnormally long, or short (Figs. 14.4A to D).

Abnormal Mode of Termination

- The cystic duct may join the left side of the common hepatic duct, passing either in front of it, or behind it, to reach its left side (Figs. 14.4E to G).
- The cystic duct may end in the right hepatic duct (Fig. 14.4H).
- The cystic duct may pass downwards anterior to the duodenum, before joining the common hepatic duct.
- The bile duct may open into the pyloric, or even the cardiac, end of the stomach.

Atresia

Parts of the duct system, and sometimes the whole of it, may be absent (Fig. 14.5).

Duplication

Parts of the duct system may be duplicated (Fig. 14.6). Accessory ducts arising from the right lobe may terminate in the right hepatic duct, the cystic duct, the bile duct, or even directly into the gall bladder.

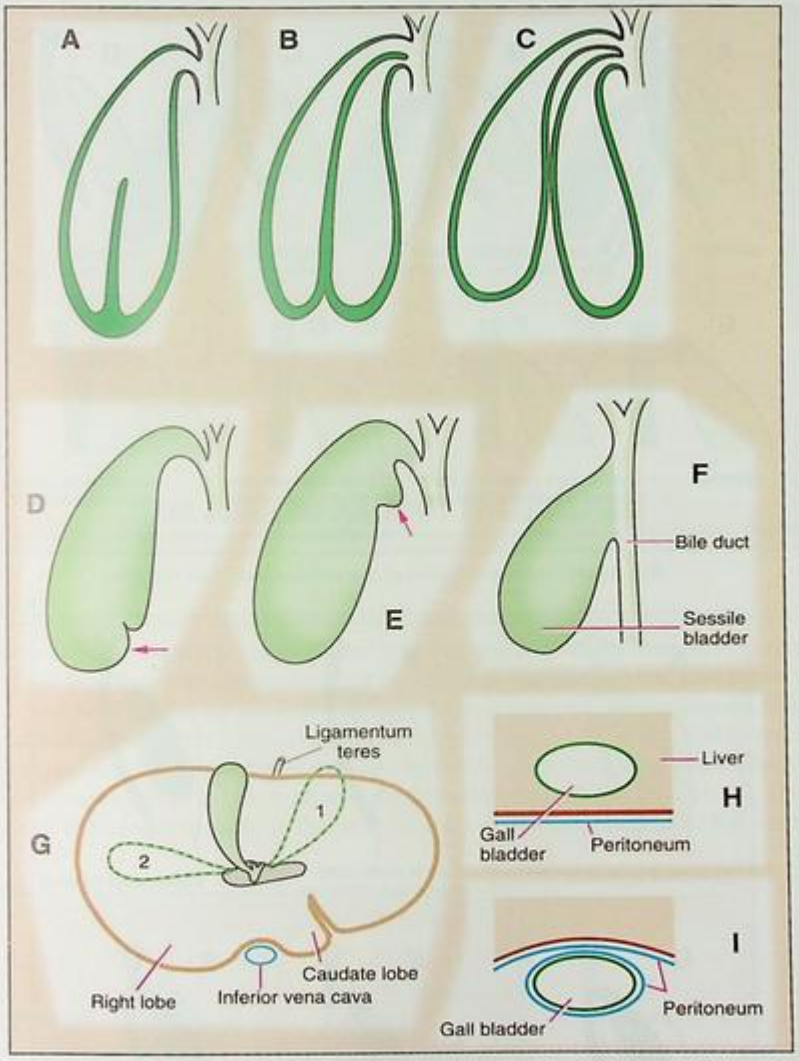

Fig. 14.3: Anomalies of the gall bladder. (A) to (C) Various degrees of subdivision. In (C) there is complete duplication. (D) Phrygian cap. (E) Hartmann's pouch. (F) Sessile gall bladder. (G) Left-sided gall bladder (1) and transverse gall bladder (2). (H) Gall bladder embedded in liver tissue. (I) Floating gall bladder, in which the organ is covered all round by peritoneum.

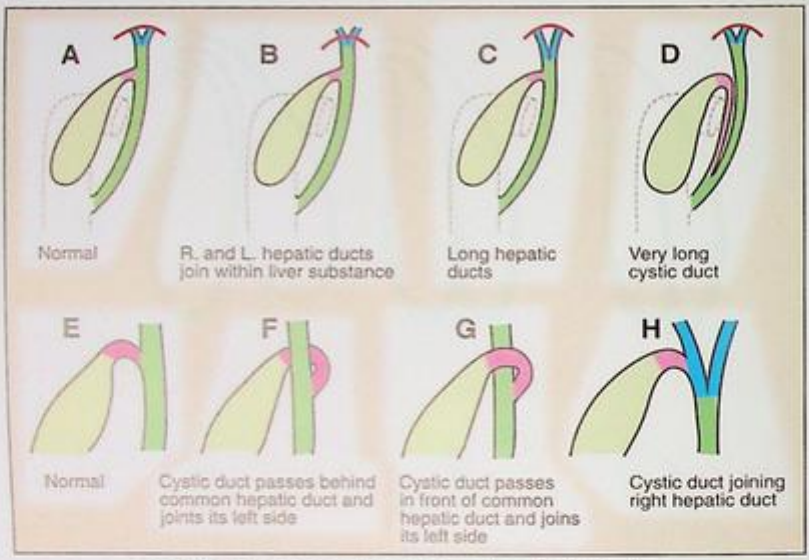

Fig. 14.4: Some anomalies of the extrahepatic duct system.

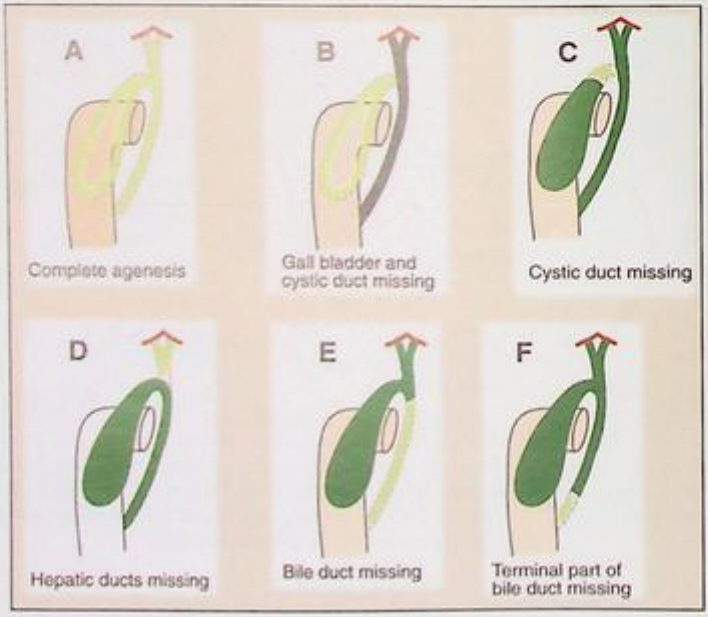

Fig. 14.5: Agenesis of parts of the extrahepatic biliary tract. Missing parts are indicated in light colours.

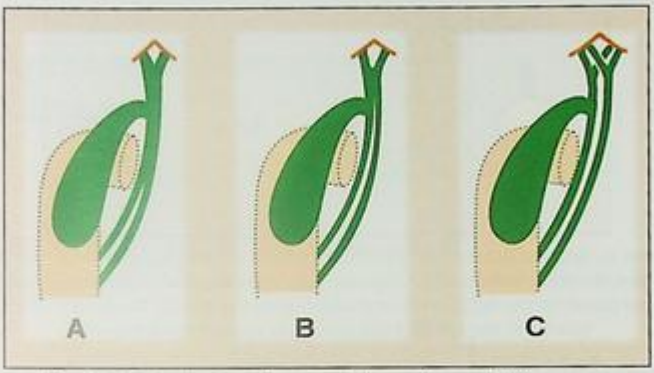

Fig. 14.6: Duplication of parts of the extrahepatic biliary tract.

THE PANCREAS AND THE SPLEEN

PANCREAS

The pancreas develops from two endodermal buds, dorsal and ventral that arise from the part of the gut that later forms the second part of the duodenum. The ***ventral bud*** arises in close relation to the hepatic bud, in the inferior angle between it and the duodenum (Fig. 14.7). The ***dorsal bud*** arises from the dorsal aspect of the gut (Figs. 14.7, 14.8A), and grows into the mesoduodenum and the dorsal mesogastrium. When the duodenal loop falls to the right, the ventral bud comes to point to the right, and the dorsal bud to the left (Fig. 14.8B). Thereafter, as a result of differential growth of the wall of the gut, the attachment of the ventral bud

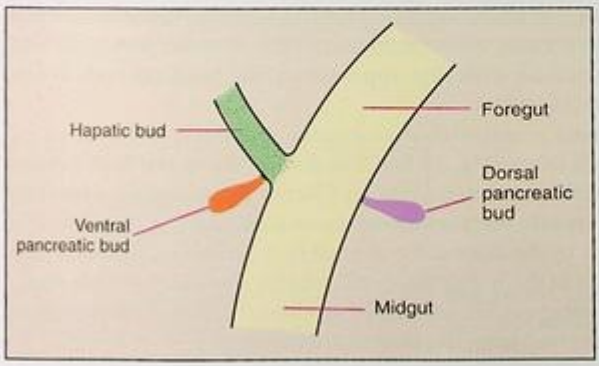

Fig. 14.7: Dorsal and ventral pancreatic buds.

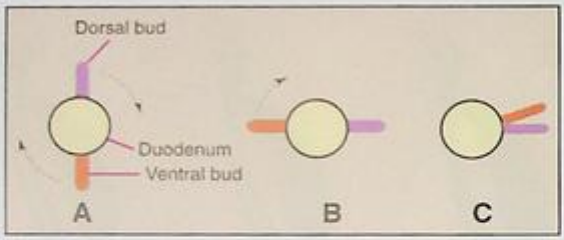

Fig. 14.8: Changes in relative position of pancreatic buds. (A) Initial position in which the ventral and dorsal buds lie in the direction indicated by their names. (B) Position after duodenal loop falls to the right. The ventral bud now points to the right, and the dorsal bud to the left. (C) The attachment of the ventral bud moves to the left and the two buds now lie close together.

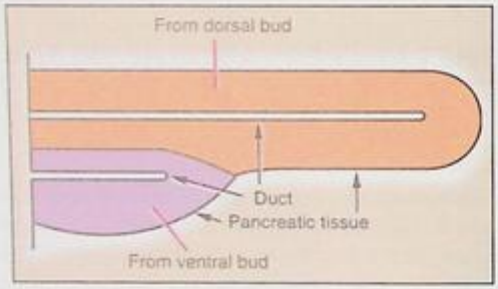

Fig. 14.9: Parts of pancreas derived from ventral and dorsal buds.

(along with the bile duct) also shifts to the left side (Fig. 14.8C). Pancreatic tissue formed from these two buds now fuses to form one mass. The ventral bud forms the lower part of the head, and the uncinate process of the pancreas, while the upper part of the head, the body and the tail are formed from the dorsal bud (Fig. 14.9).

The ***duct system*** of the pancreas is established as follows. The ducts of the dorsal and ventral buds anastomose with each other (Fig. 14.10). The duct of the dorsal bud, between this anastomosis and the duodenum remains narrow and forms the ***accessory pancreatic duct*** (Fig. 14.10C). The ***main pancreatic duct*** is formed, in its distal part, by the duct of the dorsal bud, and in its proximal part by the duct of the ventral bud. The main pancreatic duct, therefore, opens into the duodenum at the major duodenal papilla, along with the bile duct.

The secretory elements of the pancreas are formed by proliferation of the primitive ducts. The ***islets of Langerhans*** are also derived from the primitive duct system.

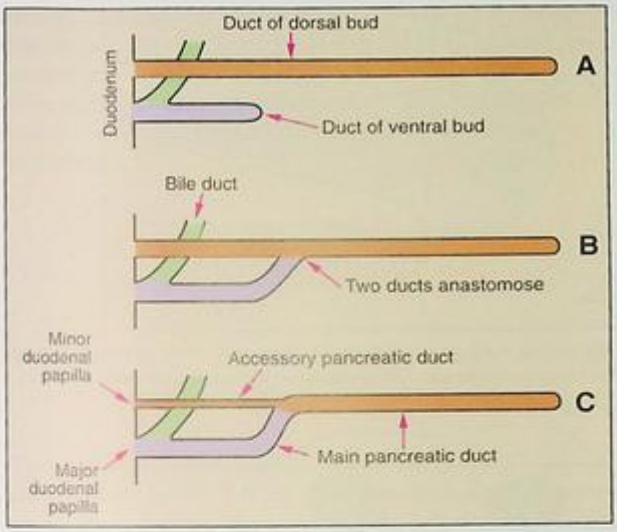

Fig. 14.10: Formation of main and accessory pancreatic ducts. Note that the distal part of the main pancreatic duct is derived from the duct of the dorsal bud; and its proximal part from the duct of the ventral bud.

CLINICAL CORRELATION

Anomalies of the Pancreas

- ***Annular pancreas***: Pancreatic tissue surrounds the duodenum completely and may obstruct it (Fig. 13.20).
- ***Divided pancreas***: The parts of the pancreas derived from the dorsal and ventral buds fail to fuse with each other (Fig. 14.11).
- ***Accessory pancreatic tissue*** may be found in the stomach, duodenum, jejunum, Meckel's diverticulum, gall bladder and spleen.
- ***Inversion of pancreatic ducts***: The embryonic arrangement of the ducts persists and the greater part of the pancreas is drained through the minor duodenal papilla (Fig. 14.12).

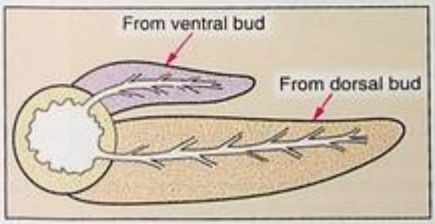

Fig. 14.11: Divided pancreas. The parts of the pancreas arising from dorsal and ventral buds remain separate.

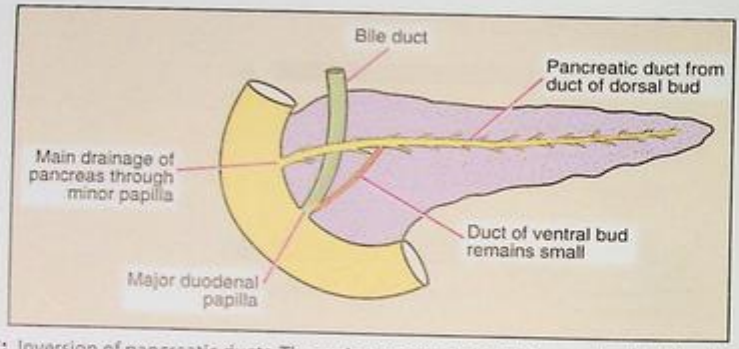

Fig. 14.12: Inversion of pancreatic ducts. The main pancreatic duct is formed entirely by the duct of the dorsal bud, and opens at the minor duodenal papilla. The duct of the ventral bud remains small.

SPLEEN

The spleen develops as a collection of mesenchymal cells in the dorsal mesogastrium (Fig. 14.13A). Some of these cells are contributed by the coelomic epithelium lining the mesogastrium. The mesenchymal cells differentiate into lymphoblasts and other blood forming cells.

As the mesenchymal cells proliferate, they form a mass which projects to the left, and is covered by peritoneum (Fig. 14.13B). The dorsal mesogastrium, in this region, can now be divided into a part extending from the stomach to the spleen (***gastrosplenic ligament***), and

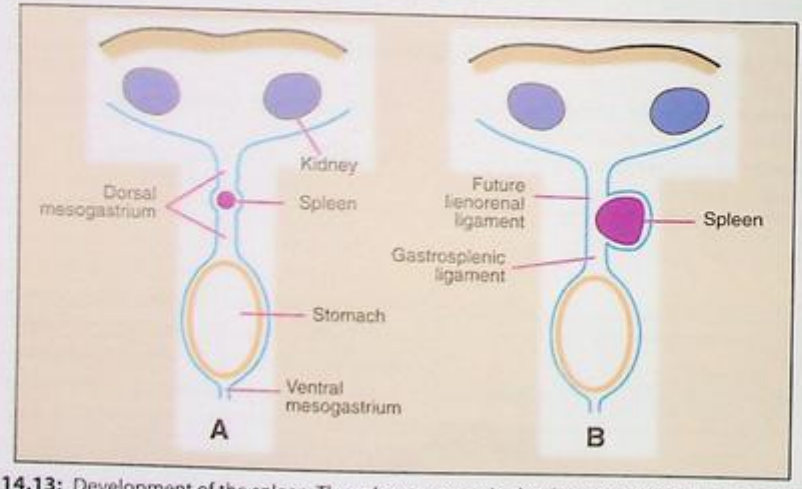

Fig. 14.13: Development of the spleen. The spleen appears in the dorsal mesogastrium as in (A) and soon bulges to the left as in (B).

another part extending from the spleen to the posterior abdominal wall. The latter part fuses with the posterior abdominal wall (Fig. 14.14A) with the result that a fold of peritoneum now passes from the spleen to the left kidney ***(lienorenal ligament)***. As a consequence of this fusion, and as a result of a change in the orientation of the stomach (Fig. 14.14B), the spleen comes to lie on the left side and takes part in forming the left boundary of the lesser sac of peritoneum.

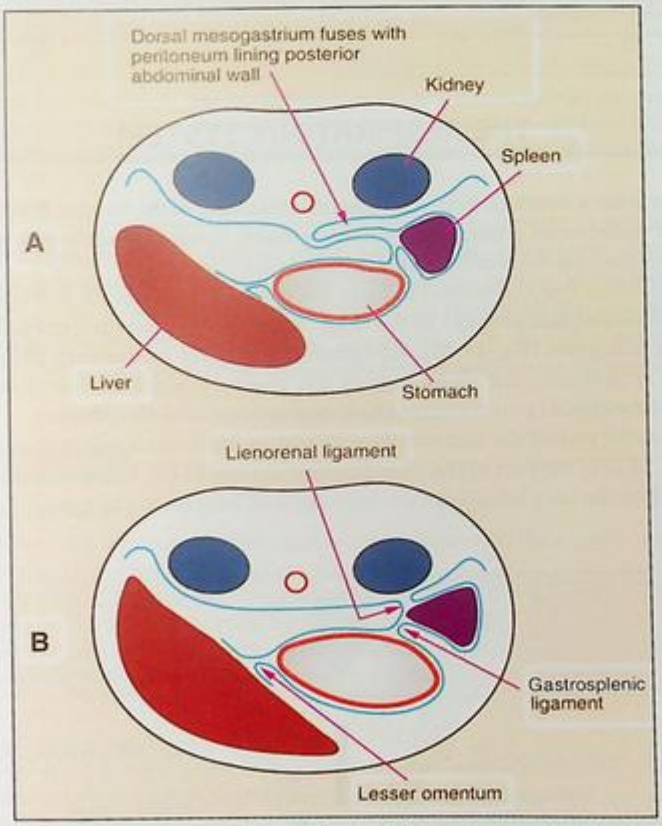

Fig. 14.14: Development of the spleen. First see Fig. 14.6. Note the changing relationship of the spleen to the dorsal mesogastrium and to the lesser sac of peritoneum. In (A) note how part of the dorsal mesogastrium fuses with the posterior abdominal wall. As a result of this change the dorsal mesogastrium is divided (at this level) into the gastrosplenic and lienorenal ligaments.

Clinical Correlation

Anomalies of the Spleen

- The spleen may be lobulated.
- The spleen may, very rarely, be absent.
- Accessory spleens may be seen:
  - at the hilum of the spleen,
  - in the gastrosplenic ligament,
  - in the lienorenal ligament,
  - within the pancreas, and
  - along the splenic artery.
- The spleen lies on the right side of the abdomen in situs inversus. The liver and pancreas are also reversed from side to side.

THE RESPIRATORY SYSTEM

The respiratory system develops from a median diverticulum of the foregut. Its lining epithelium is, therefore, of endodermal origin. The connective tissue, cartilage, and muscle, in relation to the organs of respiration, are derived from splanchnopleuric mesoderm.

The diverticulum that is destined to form the respiratory system is first seen as a midline groove ***(tracheobronchial groove)*** in the floor of the developing pharynx just caudal to the hypobranchial eminence (Fig. 14.15). This groove is flanked by the sixth pharyngeal arches. Soon after its appearance, the distal part of the groove is separated from the oesophagus (Fig. 14.16) but the cranial part continues to communicate with the pharynx.

The free caudal end of the diverticulum becomes bifid, each subdivision being called a ***lung bud*** (Fig. 14.17). The part of the diverticulum cranial to the bifurcation forms the larynx and trachea, while the lung buds form the bronchi and lung parenchyma.

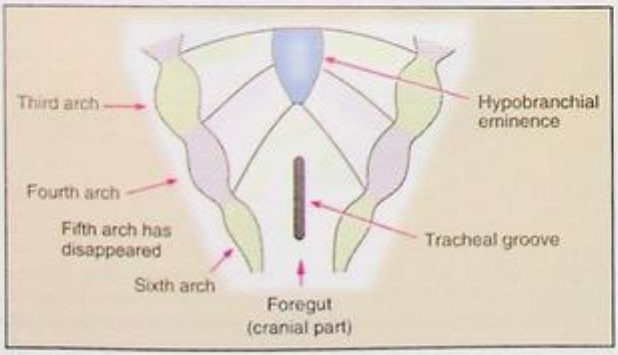

Fig. 14.15: Formation of tracheobronchial groove. Correlate with Fig. 12.1.

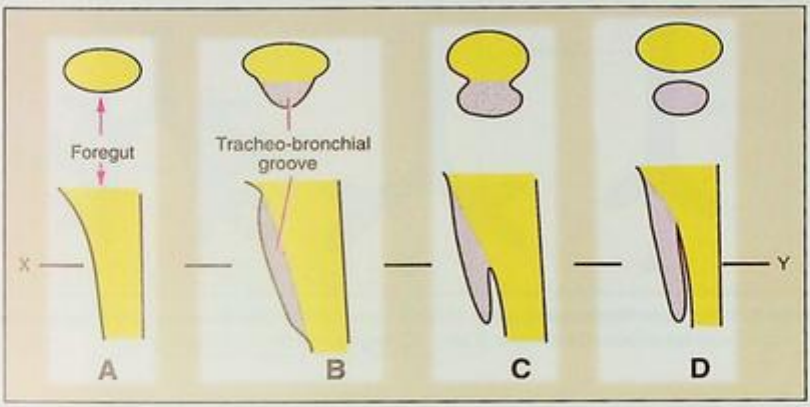

Fig. 14.16: Scheme to show how the respiratory diverticulum separates from the foregut. The upper figures are transverse sections (along the axis XY) of the figures below them. In (C) and (D) note progressive separation of respiratory diverticulum from the foregut, except at the cranial end.

LARYNX

The larynx develops from the cranial-most part of the respiratory diverticulum. The communication, between the diverticulum and the pharynx, persists as the ***inlet*** of the larynx. The caudal part of the hypobranchial eminence forms the ***epiglottis***. The ***thyroid, cricoid and arytenoid cartilages*** are derivatives of the fourth, fifth and sixth pharyngeal arches. The laryngeal muscles are also derived from branchial mesoderm as indicated by their nerve supply.

Clinical Correlation

Anomalies of the Larynx

- ***Laryngocoele:*** In this condition, the laryngeal saccule is abnormally large. It may extend beyond the larynx proper, and may even form a swelling in the neck.
- ***Congenital stenosis or atresia:*** There may be stenosis or atresia of the larynx.
- The entire larynx, or part of it (e.g. vocal cords), may be duplicated.
- ***Laryngoptosis:*** The larynx lies low down in the neck. Part of it may be behind the sternum.
- One or more of the laryngeal cartilages may be absent.

TRACHEA AND BRONCHI

The ***trachea*** develops from the part of the respiratory diverticulum, that lies between the point of its bifurcation and the larynx.

The two primary divisions of the respiratory diverticulum form the ***right and left principal bronchi***. The left division comes to lie more transversely than the right (Fig. 14.17). It soon shows two subdivisions, that represent the two ***lobar bronchi*** of the left lung. The right division divides into three lobar bronchi.

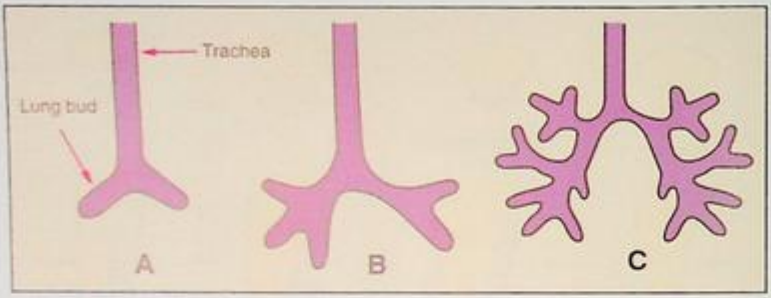

Fig. 14.17: Development of lung buds. (A) Right and left lung buds appear. (B) They divide into lobar bronchi (3 right, 2 left). (C) Segmental bronchi established.

Clinical Correlation

Anomalies of the Trachea

- ***Tracheo-oesophageal fistulae*** have already been described (see Fig. 13.22).
- A ***diverticulum*** may arise from the trachea.
- ***Accessory bronchi*** may arise from the trachea. Such a bronchus:
  - may be blind (Fig. 14.18A);
  - may supply a mass of lung tissue (accessory lobe) which is not a normal part of the lungs (Fig. 14.18B);
  - may replace a normal bronchus (e.g. apical) in one of the lungs (Fig. 14.18C).
- Very rarely the trachea may be absent. The bronchi to the lungs may arise from a blind 'bifurcation' (Fig. 14.19B); or from the oesophagus (Fig. 14.19C).

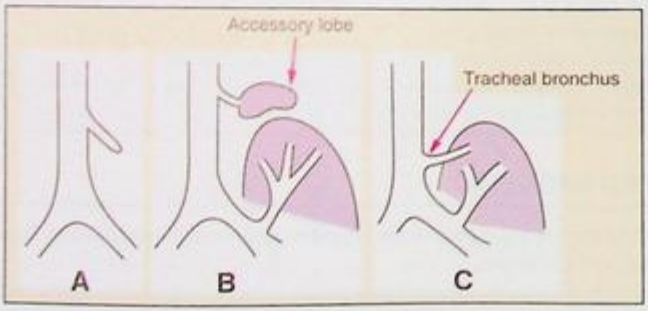

Fig. 14.18: Some varieties of tracheal bronchi. (A) Blind bronchus. (B) Supplying accessory lobe. (C) Replacing apical bronchus.

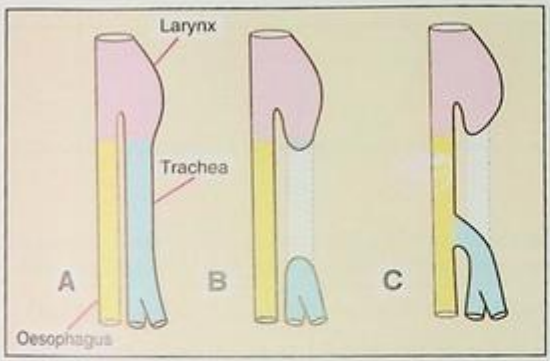

Fig. 14.19: Some anomalies of trachea. (A) Normal. (B) Agenesis. (C) Agenesis along with tracheo-oesophageal fistula.

LUNGS

The substance of the lungs is formed by further subdivisions of the lobar bronchi (Fig. 14.17). (The total number of divisions of each main bronchus are about 17 before birth, and six more after birth). After the establishment of the bronchial tree, ***alveoli*** are formed by expansion of the terminal parts of the tree.

The parts of the lung parenchyma, developing from the lobar bronchi, are separated from one another by mesoderm. This mesoderm forms the connective tissue basis of the lung, and also gives rise to the ***pleura***. As the pleura lines the surface of each lobe separately, the ***lobes*** come to be separated by ***fissures***.

During fetal life, all subdivisions of the bronchial tree are lined by a cubical epithelium. This is the canalicular phase of lung development. With the onset of respiration, after birth, the alveoli become dilated and their lining epithelium becomes thinned.

Within the respiratory passages, some cells become specialised for production of surfactant. This substance forms a thin layer over alveoli and reduces surface tension.

Before birth the respiratory passages are full of fluid which also contains surfactant. When the newborn begins to breathe, the fluid is rapidly absorbed and partly expelled. The surfactant remains as a thin layer lining the alveoli. This prevents collapse of alveoli during expiration. In premature babies, a deficiency of surfactant may cause difficulty in expansion of the lung and can be a cause of death of the baby.

There is considerable increase in the number of alveoli in the postnatal period.

The pulmonary circulation is established early in fetal life. However, most of the blood is at first short circuited through the foramen ovale and the ductus arteriosus. The amount of blood circulating through the lungs progressively increases, and by the seventh month of intrauterine life the circulation is rich enough to provide adequate oxygen for sustaining life. Hence an infant born, thereafter, is viable (i.e. it can live).

The development of the pleural cavities is considered later in this chapter.

Clinical Correlation

Anomalies of the Lungs and Bronchi

Agenesis and Hypoplasia

The whole of one lung, or one of its lobes (and associated bronchi), may fail to develop, or may remain underdeveloped.

Abnormalities of Lobes

- ***Absence of fissures*** that are normally present leads to a reduction in the number of lobes, e.g. absence of the transverse fissure of the right lung results in a right lung with only two lobes (Fig. 14.20A).
- *Presence of Abnormal Fissures*:
  - A transverse fissure may be present on the left side with the result that the left lung has three lobes (Fig. 14.20B).
  - The medial basal segment (cardiac lobe) of the left lung may be separated by a fissure from the rest of the lower lobe (Fig. 14.20D).
  - The superior segment of the lower lobe may be similarly separated (Fig. 14.20C).
  - A part of the upper lobe of the right lung may come to lie medial to the azygos vein. This part is called the azygos lobe (Fig. 14.21). In this condition the azygos vein is suspended from the wall of the thorax by a fold of parietal pleura (mesoazygos).
- *Accessory lobes* are usually connected to bronchi that are not part of the normal bronchial tree. Such bronchi may arise from the:
  - trachea above its bifurcation (upper accessory lobe) (Fig. 14.18B).
  - oesophagus (lower accessory lobe, Fig. 14.22). Occasionally, the lobe may not have any bronchus.
- ***Sequestration of lung tissue:*** An area of embryonic lung tissue may separate from the tracheobronchial tree (sequestration = separation). Such tissue may form a complete lobe (***lobar sequestration***), which may have an independent pleural covering. In other cases the sequestrated tissue may lie within a lobe ***(intralobar sequestration).***
  The sequestrated lung tissue derives its blood supply from an abnormal branch of the aorta. The condition is most frequently seen in the lower lobe of the left lung.

Lung Hernia

Part of a lung may herniate: (a) through the inlet of the thorax, (b) through a defect in the thoracic wall, (c) into the mediastinum, or (d) into the opposite pleural cavity.

Displaced Bronchi

These may arise from the trachea above its bifurcation or even from the oesophagus.

They may supply: (a) a normal segment of one of the lungs (Fig. 14.18C), (b) an accessory lobe (Figs. 14.18B, 14.18), or (c) they may be blind (Fig. 14.18A).

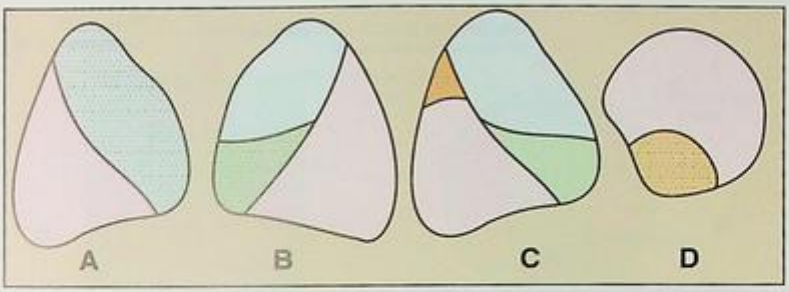

Fig. 14.20: Abnormal lobes of the lungs: (A) Right lung with only two lobes, (B) Left lung with three lobes, (C) Apical segment of lower lobe is separate. (D) Medial basal segment is separate.

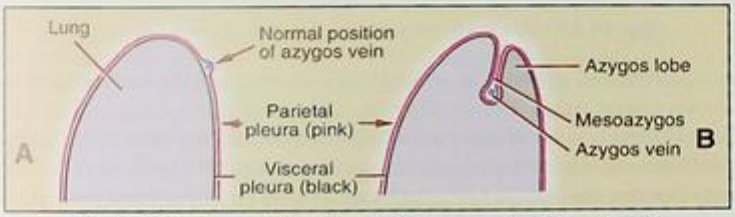

Fig. 14.21: Azygos lobe of lung (B). The normal relationship of the azygos vein to the lung is shown in (A).

THE BODY CAVITIES AND DIAPHRAGM

BODY CAVITIES

Introduction

The pericardial, pleural and peritoneal cavities are derivatives of the intra-embryonic coelom. We have seen that by the formation of this cavity the lateral plate mesoderm is split into a parietal (somatopleuric) and a visceral (splanchnopleuric) layer (Fig. 5.6). The parietal and visceral layers of pericardium, pleura and peritoneum are formed from these layers of mesoderm. The mesodermal cells lining the cavities differentiate into a flattened epithelial lining called ***mesothelium***. The mesothelium gives the peritoneum, pleura and pericardium their smooth surfaces.

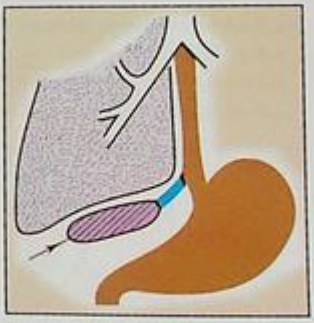

Fig. 14.22: Accesory lobe of lung (indicated by arrow) supplied by bronchus arising from oesophagus.

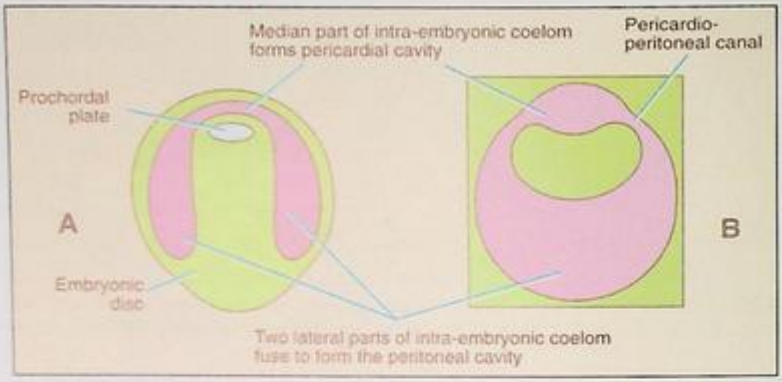

Fig. 14.23: (A) Intra-embryonic coelom, and (B) its subdivisions.

The intra-embryonic coelom is a horseshoe-shaped cavity having a narrow midline portion and two lateral parts. The midline part lies near the cranial end of the embryonic disc (Fig. 14.23A), and it is from this part of the coelom that the pericardial cavity is formed. The two lateral limbs of the coelom form the peritoneal cavity. For some time, the pericardial and peritoneal cavities are connected to each other by a pair of narrow pericardio-peritoneal canals (Fig. 14.23B). These canals undergo great enlargement to form the pleural cavities.

Details of the development of the pleural and peritoneal cavities are considered below. The pericardial cavity is considered in Chapter 15.

Pleural Cavity

After the formation of the head fold, the pericardium comes to lie on the ventral aspect of the embryo, and the pericardio-peritoneal canals wind backwards on either side of the foregut (Fig. 14.24). The lung buds, that arise from the foregut, now invaginate these canals (Fig. 14.25). As the buds enlarge to form the lungs, the canals balloon out to form the pleural cavities.

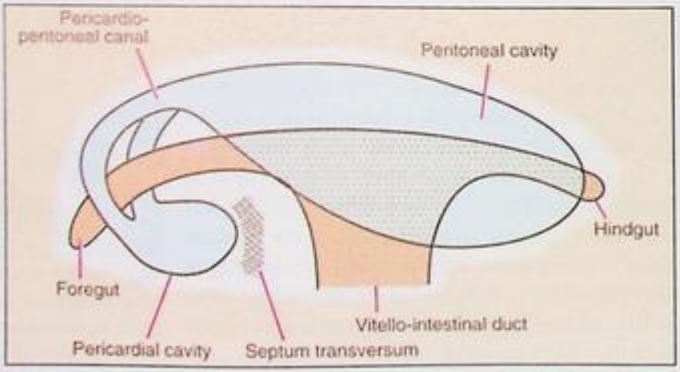

Fig. 14.24: Parts of intra-embryonic coelom and their relationship to the gut.

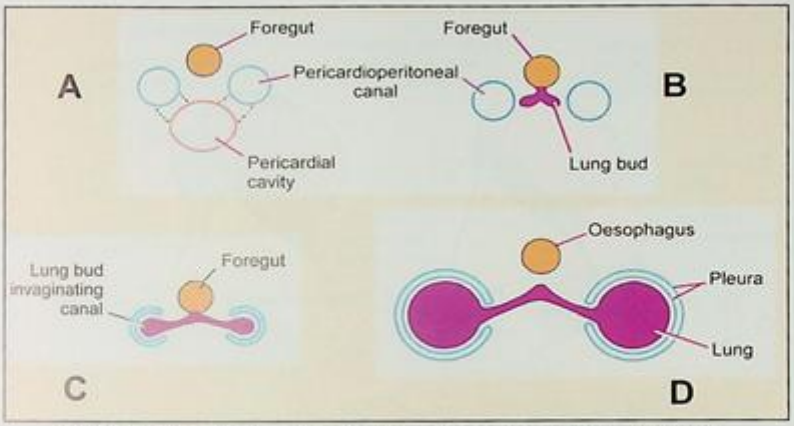

Fig. 14.25: Invagination of pericardio-peritoneal canals by the lung buds.

Each pleural cavity now communicates with the pericardial cavity through the ***pericardio-pleural opening***, and with the peritoneal cavity through the ***pleuro-peritoneal opening*** (Fig. 14.26A). In subsequent development, these openings are closed by the formation of the ***pericardio-pleural membranes***, and the formation of the ***pleuro-peritoneal membranes***, respectively (Figs. 14.26B, C).

From Figs. 14.26C and 14.27A, it will be seen that the pleural cavities are at first dorso-lateral to the pericardium. As the lungs increase in size, the pleural cavities extend into the mesoderm of the body wall (which is expanding at the same time), and gradually come to lie lateral, and to some extent ventral, to the pericardium (Fig. 14.26B). The pleural cavities also extend downwards into the mesoderm forming the posterior abdominal wall, and upwards towards the neck (Fig. 14.26C). In Fig. 14.27B note that with the expansion of the pleural cavity the mesoderm of the body wall is split into an outer part that forms the wall of the thorax, and an inner part over the pericardial cavity. The latter is called the ***pleuro-pericardial membrane***. The phrenic nerve runs through this membrane. Later this membrane forms the fibrous pericardium. This explains the course of the phrenic nerve over the pericardium.

Peritoneal Cavity

We have seen that the peritoneal cavity is formed from the two limbs of the horseshoe-shaped intra-embryonic coelom. The two parts are at first separate, but fuse to form one cavity, as a result of lateral folding of the embryonic disc (Figs. 14.28D, E, F). As illustrated in Figs. 14.28B, C, the two halves of the peritoneal cavity remain separate in the cranial part of the abdomen.

The attachment of the mesentery of the primitive gut on the posterior abdominal wall is at first in the midline (Fig. 14.29). As a result of changes, involving the rotation of the gut, and as a result of some parts of the gut becoming retroperitoneal, the line of attachment of the

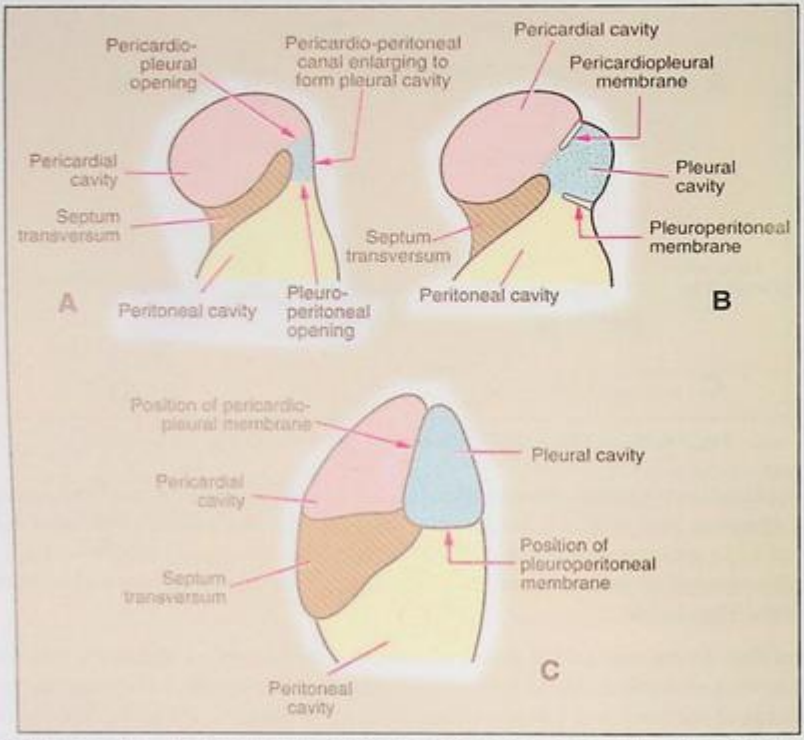

Fig. 14.26: Formation of pleural cavity and its separation from pericardial and peritoneal cavities. (A) Pericardio-peritoneal canal enlarges to form the pleural cavity. The pleural cavity communicates freely with the pericardial and peritoneal cavities. (B) Pleural cavity is gradually separated from the pericardial and peritoneal cavities by formation of pericardiopleural and pleuroperitoneal membranes.

mesentery becomes complicated (Fig. 14.30). The peritoneal cavity, therefore, comes to be subdivided into a number of pockets that are partially separated by folds of peritoneum.

Development of the Lesser Sac

Three distinct processes are involved in the formation of the lesser sac of peritoneum. These may be considered one by one.

- The dorsal mesogastrium that connects the stomach to the posterior wall of the abdomen is, initially, a thick membrane (Fig. 14.30A). Two small cavities appear in this membrane. These are the right, and left, ***pneumato-enteric recesses*** (Fig. 14.30B). The left recess soon disappears. The right recess enlarges and opens into the peritoneal cavity (Fig. 14.30C). The cavity of this recess now enlarges considerably and extends to the left to form the part of the lesser sac that lies behind the stomach (Fig. 14.30D). It also extends cranially,

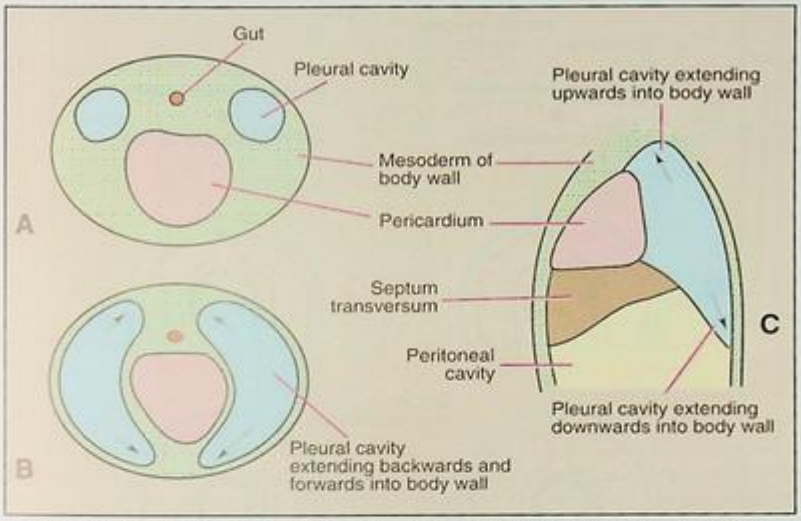

Fig. 14.27: Schemes to show how the pleural cavity expands into the body wall.

on the right side of the oesophagus, and behind the liver (Fig. 14.31). Subsequently, with the establishment of the diaphragm, the uppermost part of this cranial extension comes to lie above the diaphragm, where it gives rise to the ***infracardiac bursa***. The part of the cranial extension that remains below the diaphragm (and behind the liver) forms the ***superior recess*** of the lesser sac.

- While the right pneumato-enteric recess extends to the left, the stomach changes its orientation, so that its posterior border (to which the dorsal mesogastrium was attached), now faces to the left. This border forms the greater curvature. The ventral border (to which the ventral mesogastrium was attached), now comes to face to the right and forms the lesser curvature (Fig. 14.32). The ventral mesogastrium may now be called the ***lesser omentum***. As a result of this change in the orientation of the stomach, a part of the peritoneal cavity comes to lie behind the lesser omentum (M in Fig. 14.32C). This part of the peritoneal cavity now forms part of the lesser sac. It is continuous with the part of the lesser sac lying behind the stomach (derived from the right pneumato-enteric recess: N in Fig. 14.32C).
- With the altered orientation of the stomach, the dorsal mesogastrium, which is attached to the greater curvature, may be subdivided into two parts; A and B as shown in Fig. 14.33. If we trace these two parts to the posterior abdominal wall (Fig. 14.33), we find that the attachment of the mesogastrium on this wall can also be divided into two corresponding parts. Part A passes from the stomach to the spleen as the gastro-splenic ligament, and from the spleen to the left kidney as the lieno-renal ligament. It, therefore, forms the left margin of the lesser sac. Part B passes from the lower border of the stomach to the

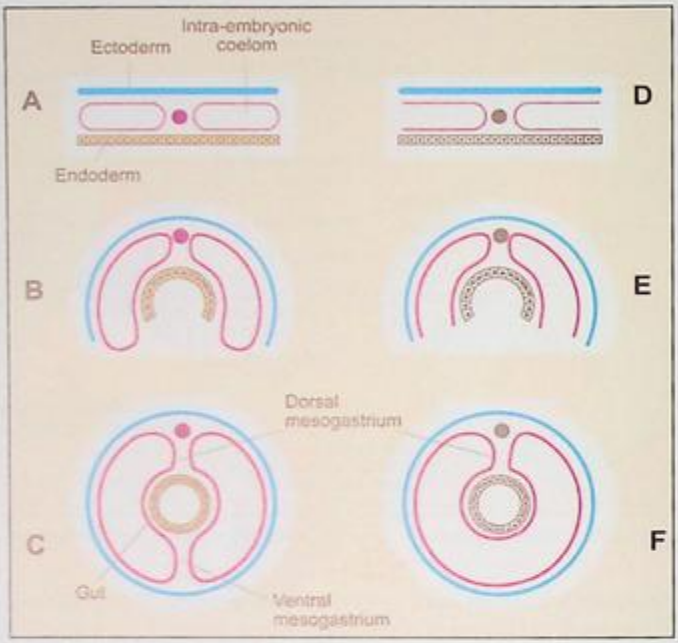

Fig. 14.28: Schemes to illustrate why the foregut has a ventral mesentery (A to C) but the midgut and hindgut do not. First read legend to Fig. 13.5. Figs. 'A' to 'C' represent the result of lateral folding of the embryonic disc in the region that will form the upper part of the abdomen. As the disc folds the two halves of the intra-embryonic coelom also undergo folding, and meet in the middle line ventral to the gut. From 'C' it will be clear how the dorsal and ventral mesogastriums are formed. Figs. 'D' to 'F' show the result of folding in the lower part of the abdomen. In 'D' note that, at this level, each half of the intra-embryonic coelom is open laterally. The result of folding is seen in 'F' from which it will be clear why there is no ventral mesentery here.

posterior abdominal wall (Fig. 14.33) and forms the ***greater omentum***. The greater omentum undergoes enlargement with the result that it comes to increasingly project below the level of the stomach, and becomes folded on itself. The space within this fold forms the lower part of the lesser sac (Fig. 14.34).

DIAPHRAGM

Introduction

The diaphragm is a partition that separates the thoracic and abdominal cavities. The pericardial, and pleural, cavities are above (or cranial to) it, whereas the peritoneal cavity is caudal to it. The development of the diaphragm is, therefore, intimately related to the development of these cavities.

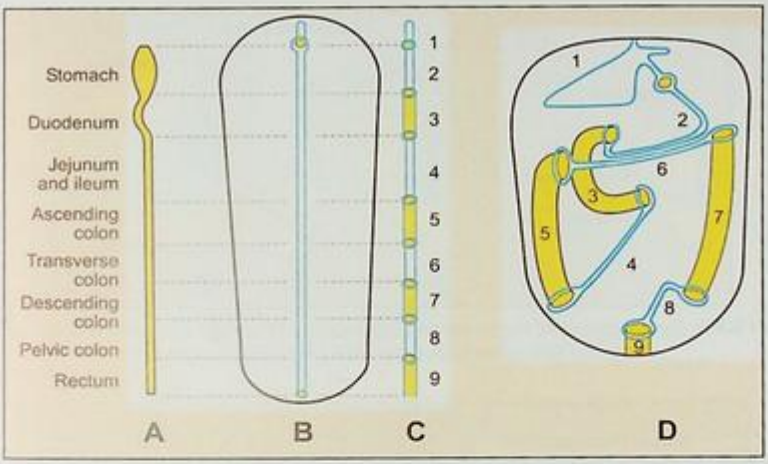

Fig. 14.29: Peritoneal relations of the gut. In (A) the gut is shown when it is a simple midline tube. In (B) the dorsal wall of the abdomen is shown to indicate the midline attachment of the dorsal mesentery. The oesophagus and rectum are seen passing through the wall. In (C) it is shown that alternate segments (3, 5, 7, 9) become retroperitoneal while the segments 2, 4, 5 and 8 retain their mesentery, (D) shows the ultimate disposition of these segments on the posterior abdominal wall. 1. represents the ventral mesogastrium, 2. the dorsal mesogastrium, 3. the duodenum, 4. the mesentery of the jejunum and ileum, 5. the ascending colon, 6. the transverse mesocolon, 7. the descending colon, 8. the pelvic mesocolon and 9. the rectum.

The formation of the septum transversum was considered in Chapter 5. We have seen that the liver develops in its caudal part. Its cranial part helps to form the diaphragm. Reference to Figs. 5.13, 5.14 and 5.15 will show that after the establishment of the head fold, the septum transversum forms a mesodermal mass lying caudal to the pericardial cavity. It, therefore, separates the pericardial and peritoneal cavities. Posterior to the septum transversum, however, the pleural and peritoneal cavities communicate through the pleuro-peritoneal canals, that lie on either side of the oesophagus (Fig. 14.35). The partition between the thorax and the abdomen is completed when the pleuro-peritoneal canals are closed by the formation of the pleuro-peritoneal membranes (Fig. 14.35).

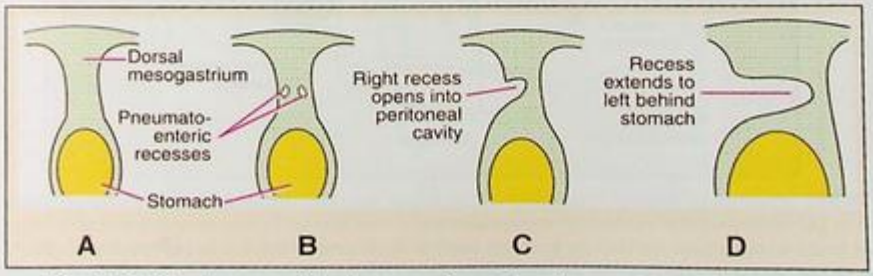

Fig. 14.30: Development of the lesser sac. Formation of pneumato-enteric recesses.

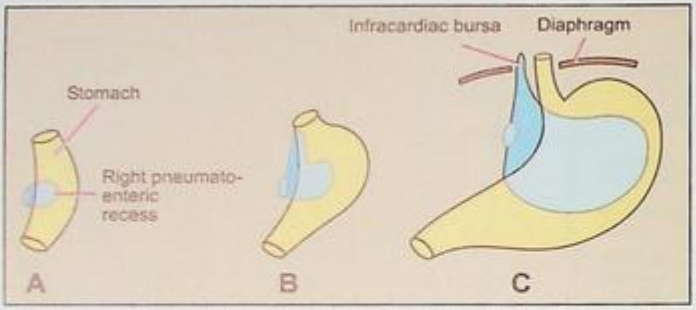

Fig. 14.31: Development of the lesser sac. Extensions of the right pneumato-enteric recess. Note the extension above the level of the diaphragm in (C).

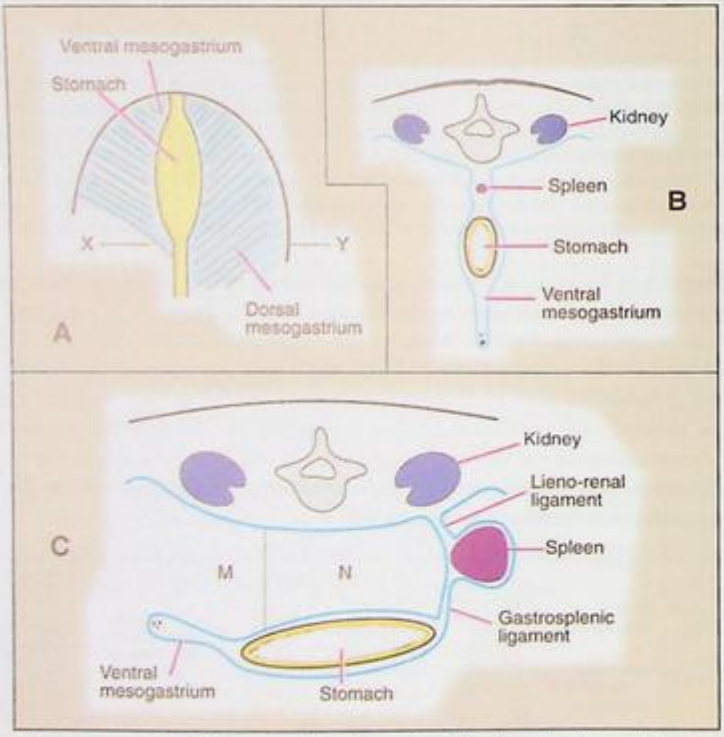

Fig. 14.32: Schemes to explain formation of the lesser sac. The dorsal and ventral mesogastriums are shown in (A). Note that the ventral mesogastrium has a free border facing downwards and forwards. If a section is cut in the plane XY, the appearance seen is illustrated in (B). Subsequently the original ventral border of the stomach comes to lie on the right side (C). Two parts of the lesser sac labelled M and N are shown. N is derived from the right pneumato-enteric recess while M is part of the peritoneal cavity that comes to lie behind the ventral mesogastrium (which is now the lesser omentum)

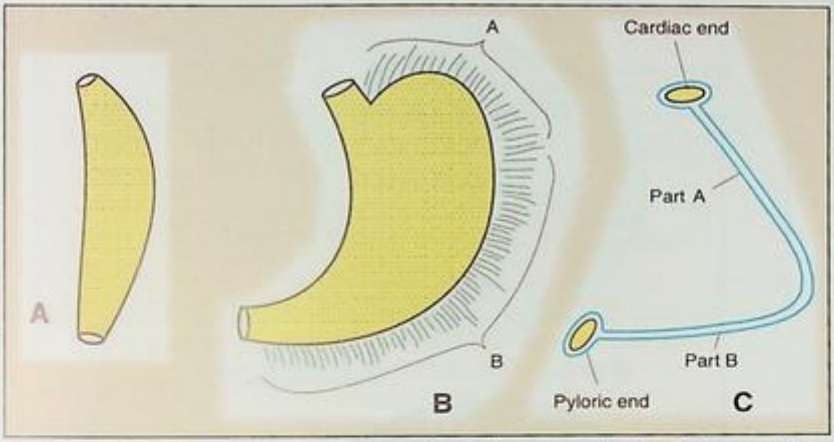

Fig. 14.33: Parts of the dorsal mesogastrium. Part A forms the gastrosplenic and lieno-renal ligaments as shown in Fig. 14.7. Part B elongates to form the greater omentum. The attachment of these parts to the stomach is shown in B and to the posterior abdominal wall in C.

Development of the Diaphragm

It will be recalled (Fig. 14.27) that as the pleural cavities increase in size, they do so at the expense of the body wall, with the result that the thorax as a whole also expands. Simultaneously, the diaphragm has also to enlarge, and this enlargement takes place at the expense of the body wall (Fig. 14.36).

The diaphragm is, therefore, formed from the following components (Fig. 14.37).

- Septum transversum.
- Pleuro-peritoneal membranes.

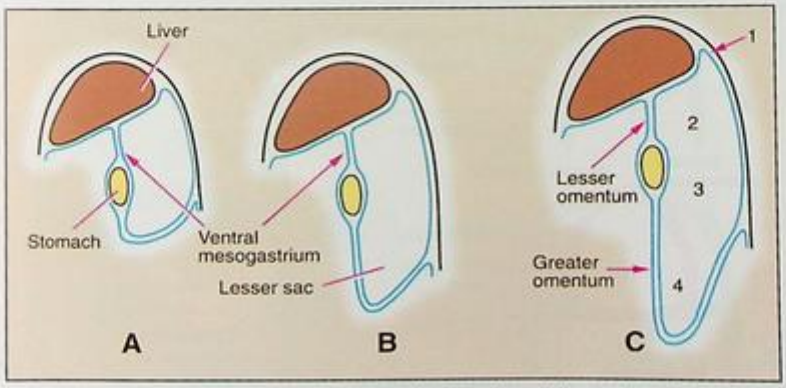

Fig. 14.34: Development of the lesser sac: Downward extension of the sac by elongation and folding of the greater omentum. The derivation of the parts numbered in (C) is (1) from cranial extension of pneumato-enteric recess; (2) part of peritoneal cavity that comes to lie behind ventral mesogastrium; (3) right pneumato-enteric recess; (4) cavity produced by elongation and folding of greater omentum on itself.

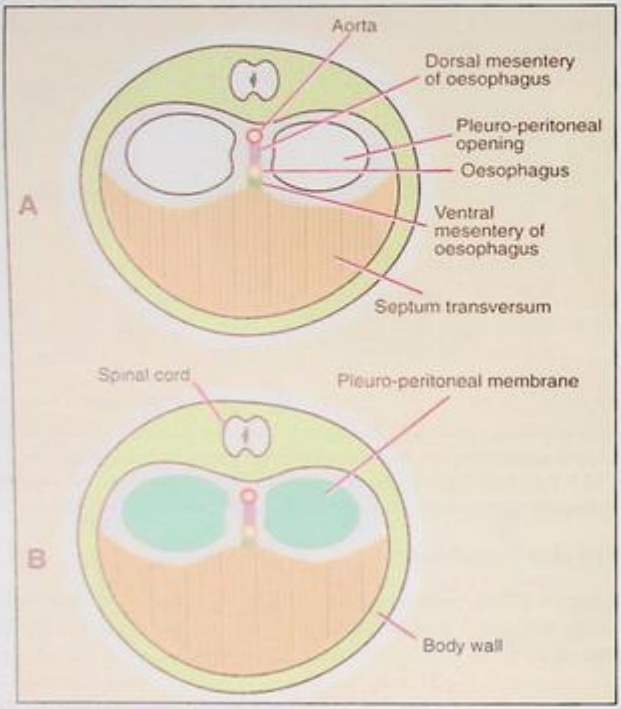

Fig. 14.35: Development of the diaphragm. Pleuroperitoneal canals and their closure. Note the other structures in relation to these canals.

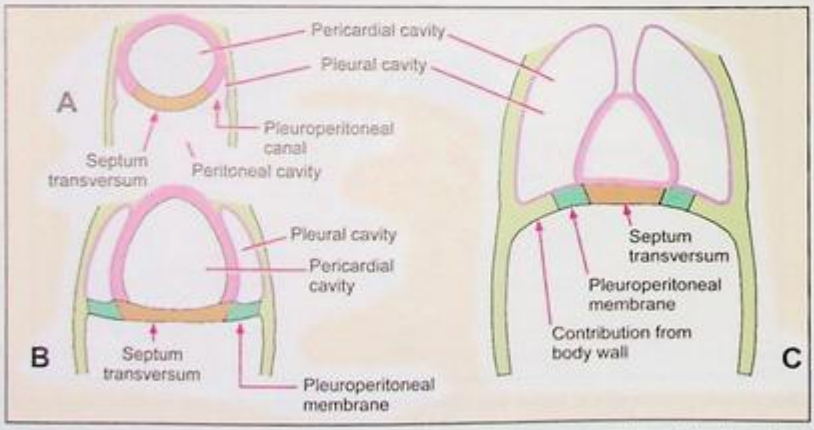

Fig. 14.36: Development of the diaphragm: Schemes to show how expansion of the pleural cavities into the body wall causes the wall to form part of the diaphragm.

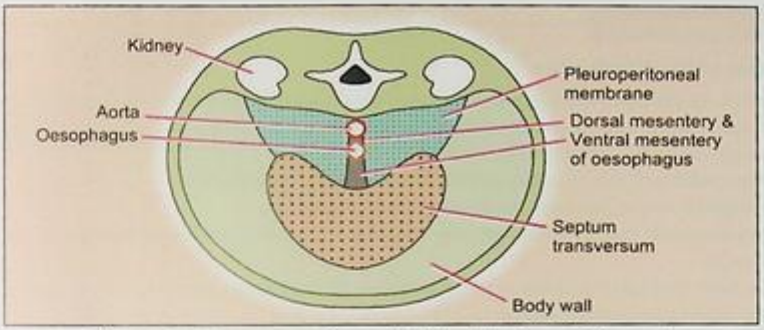

Fig. 14.37: Components from which the diaphragm is formed. These are labelled on the right side of the figure.

- Ventral and dorsal mesenteries of oesophagus.
- Mesoderm of body wall, including mesoderm around the dorsal aorta.

There is, however, considerable controversy as to how much of the diaphragm is formed from each of the constituents. According to some workers, the septum transversum forms only the central tendon, while according to others, it gives rise to almost the whole of the costal and sternal parts of the diaphragm. The crura of the diaphragm are formed from the mesoderm of the posterior abdominal wall, as a result of the downward extension of the pleural cavities into this region (Fig. 14.27).

The nerve supply of the diaphragm from the third, fourth and fifth cervical nerves (through the phrenic nerve) shows that the diaphragm has undergone great migration in a caudal direction during development. (This descent is caused by elongation of the neck, descent of the heart, and expansion of the pleural cavities). The sensory innervation of the peripheral parts of the diaphragm by the intercostal nerves is evidence of the contribution made by the body wall to the muscle.

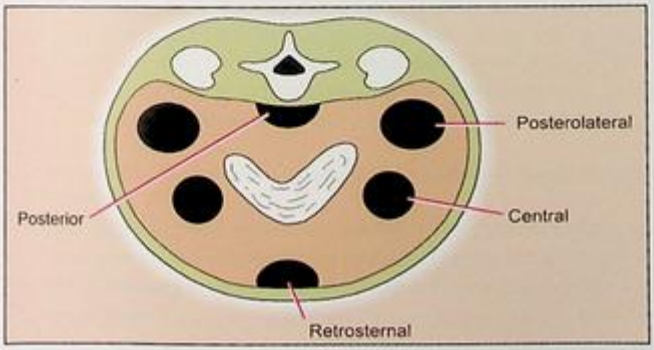

Fig. 14.38: Sites of congenital defects in the diaphragm. Abdominal contents may herniate through them resulting in diaphragmatic hernias.

Clinical Correlation

Anomalies of the Diaphragm

- Parts of the diaphragm may fail to develop resulting in gaps in the muscle. Abdominal contents may pass through these gaps to produce ***diaphragmatic hernias***.
  Diaphragmatic hernias may be (Fig. 14.38):
  - ***Posterolateral:*** due to failure of a pleuro-peritoneal canal to close.
  - ***Posterior:*** due to failure of the development of the crura.
  - ***Retrosternal:*** due to an abnormally large gap between the sternal and costal parts of the muscle.
  - ***Central:*** through the dome of the diaphragm. Occasionally one entire half (usually the left) of the diaphragm may be absent.
- Very rarely, an accessory diaphragm may be present in the thoracic cavity. When present it partially subdivides the lung into two parts.
- The muscle may be thin and aponeurotic and may bulge upwards into the thorax. The bulging may be unilateral or may be confined to a small area. This condition is called ***congenital eventration of the diaphragm***.

TIMETABLE OF SOME EVENTS DESCRIBED IN THIS CHAPTER

Age	Developmental Events
3 weeks	The hepatic bud appears. The pancreatic bud also appears soon thereafter.
4 weeks	The septum transversum is established. The tracheobronchial diverticulum is formed.
6 week	The diaphragm descends to the thoracic level.
7 weeks	Fusion of dorsal and ventral pancreas.
3 months	Bile formation begins. Pancreatic islets are formed.
5 months	Insulin secretion begins.

Chapter 15

Cardiovascular System

HIGHLIGHTS

- The *heart* develops from splanchnopleuric mesoderm related to that part of the intra-embryonic coelom that forms the pericardial cavity. This mesoderm is the ***cardiogenic area***.
- Two ***endothelial heart tubes*** (right and left) appear and fuse to form one tube. This tube has a venous end, and an arterial end (Fig. 15.1, 15.2).
- A series of dilatations appear on this tube (Fig. 15.3). These are (1) ***bulbus cordis***, (2) ***ventricle***, (3) *atrium*, and (4) ***sinus venosus***.
- Further subdivisions are named as follows (Fig. 15.3). The bulbus cordis consists of a proximal one-third (which is dilated), a middle one-third called the ***conus***, and a distal one-third called the ***truncus arteriosus***. The narrow part connecting atrium and ventricle is the ***atrioventricular canal***. The sinus venosus has right and left horns.
- The right and left atria of the heart are formed by partition of the primitive atrium. This partition is formed by the ***septum primum*** and the ***septum secundum (Fig. 15.6)***. A valvular passage, the ***foramen ovale***, is present between these two septa. It allows flow of blood from right atrium to left atrium.
- The dilated proximal one-third of the bulbus cordis, the conus, and the primitive ventricle unite to form one chamber. This is partitioned to form right and left ventricles. This partition is made up of the following. (1) ***Interventricular septum*** that grows upwards from the floor of the primitive ventricle. (2) a ***bulbar septum*** that divides the conus into two parts. (3) The gap left between these two is filled by proliferation of atrioventricular cushions that are formed in the atrioventricular canal (Fig. 15.11).
- The truncus arteriosus is continuous with the ***aortic sac*** (Fig. 15.27). This sac has right and left horns. Each horn is continuous with six ***pharyngeal (or aortic) arch arteries***. These arteries join the dorsal aorta (right or left). The first, second and fifth arch arteries disappear. The caudal parts of the right and left dorsal aortae fuse to form one median vessel (Fig. 15.28).
- The ***ascending aorta*** and ***pulmonary trunk*** are formed from the truncus arteriosus (Fig. 15.28B).
- The ***arch of the aorta*** is formed by the aortic sac, its left horn, and the left fourth arch artery (Fig. 15.29A).
- The ***descending aorta*** is formed partly from the left dorsal aorta, and partly from the fused median vessel (Fig. 15.29B).
- The ***brachiocephalic artery*** is formed from the right horn of the aortic sac (Fig. 15.29C)
- The ***common carotid artery*** is derived from part of the third arch artery (Fig. 15.30B).
- The ***pulmonary artery*** is derived from the sixth arch artery (Fig. 15.31B).
- The ***arteries to the gut*** are formed from ventral splanchnic branches of the dorsal aorta (Fig. 15.36).

Highlights *contd...*

- The ***renal***, ***suprarenal*** and ***gonadal arteries*** are formed from lateral splanchnic branches of the dorsal aorta.
- Arteries to the body wall and limbs are derived from dorsolateral (somatic intersegmental) branches of the aorta.
- The ***left subclavian artery*** is derived from part of the seventh cervical intersegmental artery. On the right side this artery is formed partly from the seventh cervical intersegmental artery, and partly from the right fourth arch artery.
- The ***portal vein*** is formed from right and left vitelline veins and anastomoses between them (Fig. 15.42).
- The ***superior vena cava*** is derived from part of the right anterior cardinal vein, and from the right common cardinal vein.
- The ***inferior vena cava*** receives contributions from several veins (and anastomoses between them). These are the right posterior cardinal vein, the right subcardinal vein, the right supracardinal vein, and the right hepato-cardiac channel.

PART 1: THE HEART

DEVELOPMENT OF THE HEART: MAIN FACTS

The development of the heart is complex. To avoid confusion that may be caused by numerous details, the main facts are presented first. Details are presented later.

Introduction

The heart (like all blood vessels) is mesodermal in origin. It is formed from splanchnopleuric mesoderm lying immediately cranial to the prochordal plate. This mesoderm constitutes the ***cardiogenic area***. It is closely related to the pericardial cavity (which is derived from part of the intraembryonic coelom). For a good understanding of the relationship between developing heart tube and the pericardial cavity students are advised to study Figs. 5.11 to 5.14.

The heart is at first seen in the form of right and left endothelial heart tubes (Fig. 15.1A) that soon fuse with each other. The single tube thus formed shows a series of dilatations. These are:

- *Bulbus* ***cordis***.
- *Ventricle*. (We will refer to it as the primitive ventricle).
- *Atrium*. (We will refer to it as the primitive atrium or atrial chamber).
- *Sinus* ***venosus***.

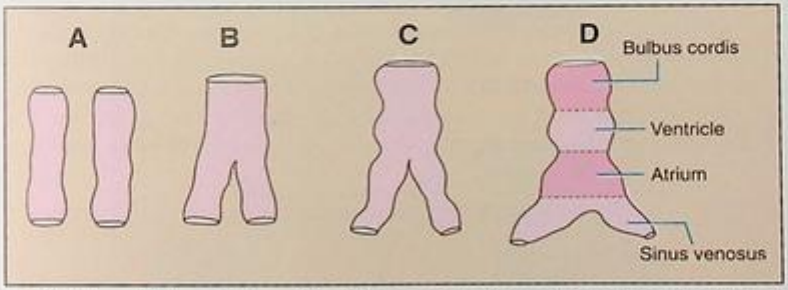

Fig. 15.1: (A) Right and left heart tubes. (B) to (D) progressive fusion of tubes from cranial to caudal end. Fusion of sinus venosus is partial.

The ventricle and atrium are connected by a narrow ***atrioventricular canal***. The sinus venosus has prolongations that are referred to as its right and left ***horns***.

The bulbus cordis lies at the arterial end of the heart. It is divisible into three parts i.e., proximal, middle and distal. The proximal one-third is dilated and does not have any special name; the middle one-third is called the ***conus***, and the distal one-third is called the ***truncus arteriosus*** (Fig. 15.2A and 15.3). The truncus arteriosus is continuous distally with the aortic sac. The aortic sac is continuous with right and left pharyngeal arch arteries. These arteries arch backwards to become continuous with the right and left dorsal aortae.

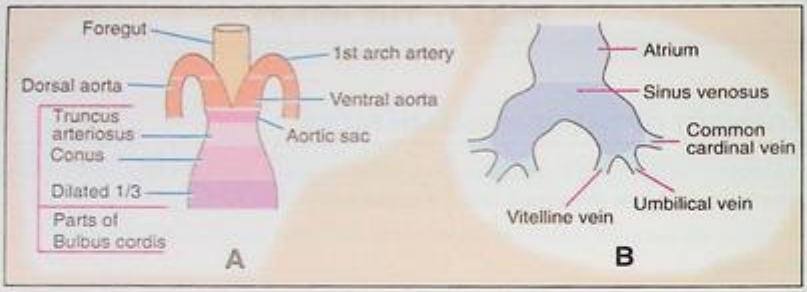

Fig. 15.2: (A) Arterial end, and (B) venous end of heart tube. Also see Fig. 15.26.

The sinus venosus lies at the venous end of the heart. It has right and left horns. One vitelline vein (from the yolk sac), one umbilical vein (from the placenta) and one common cardinal vein (from the body wall) join each horn of the sinus venosus.

The fate of the various parts of the heart tube is summarised in Fig. 15.3.

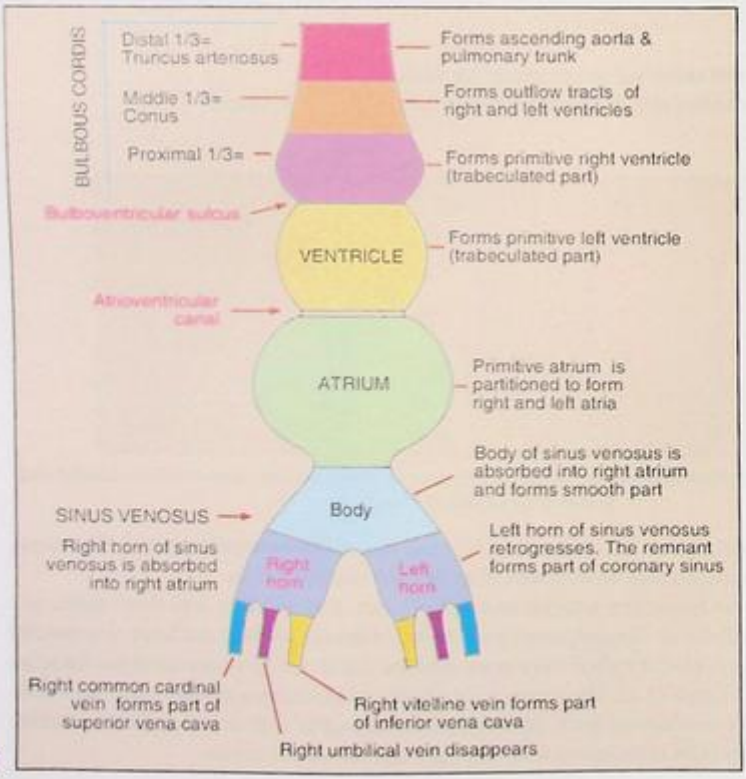

Fig. 15.3: Main subdivisions of heart tube and their fate.

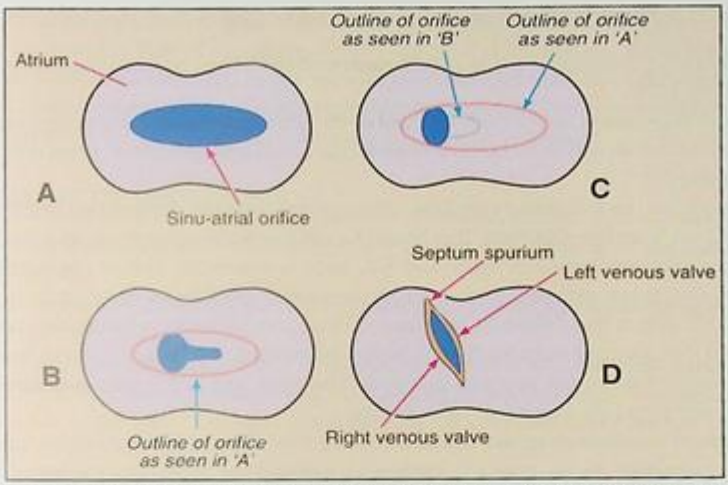

Fig. 15.4: Changes in the sinu-atrial orifice. Note that firstly, the centrally placed orifice shifts to the right. Secondly, the orifice that is at first transversely orientated becomes vertical. Dotted lines in (B) and (C) indicate the outline of the opening in the previous figure to show how the change occurs.

Formation of Atria

- The sinus venosus and the primitive atrial chamber are at first connected by a wide opening. Gradually the opening becomes narrow and shifts to the right. Finally it becomes a narrow slit. The slit has right and left margins called the right and left ***venous valves***. Cranially these two valves fuse to form a structure called the ***septum spurium*** (Fig. 15.4).
- The atrioventricular canal divides into right and left halves as follows (Fig. 15.5). Two thickenings, the ***atrioventricular cushions*** appear on its dorsal and ventral walls. They grow towards each other and fuse. The fused cushions form the ***septum intermedium*** (Fig. 15.6).

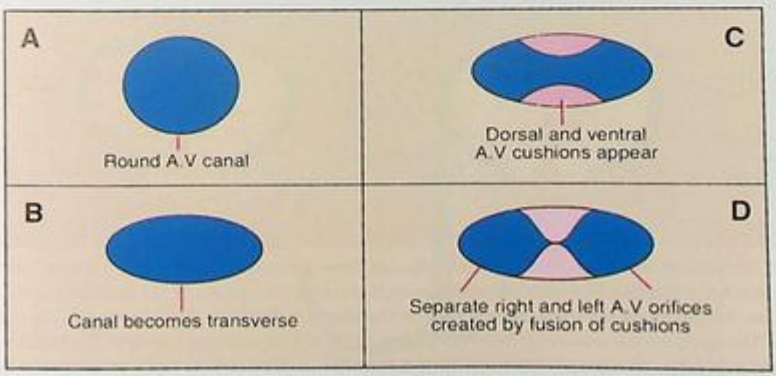

Fig. 15.5: Schemes to show how the A.V. canal undergoes division into right and left orifices.

Formation of Interatrial Septum

The atrial chamber undergoes division into right and left halves by formation of two septa (that later fuse) (Fig. 15.6).

- The ***septum primum*** arises from the roof of the atrium, to the left of the septum spurium. It grows downwards towards the atrioventricular canal and ultimately fuses with the septum intermedium.

  However note the following carefully. Throughout fetal life oxygenated blood reaches the right atrium from the placenta. This blood has to reach the left atrium, and for this purpose a communication between right and left atria is essential. Before the septum primum reaches and fuses with the septum intermedium, blood flows through the gap between them. This gap is the ***foramen primum***. Before the foramen primum can be closed it is essential that another path for flow of blood be created. This is achieved by breaking down of the upper part of the septum primum. The new gap is the ***foramen secundum***. The septum primum now has a free upper edge.
- The ***septum secundum*** grows down from the roof the atrial chamber, to the right of the septum primum. As its grows it comes to overlap the free upper edge of the septum primum. Once the two septa overlap blood has to flow through the interval between the septa. This gap is the ***foramen ovale***. It is a valvular aperture that allows blood to flow from right to left, but not from left to right.

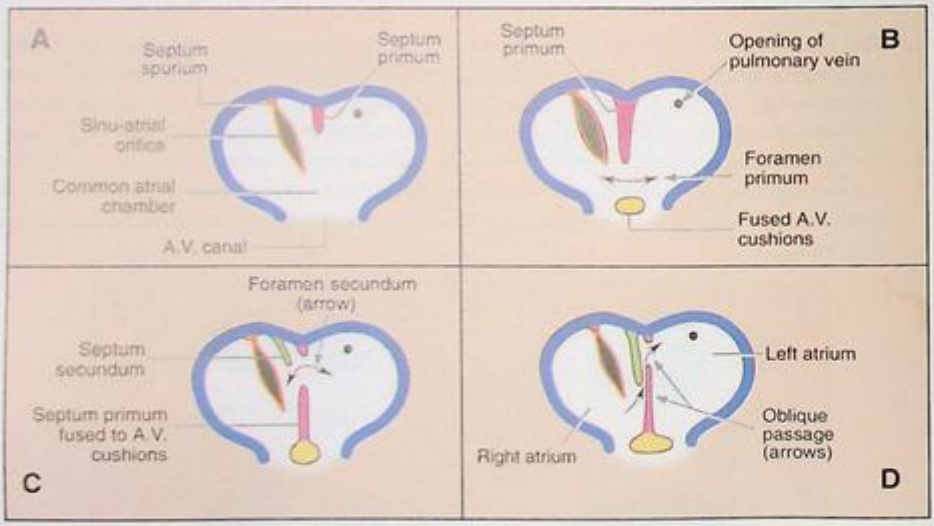

Fig. 15.6: Formation of interatrial septum. (A) Septum primum appears. (B) Septum primum grows towards fused A.V. cushions. The gap between them is the foramen primum. (C) Septum primum fuses with A.V. cushions. At the same time the upper part of the septum primum degenerates to form the foramen secundum. The septum secundum is formed to the right of the septum primum. (D) Septum secundum overlaps the free edge of septum primum. Blood now flows from left to right through the oblique cleft between the two septa.

After birth of the baby the left atrium starts receiving oxygenated blood from the lungs, and there is no need for flow of blood from right atrium to left atrium. The foramen ovale is, therefore, obliterated by fusion of the septum primum and septum secundum.
In terms of adult anatomy, the ***annulus ovalis*** represents the lower free edge of the septum secundum while the ***fossa ovalis*** represents the septum primum.

DEVELOPMENT OF RIGHT ATRIUM

- As described above, the main part of the right atrium is derived from the right half of the primitive atrium.
- The sinus venosus is absorbed into the right atrium by great enlargement of the sinuatrial orifice (Figs. 15.7, 15.8).
- The right half of the atrioventricular canal is also absorbed into the right atrium.
  Some relevant facts about the sinus venosus (and its tributaries) may be noted at this stage.
- The left horn of the sinus venosus remains very small. It becomes part of the coronary sinus (Fig. 15.7).
- The right common cardinal vein becomes part of the superior vena cava.
- The right vitelline vein forms the terminal part of the inferior vena cava.

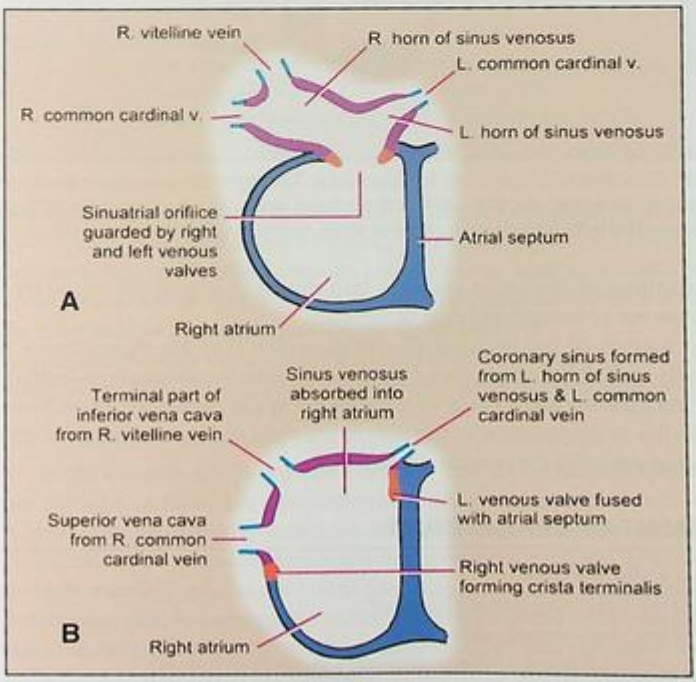

Fig. 15.7: Incorporation of sinus venosus into the right atrium.

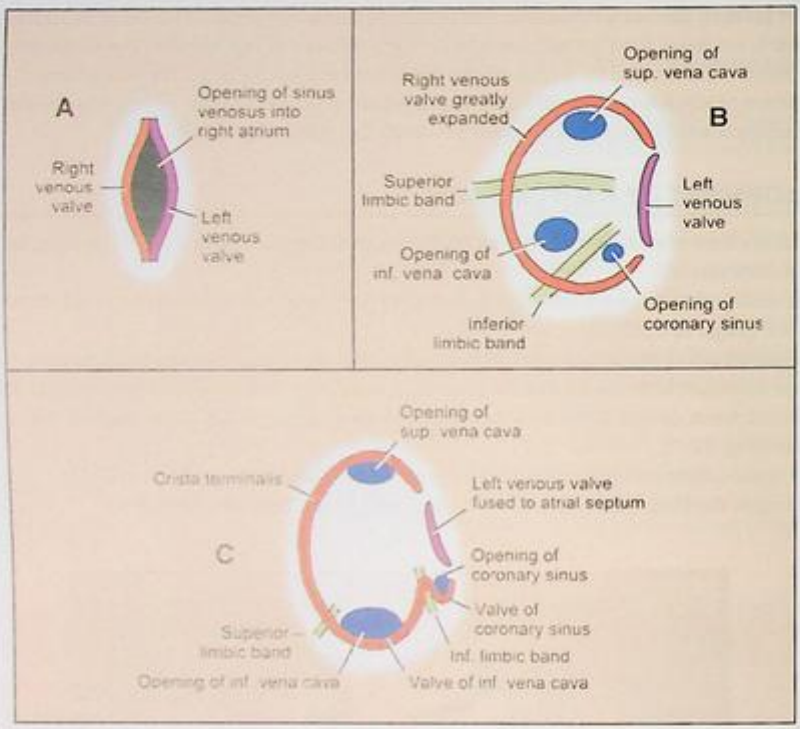

Fig. 15.8: Fate of the right and left venous valves. The right venous valve expands greatly and forms the crista terminalis, the valve of the inferior vena cava, and the valve of the coronary sinus. The left venous valve remains small and fuses with the interatrial septum.

After absorption of the sinus venosus into the right atrium the coronary sinus, and the venae cavae are seen opening into the atrium.

- The right margin of the original sinuatrial orifice (i.e. the right venous valve) expands very greatly and divides into three parts that form the ***crista terminalis*** (Fig. 15.8), the ***valve of the inferior vena cava***, and the ***valve of the coronary sinus***. Note that the crista terminalis lies at the junction of the part of the right atrium derived from the sinus venosus (***sinus venarum***) and the atrium proper.

DEVELOPMENT OF LEFT ATRIUM

The left atrium is derived from:

- Left half of the primitive atrial chamber.
- Left half of the atrio-ventricular canal.
- Absorbed proximal parts of the pulmonary veins (see below).

Absorption of Pulmonary Veins

At the time when the septum primum is just beginning to form (Fig. 15.6A), a single pulmonary vein opens into the left half of the atrium. When traced away from the heart (Fig. 15.9), the vein divides into a right and a left branch each of which again bifurcates, to drain the corresponding lung bud.

Gradually, the parts of the pulmonary veins nearest to the left atrium are absorbed into the atrium, with the result that four separate veins, two from each side, come to open into it (Fig. 15.9).

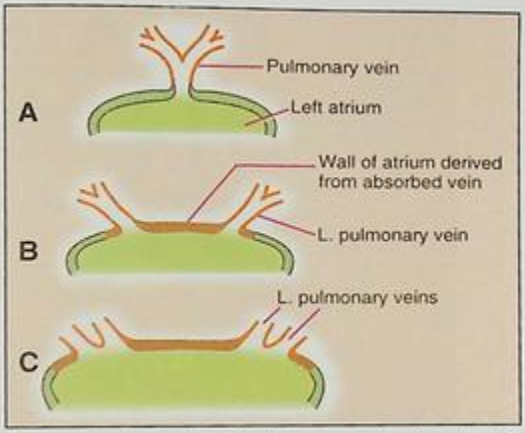

Fig. 15.9: Absorption of pulmonary veins into the left atrium. At first only one vein from the lungs enters the left atrium. The proximal part of the vein is gradually absorbed and is incorporated into the wall of the atrium. As a result of continued absorption of tributaries, four veins (two right and two left) finally open into the atrium.

DEVELOPMENT OF VENTRICLES

Fate of Bulbus Cordis

We have seen that the bulbus cordis is divisible into three parts i.e., proximal, middle (conus), and distal (truncus arteriosus).

A ***spiral septum*** appears within the truncus arteriosus and subdivides it into the ascending aorta and the pulmonary trunk. It is formed by union of right superior and left inferior ***truncus swellings*** or ***cushions***. Fusion of these cushions takes place in such a manner that at its lower end, the pulmonary trunk lies ventral to the aorta, but as it is traced upwards it comes to lie on its left side. This is because of the orientation of the spiral septum.

The conus forms the outflow tracts (smooth parts) of both the right and left ventricles. The proximal one-third of the bulbus cordis merges with the cavity of the primitive ventricle.

Important note:

Please note that in the seventh edition of this book the bulbus cordis was described as being divided into two parts i.e., a distal part the truncus arteriosus, and a proximal part the conus which was absorbed into the primitive ventricle, and later formed the smooth outflow parts of both right and left ventricles. It is now recognised that the outflow parts are formed by the middle one-third of the bulbus cordis only, and it is this part that is the conus. The proximal one-third of the bulbus cordis takes part in forming the trabeculated part of the right ventricle.(Fig. 15.3).

The right and left ventricles are formed by partitioning of this chamber. From Fig. 15.10 note that the bulbo-ventricular cavity consists of:

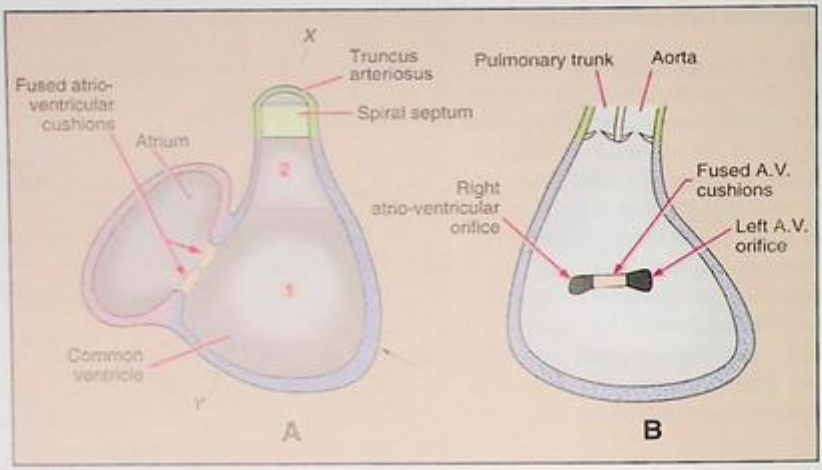

Fig. 15.10: (A) Two parts of the ventricular chamber. Part 1 lies anterior to the atrio-ventricular orifice. Part 2 is conical and lies higher up. (B) This is a section across the ventricle in the plane XY, shown in (A). Sections in the plane indicated by the arrow in (A) are shown in Fig. 15.17.

- a dilated lower part (1 in figure) that communicates with the atria; and
- a conical upper part (2 in figure) communicating with the truncus arteriosus. Part '1' is derived from the proximal one-third of the bulbus cordis and the primitive ventricle, while part '2' is from the conus.

Formation of Interventricular Septum

The cavity formed after the conus and proximal 1/3 of bulbus cordis have merged into the primitive ventricle has to be subdivided into right and left halves in such a way that:

- each half communicates with the corresponding atrium, and
- the right ventricle opens into the pulmonary trunk and the left ventricle into the aorta.

This subdivision takes place as follows:

- A septum, called the ***interventricular septum***, grows upwards from the floor of the bulbo-ventricular cavity and divides the lower dilated part of this cavity into right and left halves (Fig. 15.11A). It meets the fused atrio-ventricular cushions (septum intermedium) and partially fuses with them (Fig. 15.11C). On the external surface of the heart the site of formation of the interventricular septum corresponds to the bulbo-ventricular sulcus (Fig. 15.14A).

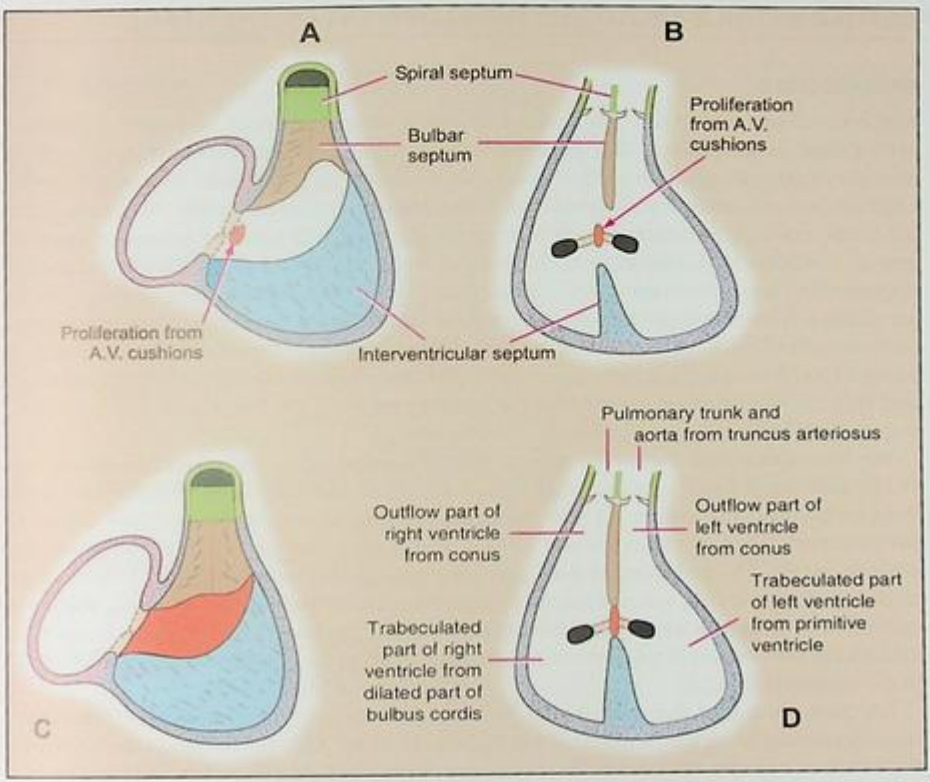

Fig. 15.11: Two stages in the formation of the ventricular septum. (B) and (D) correspond to (A) and (C) respectively. (A) Bulbar septum grows down from above, and interventricular septum grows upwards from below. (C) and (D) The gap between the bulbar septum and the interventricular septum is filled in by proliferation from A.V. cushions. For explanation of orientation of these figures see legend to Fig. 15.10.

- Two ridges, termed the ***right and left bulbar ridges***, arise in the wall of the bulboventricular cavity (in the part derived from the conus). These ridges grow towards each other and fuse to form a ***bulbar septum*** (Fig. 15.11A, B). The bulbar septum grows downwards towards the interventricular septum but does not quite reach it, with the result that a gap is left between the two.
- The gap between the upper edge of the interventricular septum, and the lower edge of the bulbar septum, is filled by proliferation of tissue from the atrioventricular cushions (Fig. 15.11D).

FURTHER DETAILS ABOUT THE DEVELOPMENT OF THE HEART

Introduction

The internal surfaces of the heart and of all blood vessels are lined by a layer of flattened cells called ***endothelium***. The endothelium is supported, on the outside, by varying amount of muscle, and connective tissue. All components of the heart and blood vessels, i.e. endothelium, muscle and connective tissue are of mesodermal origin. Very early in the life of the embryo, mesenchyme differentiates, over the yolk sac, in the connecting stalk, and in the body of the embryo itself, to form small masses of ***angioblastic tissue***. This angioblastic tissue gives rise to endothelium and also to ***blood cells***. The first blood vessels are derived from this endothelium. The vessels rapidly proliferate in number and become interconnected to form a vascular system. Soon thereafter, a primitive heart begins to pump blood through this network of vessels with the result that nutrition from the placenta and yolk sac can be made available to the growing embryo. The heart is, therefore, the first organ of the body to start functioning.

We have seen that the pericardial cavity is formed from the cranial, midline, part of the intra-embryonic coelom (Figs. 5.6, 5.11). With the formation of the coelom, the intra-embryonic mesoderm of the region splits into a somatopleuric layer adjoining the ectoderm (in roof of pericardial cavity), and a splanchnopleuric layer adjoining the endoderm (Fig. 5.6) and forming the floor of the pericardial cavity. The heart develops from angioblastic tissue that arises from this splanchnopleuric mesoderm, which is, therefore, called the ***cardiogenic area***. With the establishment of the head fold, the splanchnopleuric mesoderm and the developing heart come to lie dorsal to the pericardial cavity, and ventral to the foregut (Fig. 5.13).

We have seen that the endothelial heart tube is derived from the splanchnopleuric mesoderm related to the pericardial cavity (Fig. 15.12A). After formation of the head fold, this tube lies dorsal to the pericardial cavity and ventral to the foregut (Fig. 15.12B). The tube now invaginates the pericardial sac from the dorsal side. As it does so, the splanchnopleuric mesoderm lining the dorsal side of the pericardial cavity proliferates to form a thick layer called the ***myoepicardial mantle*** (or ***epimyocardial mantle***) (Figs. 15.12C, D). When the invagination is complete, the myoepicardial mantle completely surrounds the heart tube. It gives rise to the cardiac muscle (***myocardium***) and also to the visceral layer of pericardium (***epicardium***). The parietal layer of pericardium is derived from somatopleuric mesoderm.

Exterior of the Heart

The heart tube is, for some time, suspended from the dorsal wall of the pericardial cavity by two layers of pericardium that constitute the ***dorsal mesocardium*** (Figs. 15.12D, 15.13A). This mesocardium soon disappears and the heart tube lies free within the pericardial sac, suspended by its two ends (Figs. 15.13B, C). However, at this stage the caudal part of the heart tube (atrium, sinus venosus) is embedded within the substance of the septum transversum. The part of the heart tube lying within the pericardial cavity is thus made up of bulbus cordis and ventricle.

This part of the tube grows rapidly and, therefore, becomes folded on itself to form a 'U' shaped ***bulbo-ventricular loop*** (Fig. 15.13C). Subsequently, as the atrium and sinus

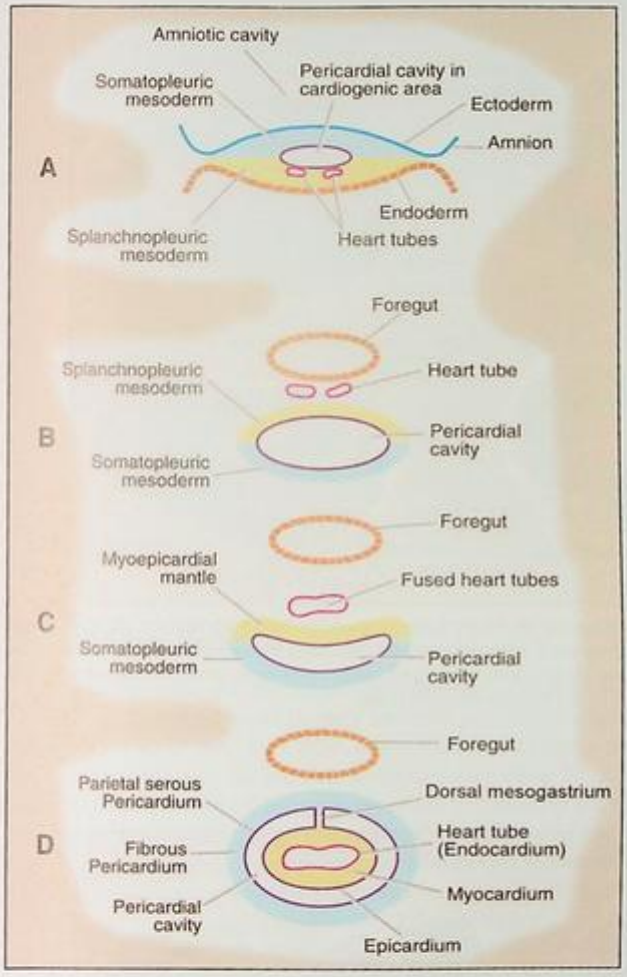

Fig. 15.12: Relationship of heart tubes to pericardial cavity: (A) Before formation of head fold. (B) After formation of head fold. (C) and (D) show the process of invagination of the pericardial cavity by the single heart tube.

venosus are freed from the septum transversum, they come to lie behind and above the ventricle, and the heart tube is now 'S' shaped (Fig. 15.13D). At this stage, the bulbus cordis, and ventricle, are separated by a deep ***bulbo-ventricular sulcus*** (Figs. 15.13D, 15.14). This sulcus gradually becomes shallower so that the conus, the proximal part of the bulbus cordis, and the ventricle, come to form one chamber (Fig. 15.14), which communicates with the truncus arteriosus. The atrial chamber which lies behind the upper part of the ventricle, and of the truncus arteriosus, expands; and as it does so parts of it come to project forwards on either side of the truncus. As a result of these changes the exterior of the heart assumes its definitive shape (Fig. 15.15).

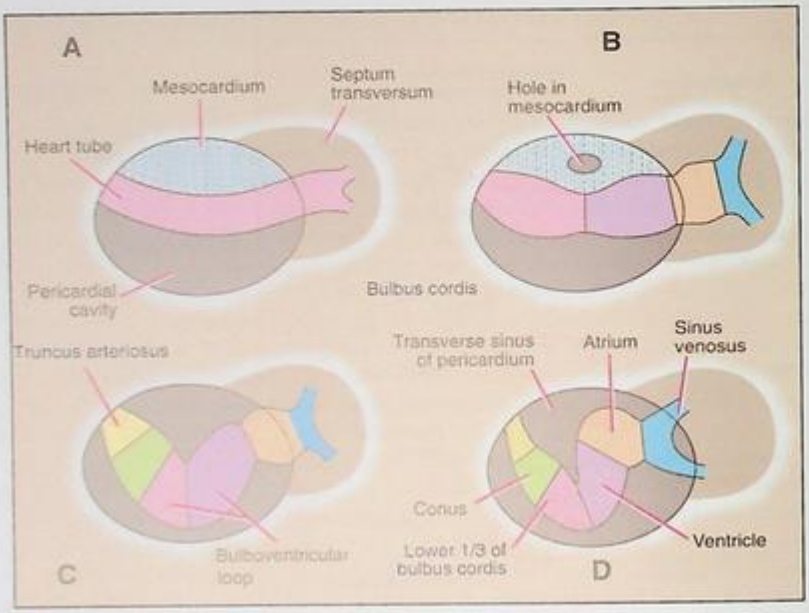

Fig. 15.13: Schemes to show the following. (A) Heart tube suspended by mesocardium. (B) Appearance of a hole in mesocardium. (C) Disappearance of mesocardium resulting in formation of transverse sinus of pericardium. In figures B to D note (1) gradual freeing of heart tube from septum transversum, and (2) folding of heart tube.

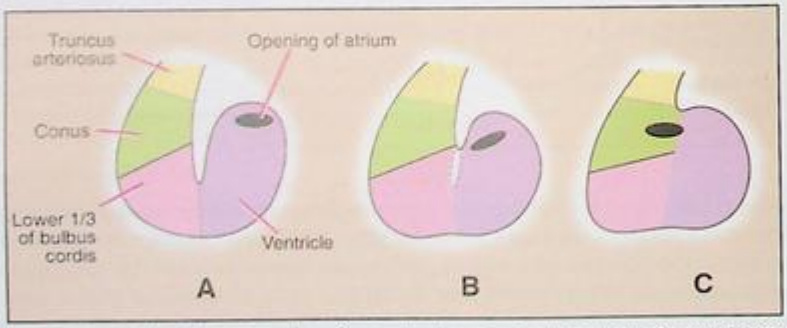

Fig. 15.14: Scheme to show incorporation of conus (and proximal dilated part of bIbus cordis) into the ventricle by disappearance of the bulbo-ventricular sulcus. Note that the opening of atrium into ventricle gradually shifts to the centre of the posterior wall of the common bulbo-ventricular chamber. The part labeled 'conus" includes the dilated part of the bulbus cordis.

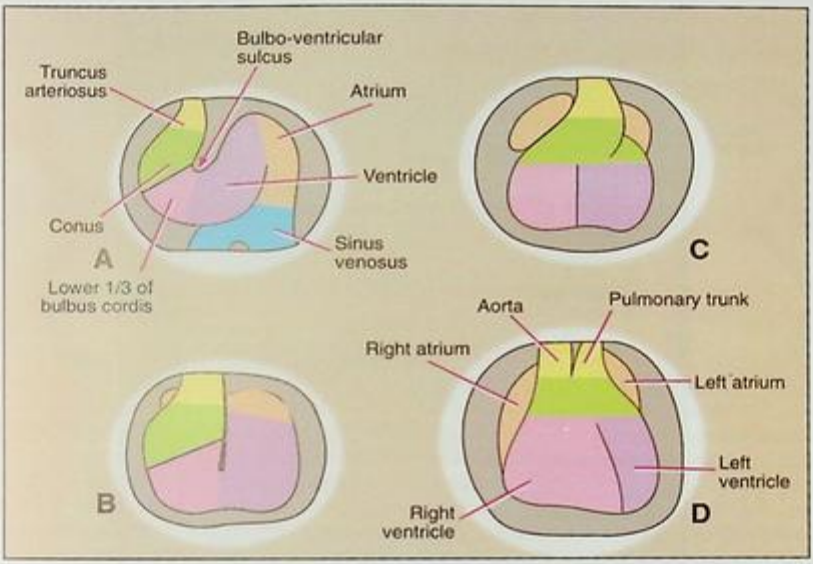

Fig. 15.15: Stages in establishment of external form of the heart.

Fate of Sinus Venosus

The sinus venosus and the atrial chamber are at first in open communication with each other (Fig. 15.16A). However, they become partially separated by grooves that appear on the lateral wall of the heart tube, at the junction of these two chambers. The right groove remains shallow but the left one becomes very deep (Figs. 15.16B, C) with the result that the left part of the sinus venosus becomes completely separated from the atrial chamber. Its blood now enters the atrium through the right half of the sinus. Simultaneously, the left horn of the sinus venosus and its tributaries become much reduced in size, and the left horn now appears to be just another tributary of the right half of the sinus venosus (Fig. 15.16C). Two important results of these changes are that:

1. The sinu-atrial orifice, that was at first situated in the middle of the posterior aspect of the atrial chamber, now comes to lie on the right side (Fig. 15.4A to C).
2. The orifice, which was at first transverse, now becomes vertical. We have already seen that the margins of this orifice form the right and left ***venous valves*** (Figs. 15.16C, 15.4D).

Some Facts about the Interatrial Septum

Note the following additional facts about the formation of the interatrial septum.

The lower edge of the septum secundum (***crista dividens***) is thick and firm. In contrast, the upper edge of the septum primum (that forms the lower boundary of the foramen

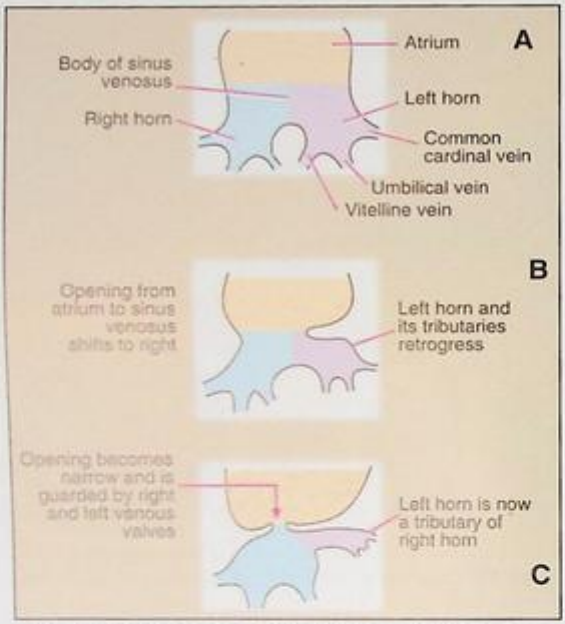

Fig. 15.16: Retrogression of the left horn of sinus venosus.

secundum) is thin and mobile like a flap. When blood tends to flow from the right to the left atrium, this thin flap moves away and there is no obstruction to blood flow. However, when there is a tendency for blood to flow from left to right, this flap comes into apposition with the septum secundum and closes the opening. After birth, the left atrium begins to receive blood from the lungs and the pressure within this chamber becomes greater than that in the right atrium. This causes a closure of the foramen ovale, which is soon permanently obliterated by fusion of the two flaps.

Some Additional Facts about the Interventricular Septum

The interventricular septum is probably formed more by downward enlargement of the right and left ventricular cavities on either side of the septum, rather than by active growth of the septum itself.

The ***membranous part of the interventricular septum*** is divisible into an anterior part, which separates the right and left ventricles, and a posterior part which separates the left ventricle from the right atrium (also called ***atrio-ventricular septum***). The anterior part is derived from the proliferation of tissue from the endocardial cushions as described above. The derivation of the posterior part is shown in Fig. 15.17. It will be seen that the interatrial

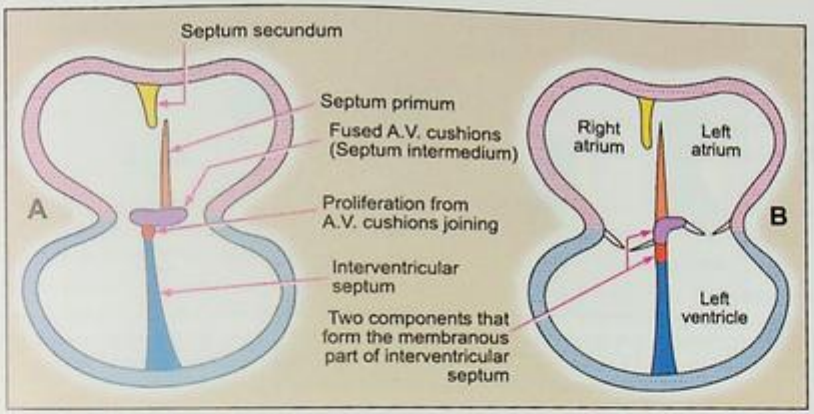

Fig. 15.17: In (A) note that the interatrial and interventricular septa do not meet the atrio-ventricular cushions in the same plane. In (B) note that the membranous part of the interventricular septum is made up (i) of the original. A.V. cushion between the attachment of the interatrial and interventricular septa, and (ii) of the endocardial proliferation from these cushions. The first part separates the left ventricle from the right atrium while the second part separates the two ventricles. The tricuspid valve is attached to the membranous septum at the junction of these parts. These figures are sections in the plane indicated by an arrow in Fig. 15.10A.

and interventricular septa do not meet the atrio-ventricular cushions in the same line. As a result, a part of these cushions separates the left ventricle from the right atrium. This part of the atrio-ventricular cushions forms the posterior part of the membranous septum.

Valves of the Heart

The ***mitral*** and ***tricuspid valves*** are formed by proliferation of connective tissue under the endocardium of the left and right atrio-ventricular canals.

The ***pulmonary*** and ***aortic valves*** are derived from ***endocardial cushions*** that are formed at the junction of the truncus arteriosus and the conus (Fig. 15.18A). Two cushions, right and left, appear in the wall of the conus. They grow and fuse with each other (Fig. 15.18B). With the separation of the aortic and pulmonary openings, the right and left cushions are each subdivided into two parts, one part going to each orifice (Fig. 15.18C). Simultaneously, two more cushions, anterior and posterior appear. As a result, the aortic and pulmonary openings each have three cushions, from which three cusps of the corresponding valve develop.

The pulmonary valve is at first ventral to the aortic valve (Fig. 15.18C). Subsequently, there is a rotation so that the pulmonary valve comes to lie ventral and to the left of the aortic valve (Fig. 15.18D). It is only after this rotation that the cusps acquire their definitive relationships (Pulmonary trunk: 1 posterior, 2 anterior; Aorta: 1 anterior, 2 posterior).

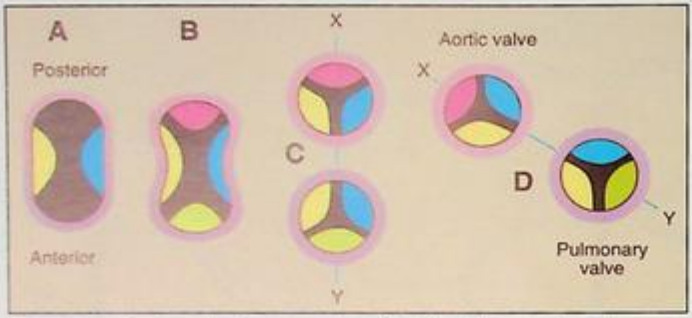

Fig. 15.18: Formation of aortic and pulmonary valves. Note that the vessels undergo an anticlockwise rotation (compare axis XY in (C) and (D)). It is only after this rotation that the cusps of the aortic and pulmonary valves acquire their definitive position.

Conducting System of the Heart

At the stage when there are two heart tubes, a pacemaker (which later forms the ***sinuatrial node***) lies in the caudal part of the left tube. After fusion of the two tubes, it lies in the sinus venosus. When the sinus venosus is incorporated into the right atrium, it comes to lie near the opening of the superior vena cava.

The atrio-ventricular node and the atrio-ventricular bundle form in the left wall of the sinus venosus, and in the atrio-ventricular canal. After the sinus venosus is absorbed into the right atrium, the atrio-ventricular node comes to lie near the interatrial septum.

PERICARDIAL CAVITY

We have already noted several important facts about the development of the pericardial cavity, and these may be briefly recapitulated as follows:

- The pericardial cavity is a derivative of the part of the intra-embryonic coelom that lies in the midline, cranial to the prochordal plate (Fig. 5.11).
- After the formation of the head fold, the pericardial cavity comes to lie on the ventral side of the body of the embryo (Fig. 5.14).
- The heart tube invaginates the pericardial sac from the dorsal aspect (Figs. 15,12C, D).
- The parietal layer of the serous pericardium, and the fibrous pericardium, are derived from the somatopleuric mesoderm lining the ventral side of the pericardial cavity (Fig. 15.12A, D).
- The visceral serous pericardium is derived from the splanchnopleuric mesoderm lining the dorsal side of the pericardial cavity (Fig. 15.12D).
- The heart tube is initially suspended within the pericardial cavity by the dorsal mesocardium, which soon disappears (Fig. 15.13).

We may now consider certain additional facts.

- After disappearance of the dorsal mesocardium, the visceral and parietal layers of pericardium are in continuity only at the arterial and venous ends of the heart tube (Figs. 15.19A, B, D, E).
- With the folding of the heart tube, the arterial and venous ends come closer to each other. The space between them becomes the ***transverse sinus of pericardium*** (Figs. 15.19C, F).
- A number of blood vessels are formed at the two ends of the heart tube. At the arterial end, these are the aorta and the pulmonary trunk. At the venous end, they are the superior vena cava, inferior vena cava, and four pulmonary veins (Fig. 15.20A).
- The definitive reflections of the pericardium are formed merely by rearrangement of these vessels as shown in Fig. 15.20B. Rearrangement of the veins at the venous end results in the formation of an isolated pouch of pericardium, in relation to the four pulmonary veins. This is the ***oblique sinus of pericardium***.

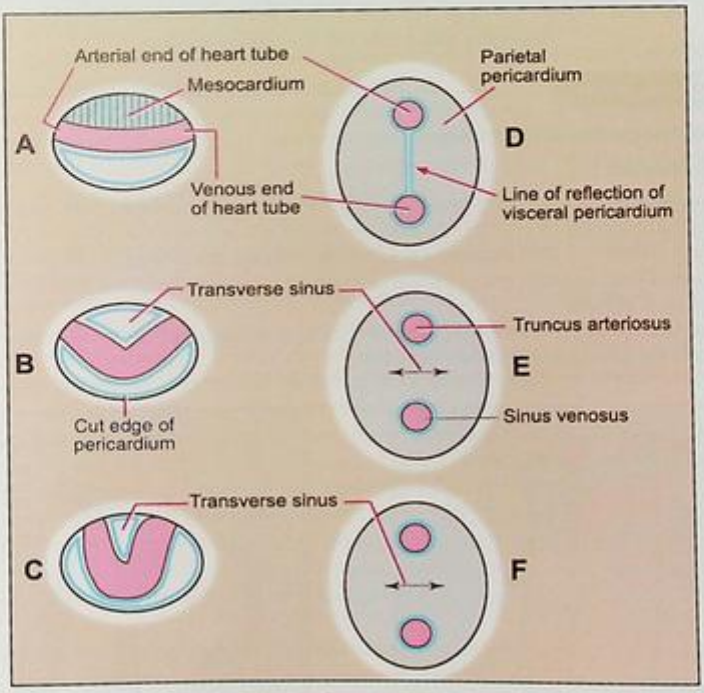

Fig. 15.19: Schemes showing the relationship of the heart tube to the pericardial sac. (A), (B) and (C) are lateral views while (D), (E) and (F) show the dorsal aspect of the interior of the pericardial sac at corresponding stages. Disappearance of the mesocardium leads to formation of the transverse sinus of pericardium. Note that with the folding of the heart tube, the arterial and venous ends of the heart tube are brought closer together, and the transverse sinus comes to lie between them.

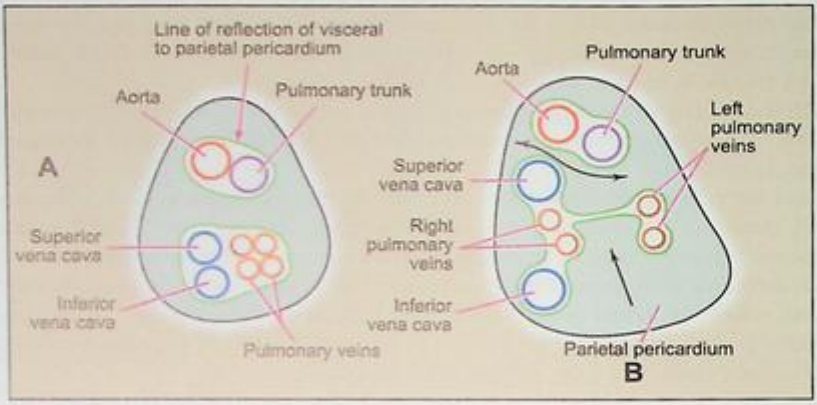

Fig. 15.20: Scheme to show that the oblique sinus of pericardium is established by rearrangement of veins entering the heart. The sinus is indicated by the lower arrow in (B). The upper arrow indicates the transverse sinus.

Clinical Correlation

Congenital Anomalies of the Heart

Anomalies of Position

- ***Dextrocardia:*** The chambers and blood vessels of the heart are reversed from side to side, i.e. all structures that normally lie on the right side are on the left, and vice versa (Fig. 15.21). This may be a part of the condition called ***situs inversus***, in which all organs are transposed. When dextrocardia is not a part of situs inversus, it is usually accompanied by anomalies of the chambers of the heart, and of the great vessels.
- ***Ectopia cordis:*** The heart lies exposed, on the front of the chest, and can be seen from the outside, due to defective development of the chest wall.

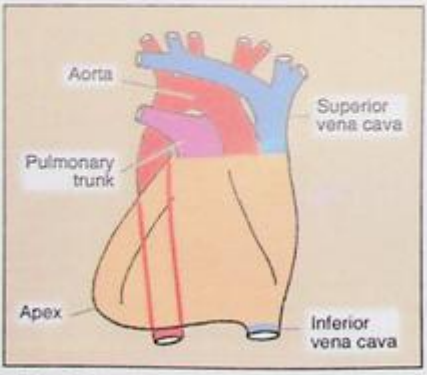

Fig. 15.21: Dextrocardia. The chambers and large blood vessels show right left reversal.

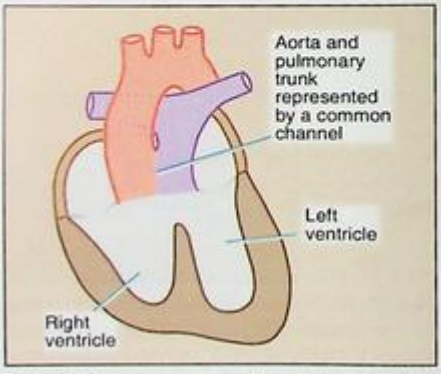

Fig. 15.22: Patent truncus arteriosus. The ascending aorta and pulmonary trunk are represented by a single channel that opens into both ventricles.

Clinical Correlation *contd...*

Atresia or Stenosis

Any of the orifices of the heart may have too narrow an opening (stenosis), or none at all (atresia). The aortic and pulmonary passages may also show supravalvular, or subvalvular, stenosis (Fig. 15.23). Alternatively, the openings may be too large as a result of which the valves become incompetent.

In pulmonary stenosis, the foramen ovale and the ductus arteriosus remain patent. In aortic stenosis also, the ductus arteriosus is patent and blood flows into the aorta through it.

Abnormal Growth

There may be accessory cusps in the valves. Congenital tumours may be formed. The left atrium may be partially subdivided by a transverse septum. The myocardium may be poorly developed (***hypoplasia***).

Defective Formation of Septa

This results in the formation of abnormal passages.

- ***Interatrial septal defects*** may be of three types:
  - The septum primum may fail to reach the atrio-ventricular endocardial cushions, as a result of which the foramen primum persists (Fig. 15.24A). This ***osteum primum defect*** can also be caused by defective formation of atrio-ventricular endocardial cushions.
  - The septum secundum may fail to develop as a result of which the foramen secundum remains wide open (***osteum secundum defect***; Fig. 15.24B).
  - The septum primum and secundum may develop normally but the oblique valvular passage between them may remain patent (***patent foramen ovale***; Fig. 15.24C). The patency is significant only if there is shunt of blood through it. In many cases a probe can be passed through the oblique slit (***probe patency***) but there is no shunt.
  - Occasionally, there is premature closure of the foramen ovale (i.e. before birth). As a result, the right atrium and ventricle undergo great hypertrophy, while the left side of the heart is underdeveloped.
- ***Interventricular septal defects*** may be seen either in the membranous or in the muscular part of the septum (Fig. 15.24D). They are the most common congenital anomalies of the heart.
- ***Defects of the spiral septum:*** The spiral septum may not be formed at all. This condition is called ***patent truncus arteriosus*** (Fig. 15.22). Partial absence of the septum leads to communications (shunts) between the aorta and the pulmonary trunk.
- ***Atrio-ventricular canal defect*** or ***persistent atrio-ventricular canal:*** Defective formation of the atrio-ventricular cushions may lead to a condition in which all four chambers of the heart may intercommunicate. The interatrial and interventricular septa are incomplete (as the normal contributions to these septa from the endocardial cushions are lacking).

If fusion of endocardial cushions is too far to the right, it causes ***tricuspid atresia***. As such cushions are not in alignment with the interventricular septum, the upper part of the latter is defective. With tricuspid atresia there is increased pressure in the right atrium, as a result of which the foramen ovale fails to close.

Defective formation of septa, if marked, can lead to a two-chambered heart (***Cor biloculare***) in which there is one common ventricle and one common atrium. Alternatively, a three-chambered heart (***Cor triloculare***) may be seen; it may consist of a single ventricle with two atria or of a single atrium with two ventricles (***Cor triloculare biventriculare***).

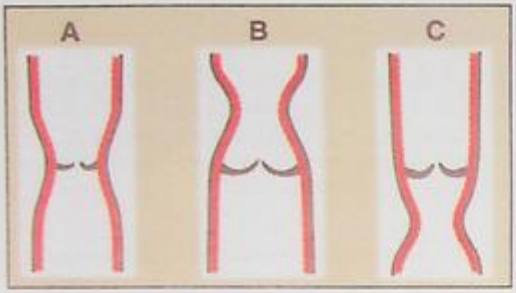

Fig. 15.23: Types of aortic stenosis.
(A) Valvular. (B) Supravalvular. (C) Infravalvular.

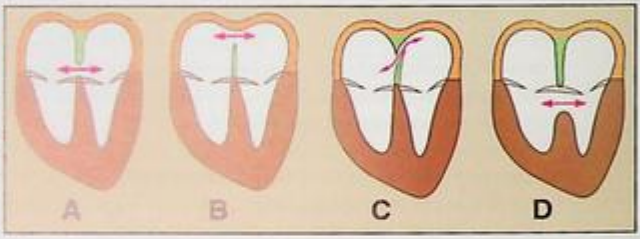

Fig. 15.24 : Septal defects:
(A) Septum primum defect,
(B) Septum secundum defect,
(C) Patent foramen ovale,
(D) Interventricular septum defect.

Clinical Correlation *contd...*

Combined Defects

Two or more of the defects may coexist. One classically recognised condition of this type is known as ***Fallot's tetrology***. It consists of (Fig. 15.25).

- Interventricular septal defect;
- Aorta overriding the free upper edge of the ventricular septum
- Pulmonary stenosis;
- Hypertrophy of the right ventricle.

Other Defects

- The pericardium may be partially or completely absent.
- may be congenital defects in the conducting system of the heart.

Anomalies of Relationship of Chambers to Great Vessels

- ***Transposition of great vessels:*** The aorta arises from the right ventricle and the pulmonary trunk from the left ventricle.
- ***Taussig-Bing syndrome:*** The aorta arises from the right ventricle; and the pulmonary trunk overrides both the right and left ventricles, there being an interventricular septal defect.
- The superior or inferior vena cava may end in the left atrium.
- The pulmonary veins may end in the right atrium or in one of its tributaries.

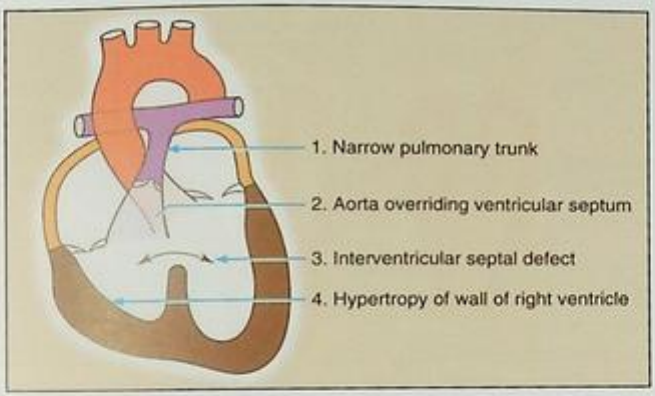

Fig. 15.25: Four features that constitute Fallot's tetrology.

PART 2: THE ARTERIES

Pharyngeal Arch Arteries and Their Fate

The first arteries to appear in the embryo are the right and left ***primitive aortae***. They are continuous with the two endocardial heart tubes. Each primitive aorta consists of a portion lying ventral to the foregut (***ventral aorta***), an arched portion lying in the first pharyngeal arch, and a dorsal portion lying dorsal to the gut (***dorsal aorta***) (Fig. 15.26A).

After the fusion of the two endocardial tubes, the two ventral aortae partially fuse to form the ***aortic sac***, the unfused parts remaining as the ***right and left horns*** of the sac (Fig. 15.26B). Successive arterial arches now appear in the second to sixth pharyngeal arches, each being connected ventrally to the right or left horn of the aortic sac and dorsally to the dorsal aorta (Fig. 15.27). The major arteries of the head and neck, and of the thorax, are derived from these arches as follows:

- The greater part of the first and second arch arteries disappear (Fig. 15.28A).

In adult life, the first arch artery is represented by the ***maxillary artery***. The second arch artery persists for some part of fetal life as the ***stapedial artery***: it may contribute to the formation of the external carotid artery.

- The fifth arch artery also disappears (Fig. 15.28A).
- The aortic sac is, therefore, now connected only with the arteries of the third, fourth and sixth arches. The third and fourth arch arteries open into the ventral part, and the sixth arch artery into the dorsal part, of the aortic sac. The spiral septum, that is formed in the truncus arteriosus, extends into the aortic sac; and fuses with its posterior wall in such a way that blood from the pulmonary trunk passes only into the sixth arch artery, while that from the ascending aorta passes into the third and fourth arch arteries (Fig. 15.28B).

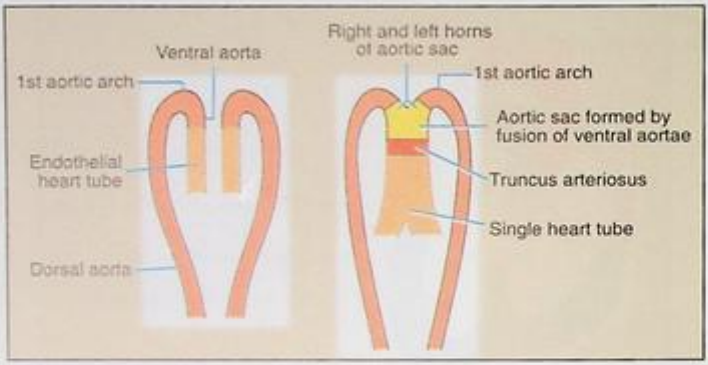

Fig. 15.26: Relation of first aortic arch to heart tubes. (A) Before fusion of heart tubes. (B) After fusion.

- Several changes now take place in the arterial arches to produce the adult pattern as follows:
  - The two dorsal aortae grow cranially, beyond the point of attachment of the first arch artery (Fig. 15.28B).
  - The portion of the dorsal aorta, between the attachment of the third and fourth arch arteries (***ductus caroticus***), disappears on both sides (Fig. 15.28B).

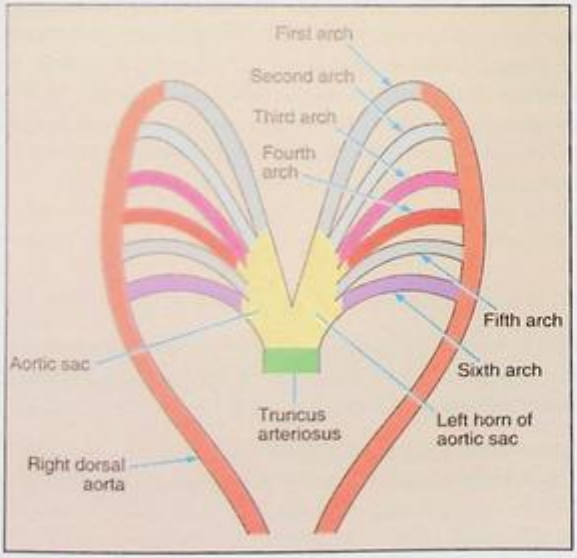

Fig. 15.27: Aortic arches. Each arch connects the aortic sac to the dorsal aorta. Note that actually all arches are never present at the same time. The first and second arches have retrogressed by the time the sixth appears.

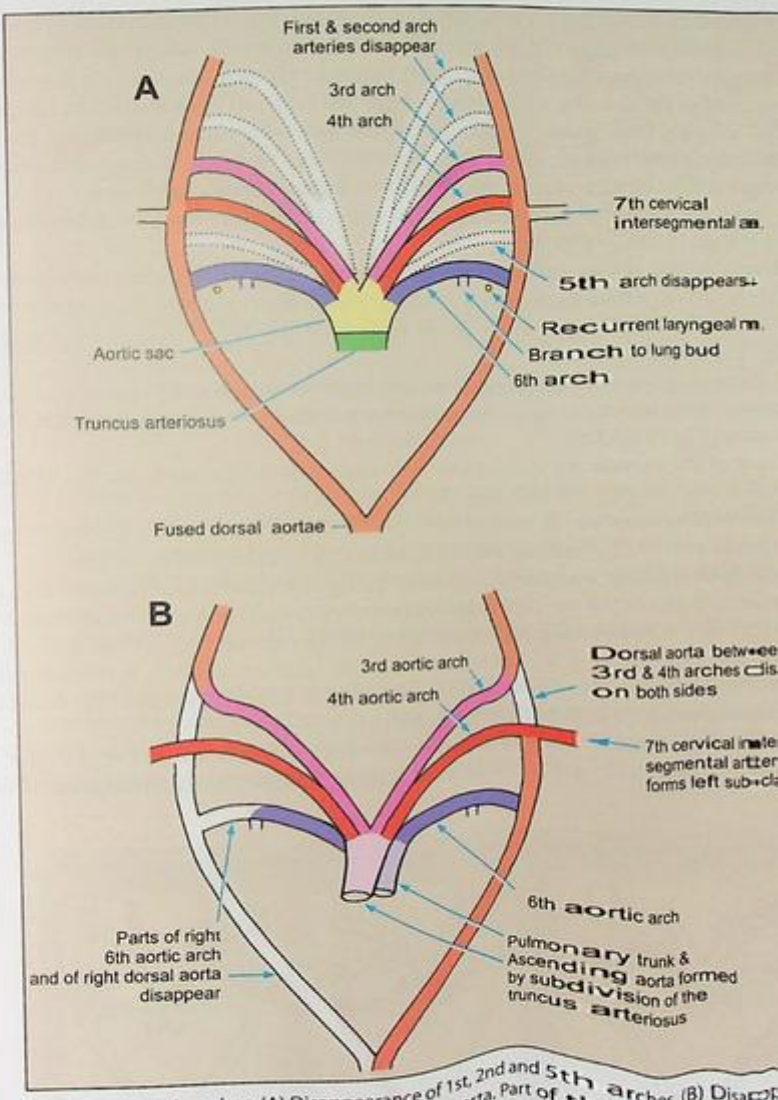

Fig. 15.28: Fate of aortic arches: (A) Disappearance of 1st, 2nd and 5th arches. (B) Disap
caroticus (on both sides), and of part of right dorsal aorta. Part of the right 6th arch a

- The portion of the right dorsal aorta, between the point of attachment of the fourth arch artery and the point of fusion of the two dorsal aortae, disappears (Fig. 15.28B).
- Each sixth arch artery gives off an artery to the developing lung bud. On the right side, the portion of the sixth arch artery between this bud and the dorsal aorta, disappears. On the left side, this part remains patent and forms the ***ductus arteriosus***. The ducts arteriosus carries most of the blood from the right ventricle to the dorsal aorta. It is obliterated after birth and is then seen as the ***ligamentum arteriosum***.
- Each third arch artery gives off a bud that grows cranially to form the ***external carotid artery*** (Figs. 15.29A, 15.31A).
- The dorsal aortae give off a series of lateral intersegmental branches to the body wall. One of these, the seventh cervical intersegmental artery supplies the upper limb bud. It comes to be attached to the dorsal aorta near the attachment of the fourth arch artery (Fig. 15.29A).

The development of the main arteries can now be summarised as follows:

- The ***ascending aorta*** and the ***pulmonary trunk*** are formed from the truncus arteriosus (Fig. 15.28B).
- The ***arch of the aorta*** is derived from the ventral part of the aortic sac (1), its left horn (2), and the left fourth arch artery (3) (Fig. 15.29A).
- The ***descending aorta*** is derived from the left dorsal aorta, below the attachment of fourth arch artery (1), along with the fused median vessel (2) (Fig. 15.29B).
- The ***brachiocephalic artery*** is formed by the right horn of the aortic sac (Fig. 15.29C).
- The proximal part of the right ***subclavian artery*** is derived from the right fourth arch artery (1), the remaining part of the artery being derived from the seventh cervical intersegmental artery (2). On the left side, the subclavian artery is derived entirely from the seventh cervical intersegmental artery (3), which arises from the dorsal aorta opposite the attachment of the fourth arch artery (Fig. 15.30A).
- The ***common carotid artery*** is derived, on either side, from part of the third arch artery, proximal to the external carotid bud (Fig. 15.30B). The ***internal carotid artery***

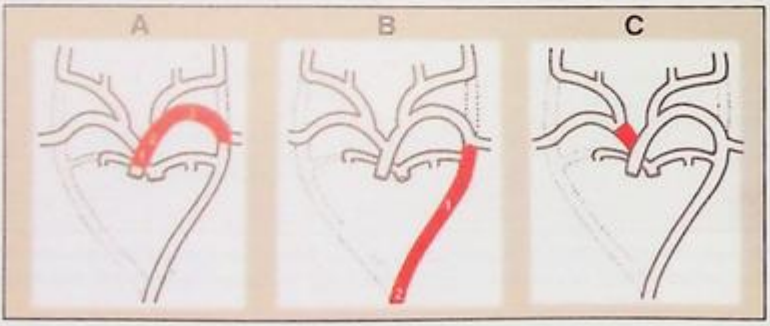

Fig. 15.29: (A) The arch of the aorta is derived from (1) the aortic sac, (2) its left horn, and (3) the left 4th arch artery. (B) The descending aorta is derived from (1) the left dorsal aorta, and (2) fused dorsal aortae. (C) The brachiocephalic artery is derived from the right horn of the aortic sac.

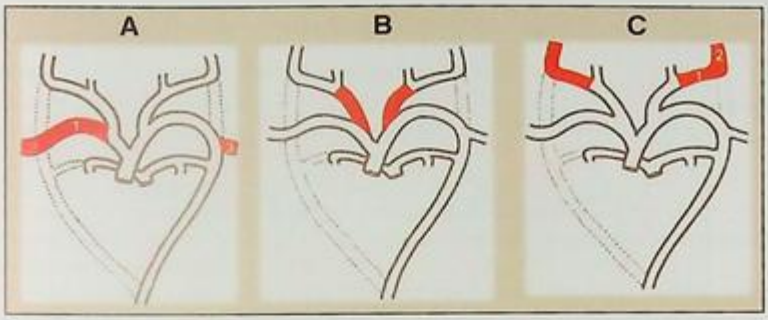

Fig. 15.30: (A) The right subclavian artery is derived (1) from the right 4th arch artery and (2) from the right 7th cervical intersegmental artery. The left subclavian artery is formed only from the left 7th cervical intersegmental artery. (B) The common carotid artery is derived from the proximal part of the 3rd arch artery. (C) The internal carotid artery is derived from (1) distal part of the 3rd arch artery and (2) dorsal aorta (cranial-most part).

is formed by the portion of the third arch artery distal to the bud (1), along with the original dorsal aorta cranial to the attachment of the third arch artery (2) (Fig. 15.30C). As the right third and fourth arch arteries arise from the right horn of the aortic sac, the common carotid and subclavian arteries become branches of the brachiocephalic artery.

- As already mentioned, the ***external carotid artery*** arises as a bud from the third arch artery (Fig. 15.31A).
- The ***pulmonary arteries*** are derived from the part of the sixth arch arteries lying between the pulmonary trunk and the branches to the lung buds (Fig. 15.31B).

As already stated, the part of the left sixth arch artery, between the branch to the lung bud and the aorta, forms the ***ductus arteriosus*** (Fig. 15.31C).

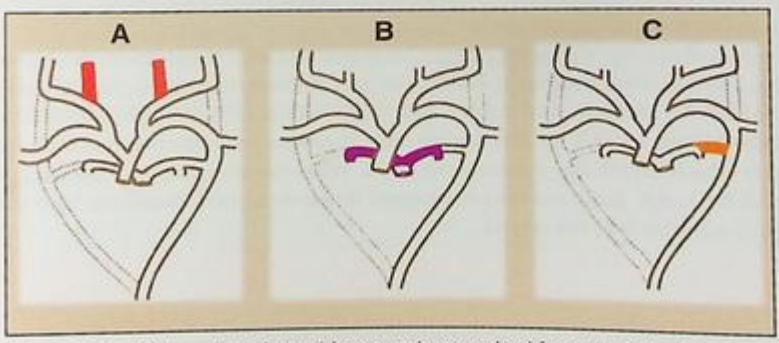

Fig. 15.31: (A) The external carotid artery arises as a bud from the 3rd arch artery. (B) The pulmonary arteries arise from the 6th arch arteries. (C) The ductus arteriosus is derived from part of the left 6th arch artery.

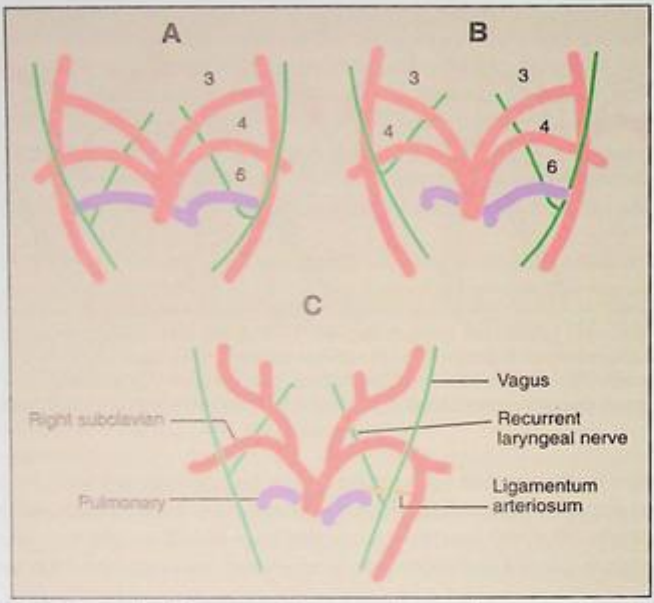

Fig. 15.32: Relationship of the vagus and recurrent laryngeal nerves to the aortic arches. For explanation see text.

The relationship of the main nerves of the head and neck to the arteries, can be explained on the basis of the development of the arteries. The nerves of the pharyngeal arches are, at first, lateral to the corresponding arteries. The nerves of the first, second and third arches (V, VII & IX) retain their lateral positions. The disappearance of the ductus caroticus, enables the nerve of the fourth arch (superior laryngeal) to move medially, and it comes to lie deep to the main arteries of the neck.

The nerve of the sixth arch (recurrent laryngeal), is at first caudal to the artery of this arch (Fig. 15.32A). With the disappearance of part of the sixth arch artery, on the right side, the nerve moves cranially and comes into relationship with the right fourth arch artery (subclavian) (Figs. 15.32B, C). On the left side, it retains its relationship to that part of the sixth arch which forms the ductus arteriosus. With the elongation of the neck, and the descent of the heart, these nerves are dragged downwards and, therefore, have to follow a recurrent course back to the larynx.

Clinical Correlation

Anomalous Development of Pharyngeal Arch Arteries

We have seen that the development of the normal arterial pattern is dependent upon the disappearance of some parts of the pharyngeal arch arteries. Occasionally this process is disturbed in that:

- Some parts that normally disappear may persist; and
- Some parts that normally persist may disappear.

As a result, several anomalies may be produced. Some of these are as follows:

- ***Double aortic arch*** (Fig. 15.33A). The arterial ring can compress the trachea and oesophagus.
- ***Right aortic arch*** (Fig. 15.33B).
- The ductus arteriosus, which is normally occluded soon after birth, may remain patent (***patent ductus arteriosus***).
- The right subclavian artery may arise as the last branch of the aortic arch (Fig. 15.33C). Such an artery runs to the right behind the oesophagus (Fig. 15.34). Along with the aorta this artery forms an arterial ring enclosing the trachea and oesophagus. The ring may press upon and obstruct these tubes. In this abnormality, the right recurrent laryngeal nerve does not hook around the subclavian artery. It passes directly to the larynx. An arterial ring can also be formed if the dorsal aorta persists on both sides.
- The ductus caroticus may persist. As a result, the left internal carotid arises directly from the aortic arch, and the right internal carotid from the subclavian (Fig. 15.33D).
- ***Interrupted aortic arch:*** A segment of the aortic arch may be missing. The ascending aorta ends by supplying the left common carotid artery. The left subclavian artery arises from the distal segment which receives blood through a patent ductus arteriosus.
- Some other anomalies of the mode of origin of the branches of the arch of the aorta are illustrated in Fig. 15.35.
- The aorta may show a localised narrowing of its lumen, leading to partial or even complete obstruction to blood flow. This condition is called ***coarctation of the aorta***. Coarctation is most frequently seen near the attachment of the ductus arteriosus to the aorta. It may be (1) distal to the attachment of the ductus (***postductal***), or (2) proximal to the attachment (***preductal***) in which case the, right ventricle supplies the distal part of the body through the ductus arteriosus.

  When coarctation is postductal, numerous anastomoses are established between branches of the aorta taking origin above the constriction and those arising below this level. Coarctation is said to be a result of the process of obliteration of the ductus arteriosus extending into the aorta. It can also occur as an abnormality in the vessel wall.

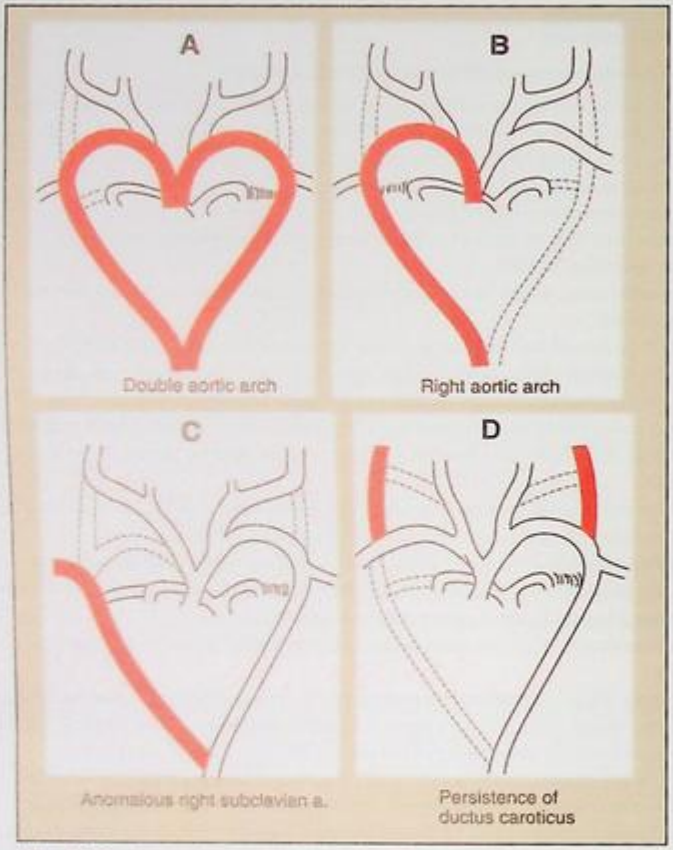

Fig. 15.33: Anomalies associated with the development of aortic arches. The abnormal vessels are shown in red.

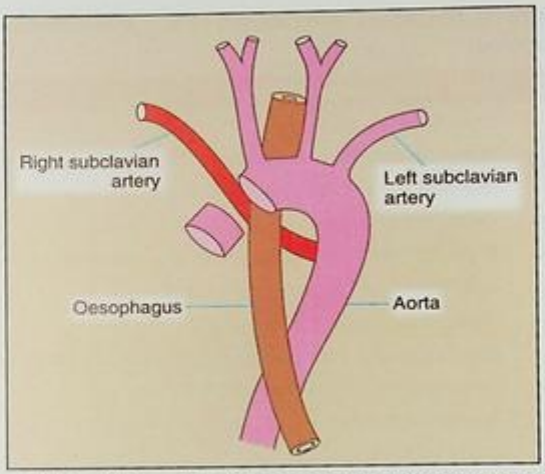

Fig. 15.34: Relationship of abnormal right subclavian artery to the oesophagus and to the arch of the aorta.

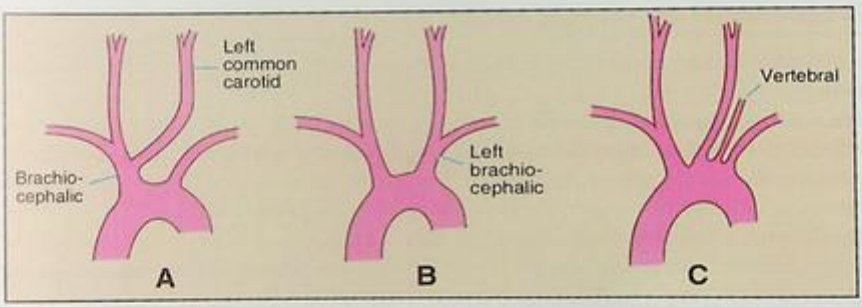

Fig. 15.35: Anomalies in the pattern of the main branches of the arch of the aorta. (A) Left common carotid arising from brachiocephalic artery. (B) Left subclavian and left common carotid arising by a common stem (left brachiocephalic). (C) Left vertebral artery arising directly from arch of aorta.

Table 15.1: Summary of the adult derivatives of truncus arteriosus, aortic sac and aortic arches.

Adult Derivatives	Embryological Structures
Ascending aorta	Truncus arteriosus
Arch of aorta	Aortic sac, left horn of aortic sac and left 4th arch artery
Descending aorta	Left dorsal aorta and fused dorsal aorta
Brachiocephalic artery	Right horn of aortic sac
Right subclavian artery	Right 4th arch artery and 7th cervical intersegmental art.
Left subclavian artery	Left 7th cervical intersegmental artery
Common carotid artery	Proximal part of 3rd arch artery
Internal carotid artery	Distal part of 3rd arch artery and cervical part of dorsal aorta.
External Carotid artery	As a bud from 3rd arch artery
Pulmonary trunk	Truncus arteriosus
Pulmonary artery	Part of 6th arch artery
Ductus arteriosus	Part of left 6th arch artery between lung bud and aorta.

DEVELOPMENT OF OTHER ARTERIES

The primitive dorsal aortae give off three groups of branches (Fig. 15.36). These are as follows:

- The ***ventral splanchnic arteries*** supply the gut. Most of these arteries disappear but three arteries, the ***coeliac, superior mesenteric*** and ***inferior mesenteric*** remain to supply the infradiaphragmatic part of the foregut, the midgut, and the hindgut respectively. Other remnants of these vessels are the ***bronchial*** and ***oesophageal*** arteries.
- The ***lateral or intermediate splanchnic arteries*** supply structures developing from the intermediate mesoderm. These persist as the ***renal, suprarenal, phrenic,*** and ***spermatic*** or ***ovarian*** arteries.
- The ***dorso-lateral*** (***somatic intersegmental***) branches run between two adjacent segments. They retain their original intersegmental arrangement in the thoracic and lumbar regions where they can be recognised as the ***intercostal*** and ***lumbar*** arteries.

Each dorso-lateral artery divides into a dorsal and a ventral division. The ventral division gives off a lateral branch that is most conspicuous in the region of the limb buds.

The dorsal division runs dorsally and supplies the muscles of the back. Each dorsal division gives off a spinal branch that runs medially to supply the spinal cord.

The branches of the dorso-lateral arteries of successive segments become interconnected by the formation of longitudinal anastomoses. In the neck, the dorsal branches are connected by anastomoses that are formed in three situations (Fig. 15.37).

1. ***Pre-costal***, in front of the necks of the ribs (or costal elements).
2. ***Post-costal***, between the costal elements and the transverse processes.
3. ***Post-transverse***, behind the transverse processes.

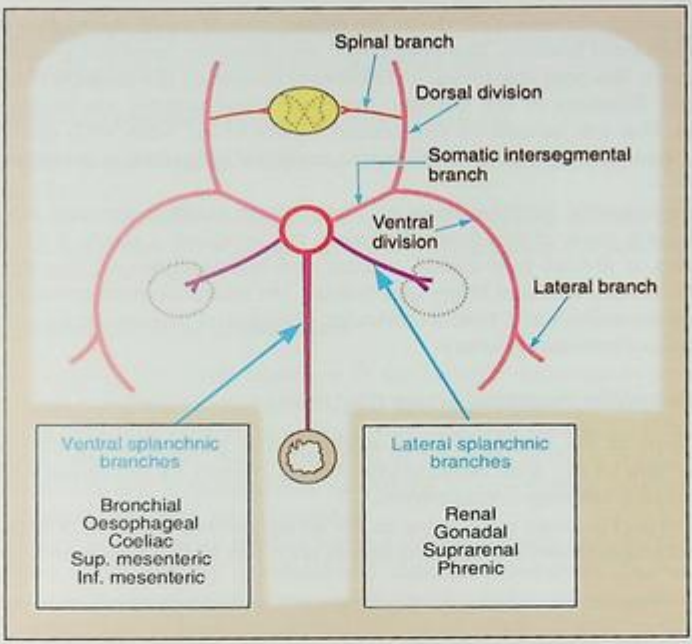

Fig. 15.36: Basic branching pattern of the embryonic dorsal aorta.

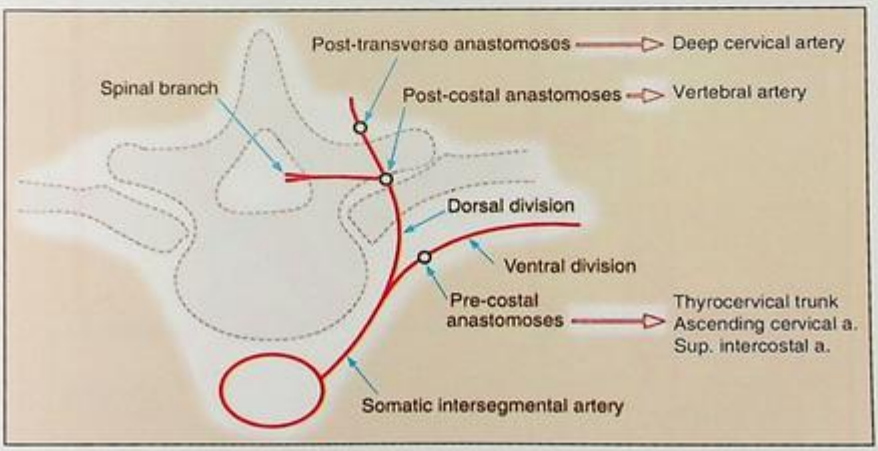

Fig. 15.37: Sites of vertical anastomoses between branches of dorsal aorta. The fate of the anastomoses is also shown.

The pre-costal anastomoses persist as the ***thyrocervical trunk***, ***ascending cervical*** and ***superior intercostal*** arteries. The post-costal anastomoses form the greater part of the ***vertebral*** artery. The post-transverse anastomoses remain as the ***deep cervical*** artery.

The ventral divisions of the somatic intersegmental arteries are interconnected by anastomoses, that are formed on the ventral aspect of the body wall, near the midline (Fig. 15.39). These form the ***internal thoracic***, ***superior epigastric*** and ***inferior epigastric*** arteries.

At this stage, special mention must be made of the ***seventh cervical intersegmental artery***. The main stem of this artery becomes the subclavian artery. Like other dorsolateral arteries, it divides into dorsal, ventral and lateral divisions. The dorsal division forms the stem of the vertebral artery (see below). The lateral division grows into the upper limb forming the axillary and brachial arteries. The ventral division forms the stem of the internal thoracic (mammary) artery.

Development of the Vertebral Artery (Fig. 15.38)

- The first part of the artery, from its origin to the point of entry into the foramen transversarium of the sixth cervical vertebra, is formed by the dorsal division of the seventh cervical intersegmental artery.
- The vertical part (second part), lying in the foramina transversaria, is formed from the post-costal anastomoses between the first to sixth cervical intersegmental arteries.

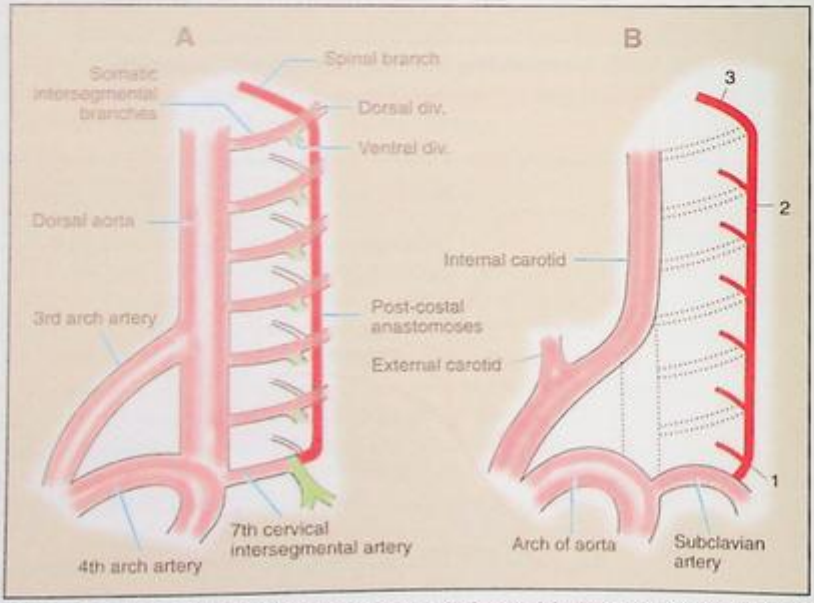

Fig. 15.38: Development of the vertebral artery. In (B) the part labelled 1 is derived from the dorsal division of the seventh cervical intersegmental artery; 2 from the post-costal anastomoses; and 3 from the spinal branch of the first cervical intersegmental artery.

- The third (horizontal) part, running transversely on the arch of the atlas, is derived from the spinal branch of the first cervical intersegmental artery.

Development of the Internal Thoracic Artery (Fig. 15.39)

- The main stem of the artery is formed by the ventral division of the seventh cervical intersegmental artery.
- The vertical part of the artery (including its superior epigastric branch) is derived from the ventral anastomoses between the ventral divisions of the thoracic intersegmental arteries (intercostal arteries).

Development of the Arteries of the Limbs

The limbs are supplied by lateral branches of the somatic intersegmental arteries, that belong to the segments from which the limb buds take origin. These vessels form an arterial plexus. However, each limb soon comes to have one ***axis artery*** that runs along the central axis of the limb. Other arteries, that are formed as branches of the axis artery, or as new formations, later take over a considerable part of the arterial supply, as a result of which much of the original axis artery may disappear.

The ***axis artery of the upper limb*** is formed by the seventh cervical intersegmental artery. It persists as the ***axillary***, ***brachial*** and ***anterior interosseus*** arteries, and as the ***deep palmar arch***. The ***radial*** and ***ulnar*** arteries appear late in development.

The ***left subclavian artery*** represents the main stem of the seventh cervical intersegmental artery, and the proximal part of its lateral division (Fig. 15.39). This explains the origin of the vertebral (dorsal division) and internal thoracic (ventral division) arteries from it. The distal part of the ***right subclavian artery*** has a similar origin, but its proximal part is derived, as already noted, from the right fourth aortic arch.

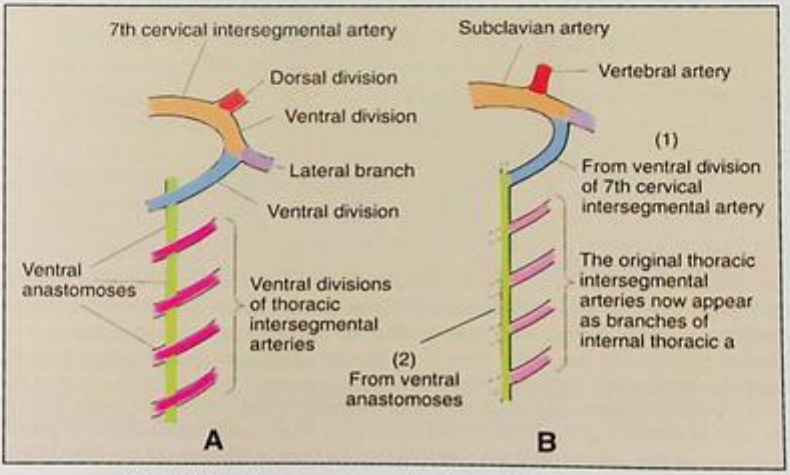

Fig. 15.39: Development of the internal thoracic artery.

The ***axis artery of the lower limb*** is derived from the fifth lumbar intersegmental artery. It is seen as a branch of the internal iliac and runs on the dorsal aspect of the limb. The femoral artery is a new vessel formed on the ventral aspect of the thigh. Proximally it gets linked above with the external iliac (which is a branch of the axis artery), and below with the popliteal artery.

In the adult, the original axis artery is represented by:

- the inferior gluteal artery,
- a small artery accompanying the sciatic nerve,
- the part of the popliteal artery above the level of the popliteus muscle,
- the distal part of the peroneal artery,
- and part of the plantar arch.

Umbilical Artery

Before the fusion of the two dorsal aortae, the umbilical arteries appear as continuations of their distal ends (Fig. 15.40A). After fusion of the dorsal aortae, they appear as lateral branches of the single dorsal aorta (Fig. 15.40B). Subsequently, each umbilical artery

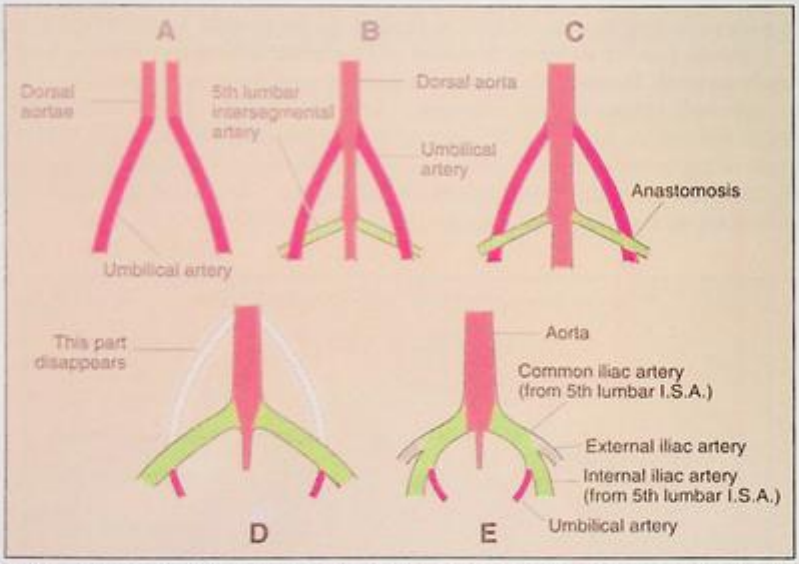

Fig. 15.40: Development of the umbilical artery. (A) Umbilical arteries are seen as continuations of the right and left dorsal aortae, before their fusion. (B) After fusion of dorsal aortae, the umbilical arteries appear as lateral branches of the aorta. They cross the 5th lumbar intersegmental artery. (C) Umbilical arteries establish anastomoses with the 5th lumbar intersegmental artery. (D) The part of the umbilical artery between the dorsal aorta and the 5th lumbar intersegmental artery disappears; and the umbilical artery is now seen as a branch of the latter. (E) The 5th lumbar intersegmental artery forms the common iliac and internal iliac arteries; and the umbilical is now seen as a branch of the internal iliac.

gets linked up with that part of the fifth lumbar intersegmental artery which forms the internal iliac artery (Fig. 15.40C). The part of the umbilical artery, between the aorta and the anastomosis with the internal iliac, disappears so that the umbilical artery is now seen as a branch of the internal iliac (Fig. 15.40 D, E). In post-natal life, the proximal part of the umbilical artery becomes the ***superior vesical artery***, while its distal part is obliterated to form the medial umbilical ligament.

PART 3: VEINS

The main veins of the embryo may be divided into two groups, visceral and somatic.

Visceral Veins

These are:

1. Right and left ***vitelline veins*** from the yolk sac. These are also called ***omphalomesenteric veins***.
2. Right and left ***umbilical veins*** from the placenta.

The umbilical and vitelline veins open into the corresponding horn of the sinus venosus (Fig. 15.41A). The parts of these veins that are nearest to the heart are embedded in the septum transversum. These veins undergo considerable changes as follows:

- With the development of the liver, in the septum transversum, the proximal parts of the vitelline and umbilical veins become broken up into numerous small channels that contribute to the sinusoids of the liver. These sinusoids drain into the sinus venosus, through the persisting terminal parts of the vitelline veins, that are now called the right and left ***hepato-cardiac channels*** (Fig. 15.41B). The proximal parts of the umbilical veins lose their communications with the sinus venosus.
- Meanwhile, the left horn of the sinus venosus undergoes retrogression and as result the left hepato-cardiac channel disappears. All blood form the umbilical and vitelline veins now enters the sinus venosus through the right hepato-cardiac channel (also called ***common hepatic vein***). This vessel later forms the cranial most part of the inferior vena cava (Fig. 15.41C).
- The right umbilical vein disappears, and all blood from the placenta now reaches the developing liver through the left vein (N.B. The left vein is 'left') (Fig. 15.41D). In order to facilitate the passage of this blood through the liver, some of the sinusoids enlarge to create a direct passage connecting the left umbilical vein to the right hepato-cardiac channel. This passage is called the ***ductus venosus***.
- While these changes are occurring within the liver, the parts of the right and left vitelline that lie outside the substance of the liver, undergo alterations leading to the formation of the portal vein.

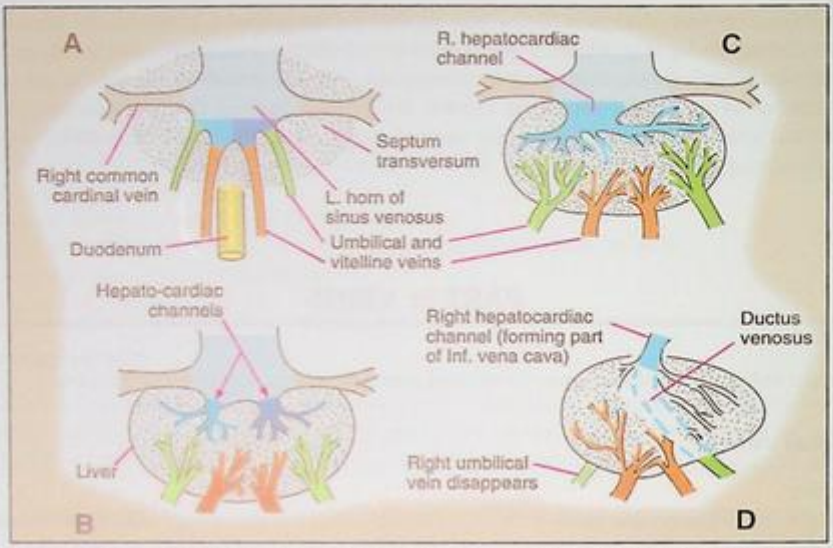

Fig. 15.41: Umbilical and vitelline veins. (A) Note the umbilical and vitelline veins passing through the septum transversum to reach the sinus venosus. (B) Growth of liver cells within the septum transversum breaks up part of the umbilical and vitelline veins into capillaries. Blood reaching the liver through the umbilical and vitelline veins now goes to the heart through the right and left hepato-cardiac channels. (C) Left hepato-cardiac channel disappears. (D) Right hepato-cardiac channel (which later forms part of the inferior vena cava) now drains the liver. Right umbilical veins disappears. All blood from the placenta now reaches the liver through the left umbilical vein. Formation of ductus venosus short circuits this blood to the right hepato-cardiac channel.

Development of the Portal Vein

- The proximal parts of the two vitelline veins lie on the right and left sides of the developing duodenum (Fig. 15.42A).
- The veins soon become interconnected by three transverse anastomoses, two of which lie ventral to the duodenum. The third anastomosis lies dorsal to the duodenum, and is between the two ventral anastomoses (Fig. 15.42B).
- The superior mesenteric and splenic veins (which develop independently) join the left vitelline vein, a short distance caudal to the dorsal anastomosis.
- Some parts of the vitelline veins now disappear. The portal vein and its right and left divisions are derived from the veins that remain (Fig. 15.42C).

The veins that disappear are:

- part of the right vitelline vein caudal to the dorsal anastomosis;
- part of the left vitelline vein caudal to the entry of the superior mesenteric and splenic veins;

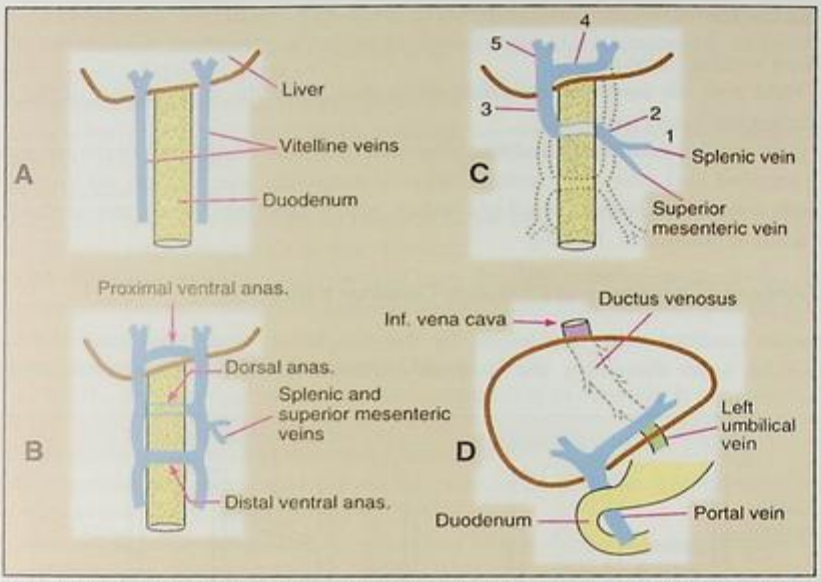

Fig. 15.42: Development of the portal vein. (A) Right and left vitelline veins. (B) Vitelline veins joined by three transverse anastomoses: Cranial ventral, caudal ventral and dorsal. (C) Some of the veins disappear. The portal vein is formed from: 1. Part of left vitelline vein. 2. Dorsal anastomosis. 3. Part of right vitelline vein. The cranial ventral anastomosis becomes the left branch of the portal vein.

- the caudal ventral anastomosis; and
- the left vitelline vein between dorsal anastomosis and cranial ventral anastomosis.

The veins that persist to form the stem of the portal vein are (Fig. 15.42C):

- the left vitelline vein between the entry of the superior mesenteric and splenic veins and the dorsal anastomosis (1, in figure);
- the dorsal anastomosis itself (2); and
- the right vitelline vein between the dorsal anastomosis and the cranial ventral anastomosis (3).

The cranial ventral anastomosis, and a part of the left vitelline vein cranial to this anastomosis, now form the left branch of the portal vein (4), while the right vitelline vein cranial to this anastomosis forms the right branch (5). The sinusoids that carry the blood of these branches to the liver substance constitute the ***venae advehentes***. Those sinusoids that drain this blood to the inferior vena cava are called the ***venae revehentes***, and form the tributaries of the hepatic veins.

The left umbilical vein now ends in the left branch of the portal vein (Fig. 15.42D), while the ductus venosus connects the left branch of the portal vein to the inferior vena cava (right hepato-cardiac channel).

Somatic Veins

The earliest somatic veins are:

- the right and left ***anterior cardinal*** veins that drain the cranial part of the embryo, including the brain; and
- the right and left ***posterior cardinal*** veins that drain the caudal part of the embryo.

The anterior and posterior cardinal veins of each side join to form the corresponding ***common cardinal vein*** (or ***duct of Cuvier***), which open into the corresponding horns of the sinus venosus (Fig. 15.43A).

Fate of Anterior Cardinal and Common Cardinal Veins

The anterior cardinal veins are joined by the subclavian veins that drain the forelimbs (Fig. 15.43B). Soon thereafter, the anterior cardinal veins become interconnected by a

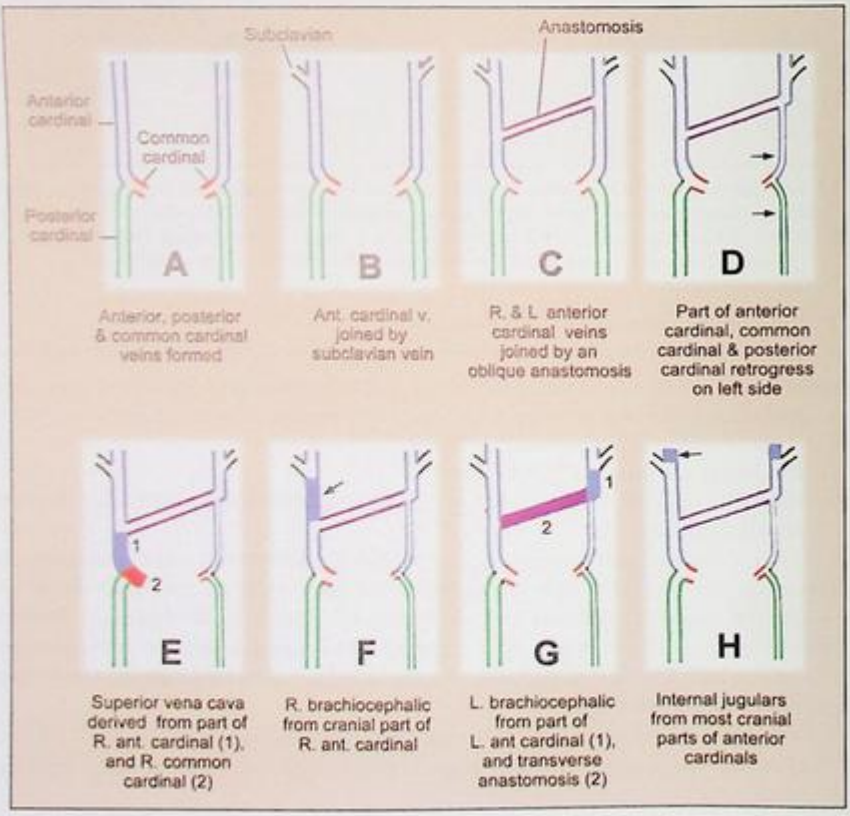

Fig. 15.43: Fate of anterior cardinal veins, and the development of major veins draining the upper part of the body.

transverse anastomosis (Fig. 15.43C), proximal to their junction with the subclavian veins. The part of the left anterior cardinal vein caudal to this anastomosis retrogresses, and so does the left common cardinal (Fig. 15.43D).

The ***Superior vena cava*** is derived from (Fig. 15.43E):

- the right anterior cardinal vein, caudal to the transverse anastomosis with the left anterior cardinal (1, in figure); and
- the right common cardinal vein (2).

Note that the right horn of the sinus venosus forms part of the right atrium, and thus the superior vena cava comes to open into this chamber.

The ***right brachiocephalic vein*** is derived from the right anterior cardinal vein, between the point of its junction with the subclavian vein and the point of its junction with the transverse anastomosis (Fig. 15.43F).

The ***left brachiocephalic vein*** is derived from (Fig. 15.43G):

- the part of the left anterior cardinal vein corresponding to the right brachiocephalic vein (1); and
- the transverse intercardinal anastomosis (2).

The ***internal jugular veins*** develop from the parts of the anterior cardinal veins cranial to their junction with the subclavian veins (Fig. 15.43H).

The ***external jugular veins*** arise as secondary channels and are not derived from the anterior cardinal veins.

The anterior and posterior cardinal veins receive a series of ***intersegmental veins*** from the body wall (corresponding to the intersegmental branches of the dorsal aortae; Fig. 15.44). The ***subclavian veins*** are formed by considerable enlargement of one of these veins in the region of the upper limb bud (Fig. 15.44).

We have seen that the caudal part of the anterior cardinal vein, and the whole of the common cardinal vein, of the left side undergo retrogression. The greater part of the posterior cardinal vein of this side disappears, but a small part adjoining the common cardinal vein persists as a small vein. We have also noted that the left horn of the sinus venosus undergoes considerable retrogression and is reduced to a tributary of the right horn.

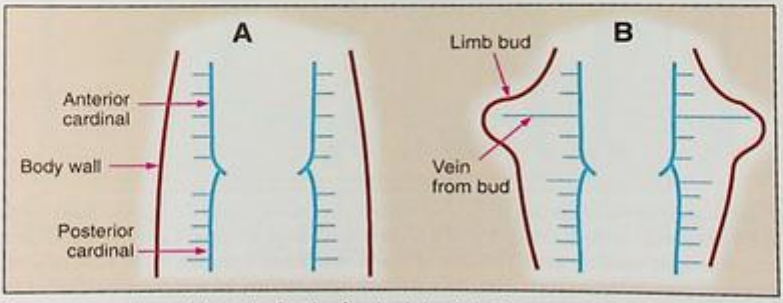

Fig. 15.44: Formation of the vein for the forelimb bud. In (A) we see veins from the body wall draining into the anterior and posterior cardinal veins. In (B) we see that one of these veins lying at the level of the limb bud enlarges to drain the limb.

These retrogressing veins of the left side persist into adult life as the left superior intercostal vein and the coronary sinus which are derived as follows:

The ***left superior intercostal vein*** is formed by (Fig. 15.45)

- the left anterior cardinal vein caudal to the transverse anastomosis; and
- the most cranial part of the left posterior cardinal vein. The second and third intercostal veins drain into this vein.

The medial part of the ***coronary sinus*** is derived from the left horn of the sinus venosus (Fig. 15.46). The lateral part of the coronary sinus is derived from the proximal part of the left common cardinal vein. The remaining part of the left common cardinal vein persists as the ***oblique vein of the left atrium.***

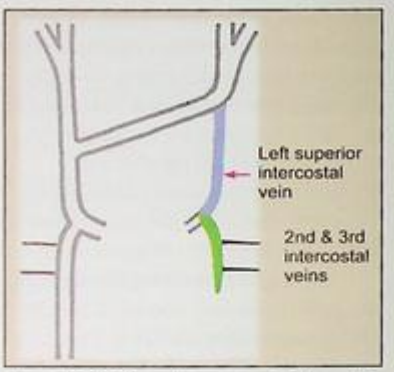

Fig. 15.45: Development of the left superior intercostal vein. The part labelled 1 is derived from the anterior cardinal vein; and 2 from posterior cardinal vein. Note the intercostal veins draining into it.

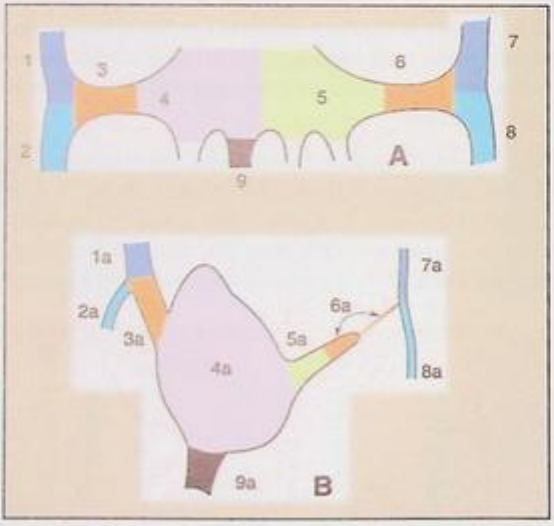

Fig. 15.46: Derivation of the coronary sinus and related structures. 1 and 7 = right and left anterior cardinal veins; 2 and 8= posterior cardinal veins; 3 and 6 = common cardinal veins; 4 and 5= right and left horns of sinus venosus; 9 = right vitelline vein. The fate of these structures is shown in (B) 1a + 3a = superior vena cava; 2a = terminal part of the azygos vein; 4a = part of right atrium; 5a and proximal half of 6a= coronary sinus; distal half of 6a = oblique vein of left atrium; 7a + 8a = left superior intercostal vein; 9a = inferior vena cava.

Veins of the Abdomen

The inferior vena cava, the veins of the kidneys, gonads and suprarenals, and the veins draining the walls of the thorax and abdomen, are derived from a series of longitudinal venous channels that appear in the embryo. Some of these are as follows:

- The ***posterior cardinal veins:*** We have already seen that at their cranial ends these veins join the anterior cardinal veins to form the common cardinal veins.
  Near their caudal ends they receive the veins of the lower limb bud (external iliac) and of the pelvis (internal iliac) (Fig. 15.47A). The caudal ends of the two posterior cardinal veins become interconnected by a transverse anastomosis (Fig. 15.47B).
- The ***subcardinal veins*** (green in Fig. 15.48) are formed in relation to the mesonephros. Cranially and caudally they communicate with the posterior cardinal veins. The subcardinals receive the veins from the developing kidneys.
  At the level of the renal veins, the two subcardinals become connected by a transverse ***intersubcardinal anastomosis*** (Fig. 15.47D).
  The cranial part of the right subcardinal vein also establishes an anastomosis with the right hepato-cardiac channel (Fig. 15.48A).
- The ***supracardinal veins*** (also called thoracolumbar veins) (red in Fig. 15.48) communicate cranially and caudally with posterior cardinal veins. They also communicate with the subcardinal veins through anastomoses which join the subcardinals just below the renal veins (Fig. 15.48B).

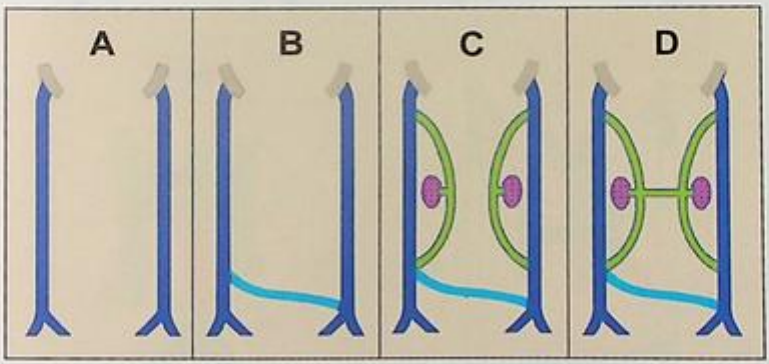

Fig. 15.47: (A) Posterior cardinal veins. (B) Formation of transverse anastomosis. (C) Formation of subcardinal veins. Note that they drain the developing kidney. (D) The two subcardinal veins become interconnected.

Many parts of these longitudinal venous channels disappear (Fig. 15.48C). The veins that remain give rise to the inferior vena cava, renal veins, veins of gonads and the suprarenal veins as follows:

The ***inferior vena cava*** is derived from the following in caudal to cranial sequence (Fig. 15.48D):

- The ***lowest part of the right posterior cardinal vein*** (between its junction with the supracardinal, and the anastomosis between the two posterior cardinals.
- The ***lower part of the right supracardinal vein*** (between its junction with the posterior cardinal, and the supracardinal-subcardinal anastomosis).
- The ***right supracardinal-subcardinal anastomosis.***

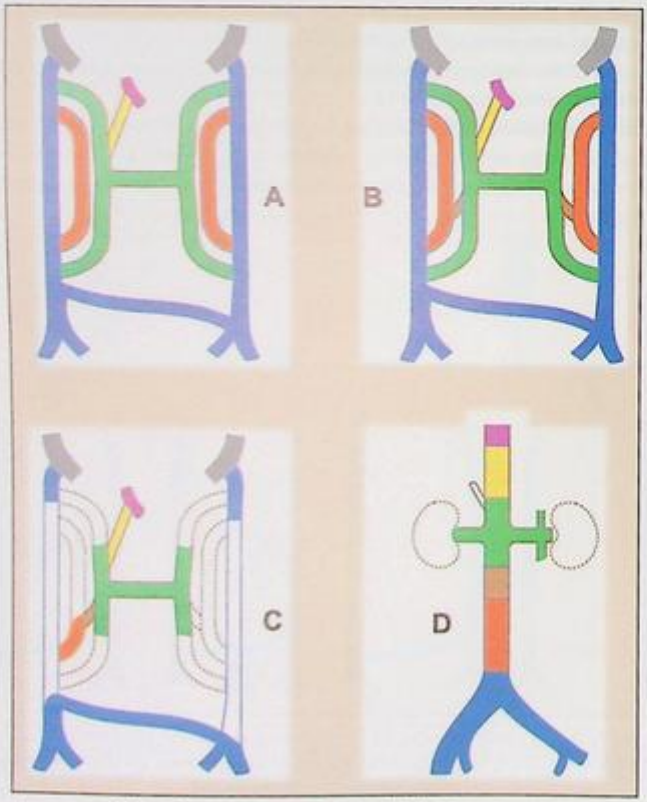

Fig. 15.48: Development of the inferior vena cava. Subcardinal veins are green; supracardinal veins are orange; the subcardinal-hepato-cardiac anastomosis is yellow; the hepato-cardiac channel itself is purple; and the supracardinal-subcardinal anastomosis is brown. The inferior vena cava receives contributions from each of these components as indicated by the colour in (D).

- The ***right subcardinal vein*** (between the supracardinal-subcardinal anastomosis and the anastomosis between the subcardinal vein and the right hepato-cardiac channel). This is the ***renal segment*** of the vena cava.
- The ***subcardinal-hepato-cardiac anastomosis***.
- The ***right hepato-cardiac channel***. (This is the ***hepatic segment*** of the vena cava).

The ***right common iliac vein*** is derived from the most caudal part of the right posterior cardinal vein.

The ***left common iliac vein*** represents the anastomosis between the two posterior cardinal veins.

The ***right renal vein*** is a mesonephric vein that originally drains into the subcardinal vein (Fig. 15.49A). It opens into that part of the vena cava that is derived from the subcardinal vein (Fig. 15.49B).

The ***left renal vein*** is derived from:

- The mesonephric vein that originally drains into the left subcardinal vein (Fig. 15.49A);
- A small part of the left subcardinal vein;
- The inter-subcardinal anastomosis. As this anastomosis lies in front of the aorta, the left renal vein has a similar relationship (Fig. 15.49B).

The ***suprarenal veins*** are remnants of the part of the subcardinal veins above the inter-subcardinal anastomosis. It is clear from Fig. 15.49B that the termination of the right suprarenal vein in the inferior vena cava, and that of the left suprarenal vein in the left renal vein, is because of their developmental origin.

The ***testicular or ovarian veins*** are remnants of the parts of the subcardinal veins below the inter-subcardinal anastomosis. The reason for the difference in the manner of termination of the veins of the two sides, is obvious from Fig 15.49B.

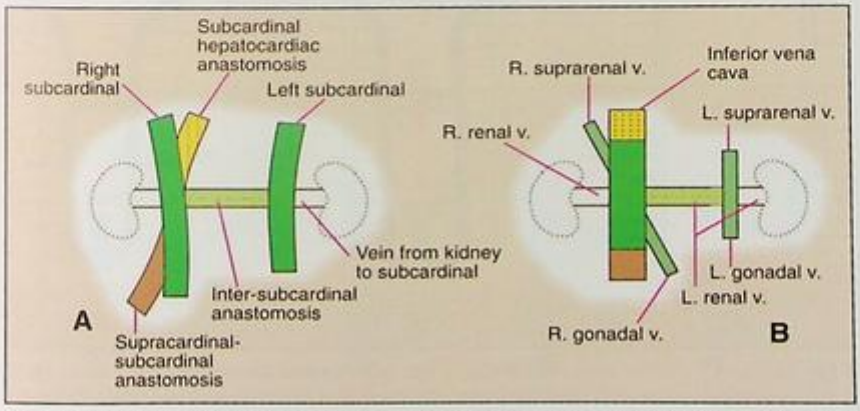

Fig. 15.49: Formation of renal, suprarenal and gonadal veins. The right renal vein is formed as a tributary of the right subcardinal vein. The left renal vein is derived from (1) vein draining left kidney into left subcardinal vein; (2) part of left subcardinal vein itself; and (3) intersubcardinal anastomosis. On each side, the suprarenal veins and gonadal veins represent remnants of the subcardinal veins. From (B) it is seen why these veins drain, on the right side into the inferior vena cava; and on the left side into the left renal vein.

The Azygos System of Veins

The veins draining the body wall at first drain into the posterior cardinal vein (Fig. 15.50A). Their drainage is soon transferred to longitudinal venous channels called the ***veins of the azygos line*** (or medial sympathetic line) (Fig. 15.50B). Cranially these channels drain into the posterior cardinal veins. The channels of the two sides are brought into communication with each other by vessels that run dorsal to the aorta (Fig. 15.50B).

With the retrogression of the left common cardinal vein, the left azygos line loses its communication with the posterior cardinal, and the blood of this channel now drains into the right azygos line through the post-aortic anastomoses. The development of the azygos system of veins can now be summarised as follows (Fig. 15.50C).

- The ***azygos vein*** is formed from:
  - the vein of the right azygos line; and
  - the most cranial part of the right posterior cardinal vein through which it opens into the superior vena cava (formed from the right common cardinal).
- The vertical parts of the ***hemiazygos*** and the ***accessory hemiazygos*** veins represent the left azygos line. Their horizontal parts are formed by the post-aortic anastomoses between the azygos lines of the two sides.
- The second and third left intercostal veins retain their connection with the left posterior cardinal vein, and are drained through the left superior intercostal vein.
- The abdominal parts of the veins of the azygos line are represented by the ascending lumbar veins.

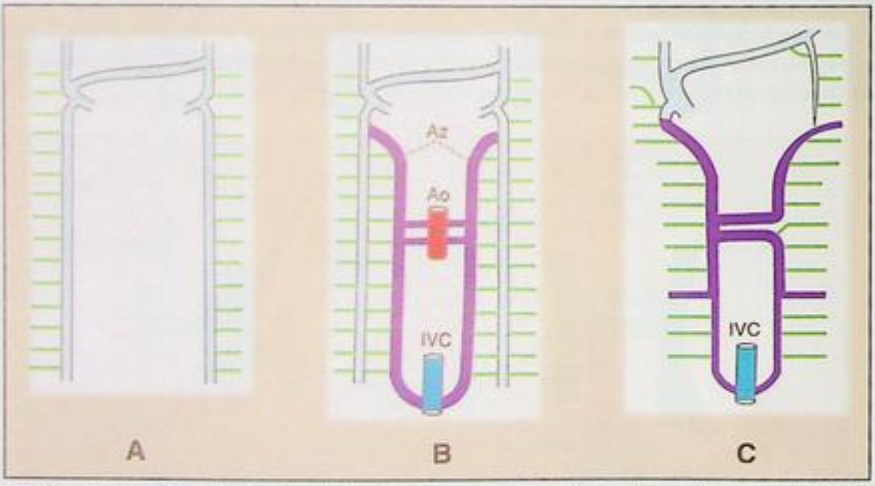

Fig. 15.50: (A) Veins from the body wall draining into anterior and posterior cardinal veins. (B) With the formation of the azygos venous channel (Az) most of the veins of the body wall now drain into it. (C) shows the ultimate arrangement. Note that veins from the 1st intercostal space drain into the innominate veins directly (anterior cardinal). The veins of the left 2nd and 3rd spaces drain into the left superior intercostal vein which is formed partly by the anterior cardinal and partly by the posterior cardinal veins. On the right side the veins of these spaces drain into the part of the azygos vein representing the terminal part of the right posterior cardinal.

Clinical Correlation

Anomalies of Veins

Minor anomalies in the mode of formation of various veins are extremely common. Anomalies of major veins are, however, rare. Some of these are as follows:

- ***Left superior vena cava:*** This is due to the failure of the left anterior and common cardinal veins to retrogress. The left superior vena cava opens into the right atrium through a large coronary sinus. In this condition, the normal (right) superior vena cava may be reduced in size or may even be absent (Fig. 15.51).
- ***Double inferior vena cava*** (Figs. 15.52A to D): Generally the vena cava is double only below the level of the renal veins.
  - Both channels may be present on the right side (Fig. 15.52B). This is caused by persistence of both the subcardinal, and supracardinal veins, below the level of the kidneys.
  - There may be an additional channel on the left side (Figs. 15.52C, D).
- ***Left inferior vena cava:*** The infrarenal part of the vena cava may be present on the left side only (Fig. 15.52E).
- ***Azygos continuation of inferior vena cava:*** The hepatic segment of the inferior vena cava may be absent. This is due to non-development of the anastomosis between the right subcardinal vein and the right hepato-cardiac channel. In such cases the upper part of the inferior vena cava follows the course of the azygos vein and opens into the superior vena cava. The hepatic veins open into the right atrium at the usual site of the inferior vena cava (Figs. 15.52F, G).
- ***Pre-ureteric vena cava:*** The inferior vena cava normally lies posterior to the right ureter. Sometimes it may be anterior to the right ureter. The ureter then hooks around the left side of the vena cava. This anomaly is caused when the infrarenal part of the vena cava develops from the subcardinal vein (which lies anterior to the ureter), instead of the supracardinal vein (which lies posterior to the ureter).

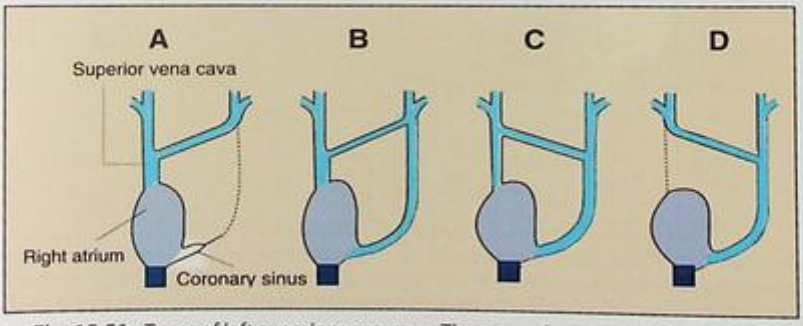

Fig. 15.51: Types of left superior vena cava. The normal pattern is shown in (A).

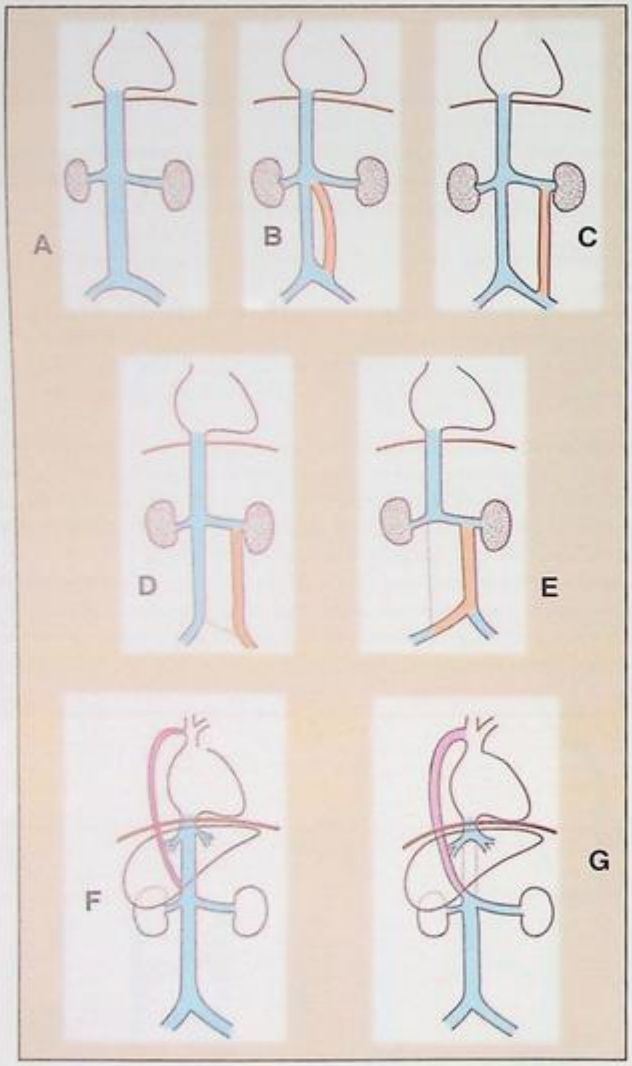

Fig. 15.52: Anomalies of the inferior vena cava. (A) shows the normal pattern while (B), (C) and (D) show various types of duplication of the infrarenal segment. In (E) the normal infrarenal segment is absent and is replaced by a vessel on the left side. (G) shows absence of the hepatic segment of the vena cava, the blood flow taking place along a much enlarged vena azygos. (F) shows the corresponding normal pattern.

PART 4: FETAL CIRCULATION

The circulation in the fetus is essentially the same as in the adult except for the following (compare Fig. 15.53 with Fig. 15.54).

- The source of oxygenated blood is not the lung but the placenta.
- Oxygenated blood from the placenta comes to the fetus through the umbilical vein, which joins the left branch of the portal vein. A small portion of this blood passes through the substance of the liver to the inferior vena cava, but the greater part passes direct to the inferior vena cava through the ductus venosus (Fig. 15.42D). A sphincter mechanism in the ductus venosus controls blood flow.
- The oxygen-rich blood reaching the right atrium through the inferior vena cava is directed by the valve of the inferior vena cava towards the foramen ovale. Here it is divided into two portions by the lower edge of the septum secundum (***crista dividens***):

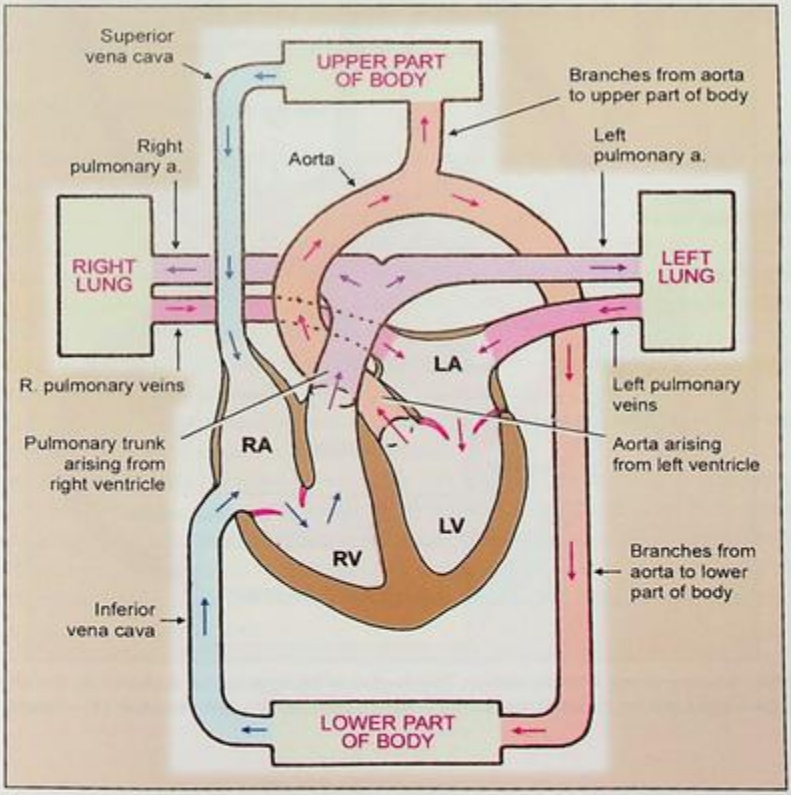

Fig. 15.53: Scheme of the circulation in the human adult.

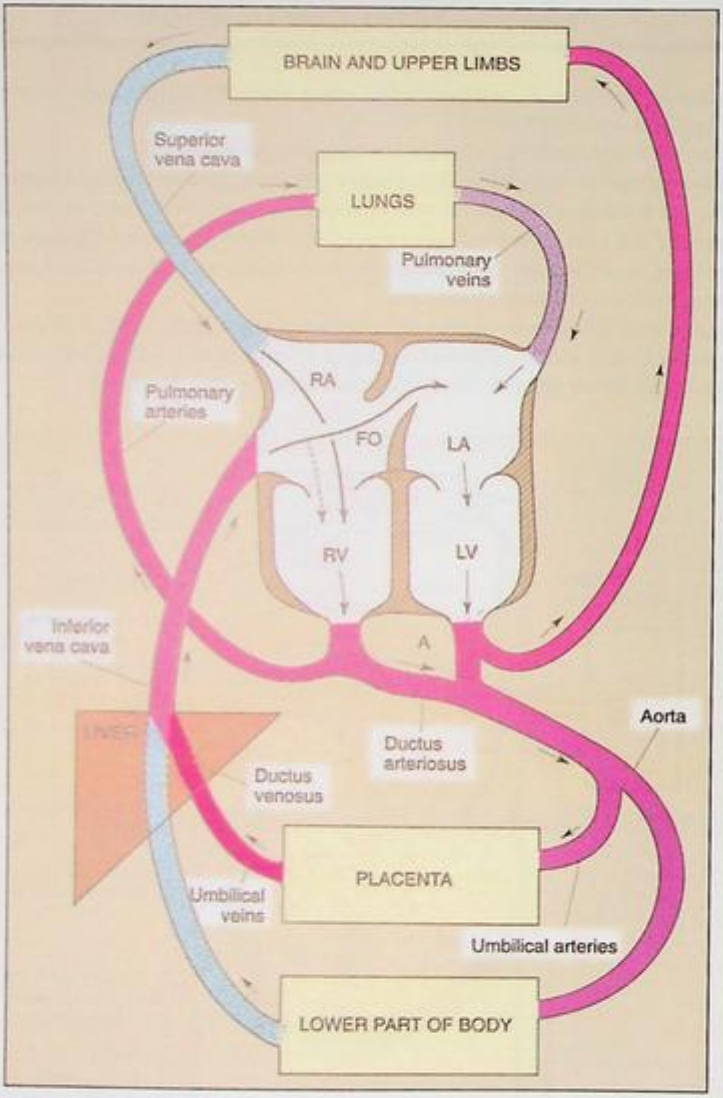

Fig. 15.54: Scheme of the fetal circulation. The degree of deoxygenation is shown by the intensity of shading. RA = right atrium; LA = left atrium; RV = right ventricle; LV = left ventricle; FO = foramen ovale.

- Most of it passes through the foramen ovale into the left atrium.
- The rest of it gets mixed up with the blood returning to the right atrium through the superior vena cava, and passes into the right ventricle.

- From the right ventricle, the blood (mostly deoxygenated) enters the pulmonary trunk. Only a small portion of this blood reaches the lungs, and passes through it to the left atrium. The greater part is short-circuited by the ductus arteriosus into the aorta.
- We have seen that the left atrium receives:
  - oxygenated blood from the right atrium, and
  - a small amount of deoxygenated blood from the lungs.

  The blood in this chamber is, therefore, fairly rich in oxygen. This blood passes into the left ventricle and then into the aorta. Some of this oxygen-rich blood passes into the carotid and subclavian arteries to supply the brain, the head and neck, and the upper extremities. The rest of it gets mixed up with poorly oxygenated blood from the ductus arteriosus. The parts of the body that are supplied by branches of the aorta arising distal to its junction with the ductus arteriosus, therefore, receive blood with only a moderate oxygen content.
- Much of the blood of the aorta is carried by the umbilical arteries to the placenta where it is again oxygenated and returned to the heart.

Changes in the Circulation at Birth

Soon after birth, several changes take place in the fetal blood vessels. These lead to the establishment of the adult type of circulation. The changes are as follows:

- The muscle in the wall of the umbilical arteries contracts immediately after birth, and occludes their lumen. This prevents loss of fetal blood into the placenta.
- The lumen of the umbilical veins and the ductus venosus is also occluded, but this takes place a few minutes after birth, so that all fetal blood that is in the placenta has time to drain back to the fetus.
- The ductus arteriosus is occluded, so that all blood from the right ventricle now goes to the lungs, where it is oxygenated.

  Initial closure of the ductus arteriosus is caused by contraction of muscle in the vessel wall. Later intima proliferation obliterates the lumen.
- The pulmonary vessels increase in size and, consequently, a much larger volume of blood reaches the left atrium from the lungs. As a result, the pressure inside the left atrium is greatly increased. Simultaneously, the pressure in the right atrium is diminished because blood from the placenta no longer reaches it. The net result of these pressure changes is that the pressure in the left atrium now exceeds that in the right atrium causing the valve of the foramen ovale to close.

The vessels that are occluded soon after birth are, in due course, replaced by fibrous tissue, and form the following ligaments:

Vessel	*Remnant*
Umbilical arteries	Medial umbilical ligaments
Left umbilical vein	Ligamentum teres of the liver
Ductus venosus	Ligamentum venosum
Ductus arteriosus	Ligamentum arteriosum

PART 5: LYMPHATIC SYSTEM

The first signs of the lymphatic system are seen in the form of a number of endothelium lined ***lymph sacs***. Traditionally these sacs have been considered to be outgrowths from veins. However, they are now regarded to be predominantly independent formations from mesenchyme.

Six sacs can be recognised. The right and left ***jugular sacs*** lie near the junction of the posterior cardinal and subclavian veins (i.e. at the future junction between the internal jugular and subclavian veins). The right and left ***posterior (or iliac) sacs*** lie around the corresponding common iliac vein. The ***retroperitoneal sac*** (unpaired) lies in relation to the root of the mesentery. The sixth sac (again unpaired) is the ***cisterna chyli***. It lies in the midline some distance caudal to the retroperitoneal sac.

Lymphatic vessels are formed either by extension from the sacs or may form ***de novo***, and extend into various tissues. Ultimately all the sacs except the cisterna chyli are invaded by connective tissue and lymphocytes, and are converted into groups of lymph nodes.

The ***thoracic duct*** is derived from right and left channels that connect the cisterna chyli to the corresponding jugular sac. The two channels anastomose across the midline. The thoracic duct is formed from the caudal part of the right channel, the anastomosis between the right and left channels, and the cranial part of the left channel. The cranial part of the right channel becomes the ***right lymphatic duct***.

TIMETABLE OF SOME EVENTS DESCRIBED IN THIS CHAPTER

Age	Developmental Events
3rd week	Blood and vessels forming cells (angioblastic islands) appear. The cardiogenic area, heart tubes and pericardium have formed.
4th week	Heart and pericardium lie ventral to foregut. Subdivisions of heart tube are visible. Heart begins to beat (becomes functional). Heart septa begin to form. Aortic arches begin to establish in cranial to caudal sequence. Most of the first aortic arch disappears at the end of 4th week. Veins start forming.
5th week	The spiral septum is formed. Formation of aortic arches is complete. Lymphatic sacs form. The cardinal, umbilical and vitelline veins are formed. Conduction system of heart forms.
6th week	Coronary circulation is becoming established. Atrio-ventricular valves and papillary muscles are forming.
7th week	Heart septa are completely formed.

The heart is most susceptible to teratogens between three and six weeks. It can be affected up to the eighth week.

Chapter 16

Urogenital System

- The ***urogenital system*** is derived from the ***intermediate mesoderm***, and the ***primitive urogenital sinus*** (UGS) which is a part of the cloaca.
- The primitive UGS divides into the ***vesicourethral canal*** and the ***definitive UGS*** (Fig. 16.3).
- The vesicourethral canal divides into the ***urinary bladder*** and the ***primitive urethra***.
- The definitive UGS has a ***pelvic part*** and a ***phallic part***.
- The ***kidneys*** develop from two sources. The excretory tubules (nephrons) are derived from the ***metanephros*** (= lowest part of nephrogenic cord which is derived from intermediate mesoderm). The collecting part is formed by ramification of the ***ureteric bud*** (which arises from the mesonephric duct).
- The ***ureter*** arises from the ureteric bud.
- The ***urinary bladder*** is derived from the cranial part of the vesicourethral canal (endoderm). The epithelium of the trigone is derived from absorbed mesonephric ducts.
- The ***female urethra*** is derived from the primitive urethra and the pelvic part of the UGS.
- In the male, the ***prostatic urethra*** corresponds to the female urethra. The ***membranous urethra*** is derived from the pelvic part of UGS and the ***penile urethra*** from the phallic part of the UGS. The terminal part is ectodermal.
- The ***prostate*** is formed by buds arising from the caudal part of the vesicourethral canal and the pelvic part of the UGS.
- The ***uterine tubes*** are derived from ***paramesonephric ducts*** (mesoderm).
- The ***uterus*** is formed from the uterovaginal canal (fused right and left paramesonephric ducts).
- ***External genitalia*** are formed from swellings that appear around the urogenital membrane.
- ***Gonads*** (testis and ovary) are derived from coelomic epithelium covering the nephrogenic cord. Ova and spermatozoa arise from ***primordial germ cells*** that arise in the region of the yolk sac. The testis is formed in the lumbar region, and later descend to the scrotum.
- The ***duct system of the testis*** is derived from mesonephric tubules and from the mesonephric duct.

INTRODUCTION

Two embryonic structures that play an important role in the development of the urogenital system are the intermediate mesoderm and the cloaca. These are briefly considered below.

Intermediate Mesoderm

We have seen (Chapter 5) that the intra-embryonic mesoderm is subdivided into:

1. the paraxial mesoderm which becomes segmented to form the somites,
2. the lateral plate mesoderm in which the intra-embryonic coelom appears, and
3. the intermediate mesoderm lying between the two (Fig. 16.1).

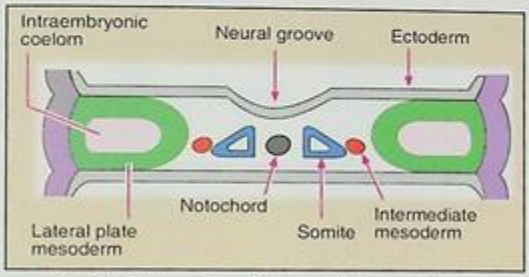

Fig. 16.1: Location of intermediate mesoderm.

After the folding of the embryonic disc and the formation of the peritoneal cavity, the intermediate mesoderm forms a bulging on the posterior abdominal wall lateral to the attachment of the dorsal mesentery of the gut. This bulging is now called the ***nephrogenic cord*** (Fig. 16.2A). Its surface is covered by the epithelium lining the peritoneal cavity (coelomic epithelium). It extends from the cervical region to the sacral region of the embryo. At varying stages of development, a number of important structures are formed in relation to the nephrogenic cord on each side.

These are (Fig. 16.2B):

- ***Excretory tubules*** associated with the development of the kidney.
- The ***nephric duct*** which is formed in relation to the developing excretory tubules mentioned in (a). At later stages, this becomes the ***mesonephric duct***.
- The ***paramesonephric duct***, which is formed lateral to the nephric duct.
- The ***gonad*** (***testis*** or ***ovary***), which develops from the coelomic epithelium lining the medial side of the nephrogenic cord.

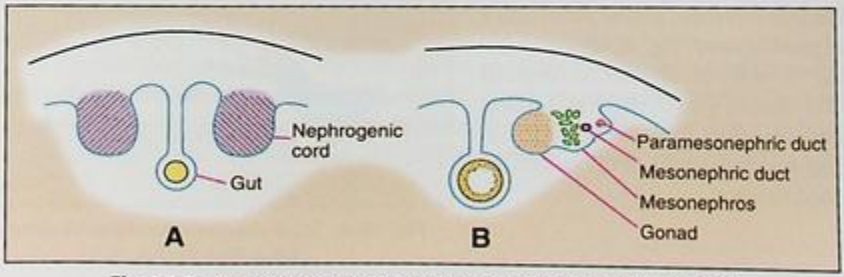

Fig. 16.2: Nephrogenic cord (A) and structures that develop in it (B).

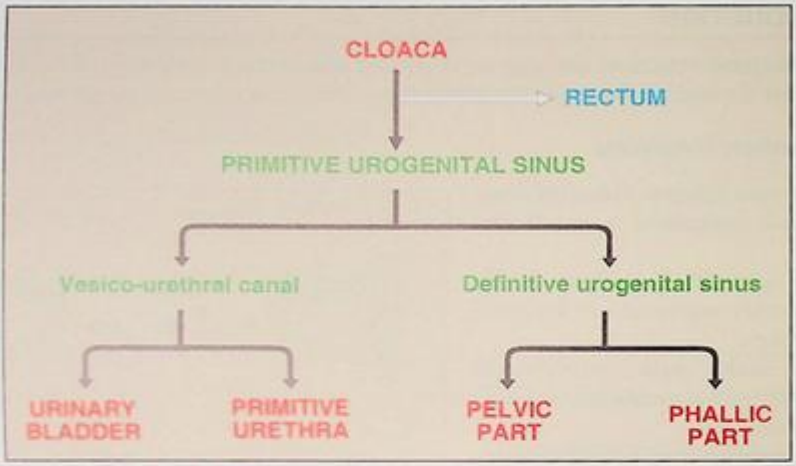

Fig. 16.3: Subdivisions of the cloaca. Also see Fig. 16.4.

Cloaca

The formation of the cloaca and its subdivision into the primitive urogenital sinus and rectum have been considered in Chapter 13 (see Figs. 13.3 and 13.4).

In further development, the primitive urogenital sinus is subdivided into a cranial part, called the ***vesico-urethral canal***, and a caudal part, called the ***definitive urogenital sinus***. The openings of the mesonephric ducts (see below) lie at the junction of these two subdivisions (Fig. 16.4A). Still later, the definitive urogenital sinus shows a division into a cranial, ***pelvic part***, and a caudal ***phallic part*** (Fig. 16.4B).

The urogenital system is derived from the various structures that develop in the intermediate mesoderm, and from the various subdivisions of the cloaca, as described below.

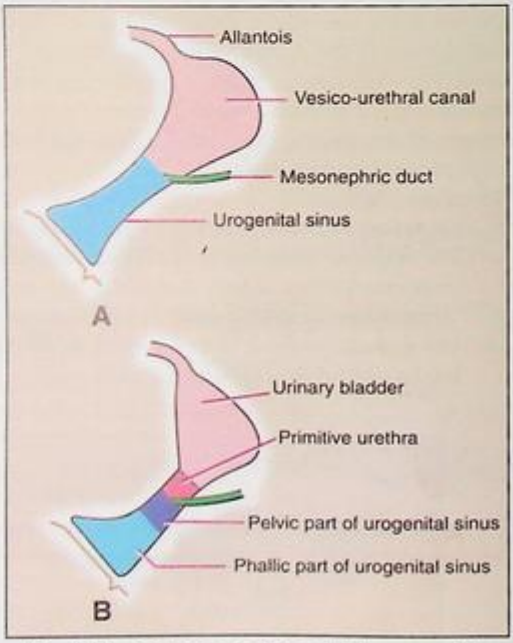

Fig. 16.4: Subdivisions of the primitive urogenital sinus. Also see Fig. 16.3.

DEVELOPMENT OF KIDNEYS

The definitive human kidney arises from two distinct sources. The excretory tubules (or ***nephrons***) are derived from the lowest part of the nephrogenic cord. This part is the ***metanephros***, the cells of which form the ***metanephric blastema***.

The collecting part of the kidney is derived from a diverticulum called the ***ureteric bud*** which arises from the lower part of the mesonephric duct (Fig. 16.5).

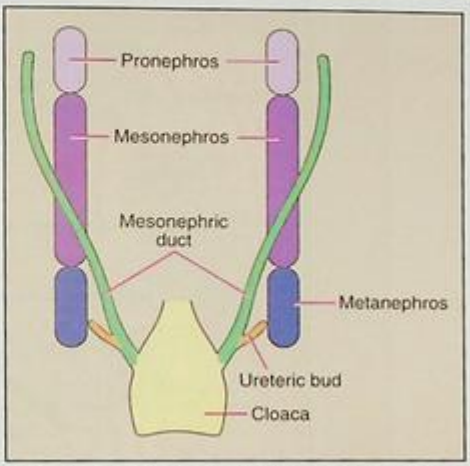

Fig. 16.5: Pronephros, mesonephros and metanephros. Note that the mesonephric duct opens into the cloaca; and gives off the ureteric bud.

Some of the features of the development of the kidney in the human embryo can be appreciated only if the evolutionary history of the organ is kept in mind. The vertebrate kidney has passed through three stages of evolution. The most primitive of these is called the ***pronephros***. It is the functioning kidney in some cyclostomes and fishes. This has been succeeded in higher vertebrates by the ***mesonephros*** that is the functioning kidney of most anamniotes. The kidney of amniotes (including man) is called the ***metanephros*** (Fig. 16.6).

During the development of the human embryo, the evolutionary history of the kidney repeats itself being a classic example of the saying that ***ontogeny repeats phylogeny***. The pronephros is formed in relation to the cervical region of the nephrogenic cord. This is followed by appearance of the mesonephros in the thoracolumbar region, and finally by formation of the metanephros in the sacral region (Fig. 16.5). The human pronephros is non-functional, and disappears soon after its formation. A ***nephric duct*** formed in relation to the pronephros and ending in the cloaca, however, persists. The mesonephros consists of a series of excretory tubules that develop in the thoracolumbar region. These tubules drain into the nephric duct which may now be called the ***mesonephric duct***. Most of the mesonephric tubules disappear, but some of them are modified and take part in forming the duct system of the testis.

As the ureteric bud grows cranially towards the metanephric blastema, its growing end becomes dilated to form an ***ampulla***. The ampulla divides repeatedly. The first three to five generations of branches fuse to form the ***pelvis*** of the kidney. The next divisions become the ***major calyces*** while further divisions form the ***minor calyces*** and collecting tubules (Fig. 16.7).

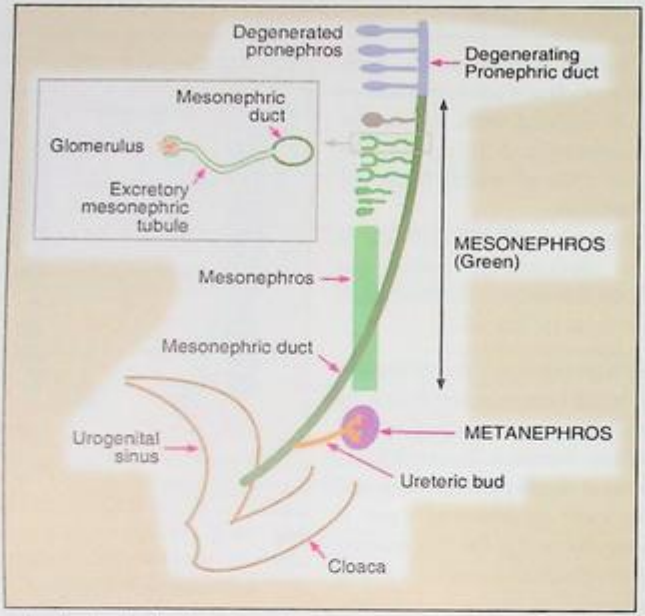

Fig. 16.6: Some details of developing pronephros, mesonephros and metanephros. The pronephros and pronephric duct degenerate soon after formation. The proximal part of the mesonephros shows segmentation (in cranio-caudal sequence). The segments contain functional excretory tubules that drain into the mesonephric duct. Most of these tubules disappear by the time the metanephros forms the definitive kidney.

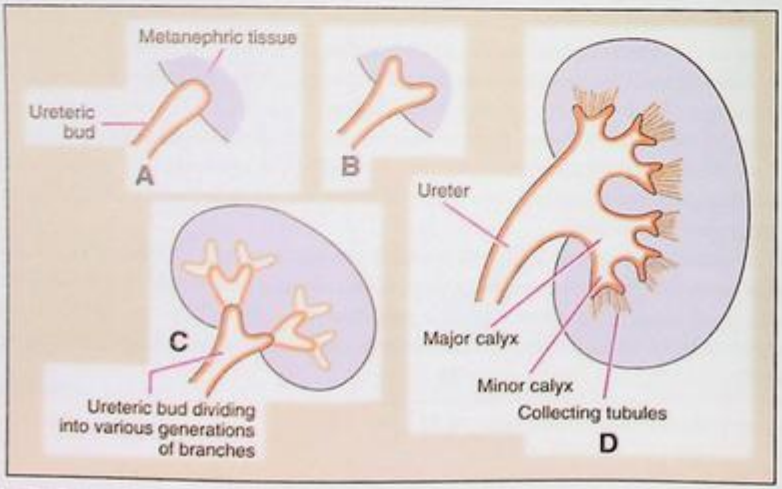

Fig. 16.7: Formation of the collecting system of the kidney, from ramifications of the ureteric bud.

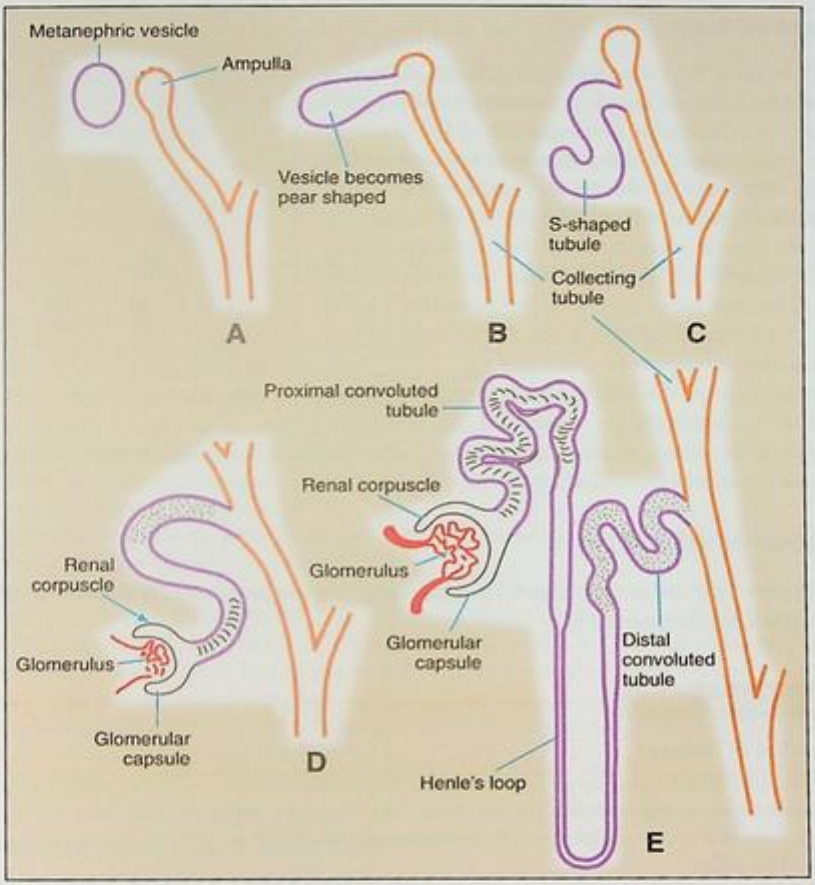

Fig. 16.8: Scheme to show stages in the development of the nephron.

Collecting tubules formed number one to three million. The growing tip of each of the numerous branches of the ureteric bud is dilated to form an ***ampulla***. The cells of the metanephric blastema in contact with an ampulla undergo differentiation to form a nephron. This differentiation is induced by the ampulla.

Loosly arranged cells of the metanepric blastima form solid clumps in relation to the ampulae. Each solid clump is converted into a vesicle. The vesicle soon becomes pear-shaped and opens into the ampulla. The vesicle now becomes an S-shaped tube. Its distal end comes to be invaginated by a tuft of capillaries which form a ***glomerulus***. The various parts of the nephron are derived from this S-shaped tube as shown in Fig. 16.8.

Ascent of the Kidney

We have seen that the definitive human kidney is derived from the metanephros, which lies in the sacral region. In subsequent development of the embryo, differential growth of the abdominal wall causes the kidney to ascend to the lumbar region (Fig. 16.9). The metanephros, at first, receives its blood supply from the lateral sacral arteries, but with its ascent, higher branches of the aorta take over the supply. The definitive renal artery represents the lateral splanchnic branch of the aorta at the level of the second lumbar segment.

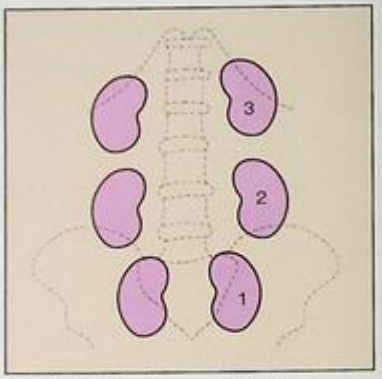

Fig. 16.9: Ascent of the kidney.

During ascent, the kidneys pass through the fork like interval between the right and left umbilical arteries. If the arteries come in the way of ascent, the kidney may remain in the sacral region (see 'Anomalies of Kidneys').

Rotation of the Kidney

The hilum of the kidney, at first, faces anteriorly. The organ gradually rotates so that the hilum comes to face medially.

Clinical Correlation

Anomalies of Kidneys

- One or both kidneys may be absent (***agenesis***). The kidney may be underdeveloped (***hypoplasia***) or overdeveloped (***hyperplasia***). Adrenal tissue may be present within the substance of the kidney. Distension of the pelvis with urine (***hydronephrosis***) may occur as a result of obstruction in the urinary passages.
- ***Duplication:*** There may be an extra kidney on one side. It may be separate, or may be fused to the normal kidney (Fig. 16.12).
- ***Anomalies of Shape***
  - ***Horseshoe kidney:*** The lower poles of the two kidneys (or sometimes the upper poles) may be fused. The connecting isthmus may lie either in front of, or behind, the aorta and inferior vena cava (Figs. 16.10G, H). A horseshoe kidney does not ascend higher than the level of the inferior mesenteric artery as the latter prevents its higher ascent.
  - ***Pancake kidney:*** The two kidneys may form one mass, lying in the midline or on one side (Fig. 16.10I).
  - The two kidneys may lie on one side, one above the other, the adjacent poles being fused.
  - ***Lobulated kidney:*** The fetal kidney is normally lobulated. This lobulation may persist (Fig. 16.10C).

Clinical Correlation ***contd...***

- ***Anomalies of Position***
  - The kidneys may fail to ascend. They then lie in the sacral region.
  - The ascent of the kidneys may be incomplete as a result of which they may lie opposite the lower lumbar vertebrae.
  - The kidneys may ascend too far, and may even be present within the thoracic cavity.
  - Both kidneys may lie on one side of the midline. They may lie one above the other or side by side (Figs. 16.10 D, E). The ureter of the displaced kidney crosses to the opposite side across the midline.
  - Both kidneys may be displaced to the opposite side. The two ureters then cross each other in the midline (Fig. 16.10 F).
- *Abnormal Rotation*
  - ***Non-rotation:*** The hilum is directed forwards.
  - ***Incomplete rotation:*** The hilum is directed anteromedially.
  - ***Reverse rotation:*** The hilum is directed anterolaterally.
- ***Congenital Polycystic Kidney:*** Failure of the excretory tubules of the metanephros to establish contact with the collecting tubules, leads to the formation of cysts. Isolated cysts are commonly seen, but sometimes the whole kidney is a mass of such cysts (Fig. 16.10A). The cysts press upon normal renal tissue and destroy it.
  An alternative recent view about the formation of cysts in the kidney is that they are derived from abnormally developed collecting tubules.
- ***Aberrant Renal Arteries:*** The kidney may receive its blood supply partially or entirely, from arteries arising at an abnormal level (Fig. 16.10 B). In the case of non-ascent, or of incomplete ascent, the aberrant arteries may constitute the only supply to the organ. An aberrant artery may be the only source of arterial blood to a segment of the kidney. It may press upon the ureter and cause obstruction, leading to hydronephrosis.
- ***Multiple Anomalies:*** Two or more of the above anomalies may coexist. Anomalies of position are frequently associated with those of rotation.

ABSORPTION OF LOWER PARTS OF MESONEPHRIC DUCTS INTO CLOACA

It has been noted above, that the lower ends of the mesonephric ducts open into that part of the cloaca that forms the urogenital sinus. It has also been seen that the ureteric buds arise from the mesonephric ducts, a little cranial to the cloaca (Fig. 16.11A). The parts of the mesonephric ducts, caudal to the origin of the ureteric buds, are absorbed into the vesico-urethral canal, with the result that the mesonephric ducts and the ureteric buds now have separate openings into the cloaca (Fig. 16.11B). These openings are at first close together (Fig. 16.11C). However, the openings of the ureteric buds move cranially and laterally due to continued absorption of the buds. The triangular area (on the dorsal wall of the vesico-urethral canal) between the openings of the ureteric buds and those of the mesonephric ducts, is derived from the absorbed ducts and is, therefore, of mesodermal origin (Fig. 16.11D).

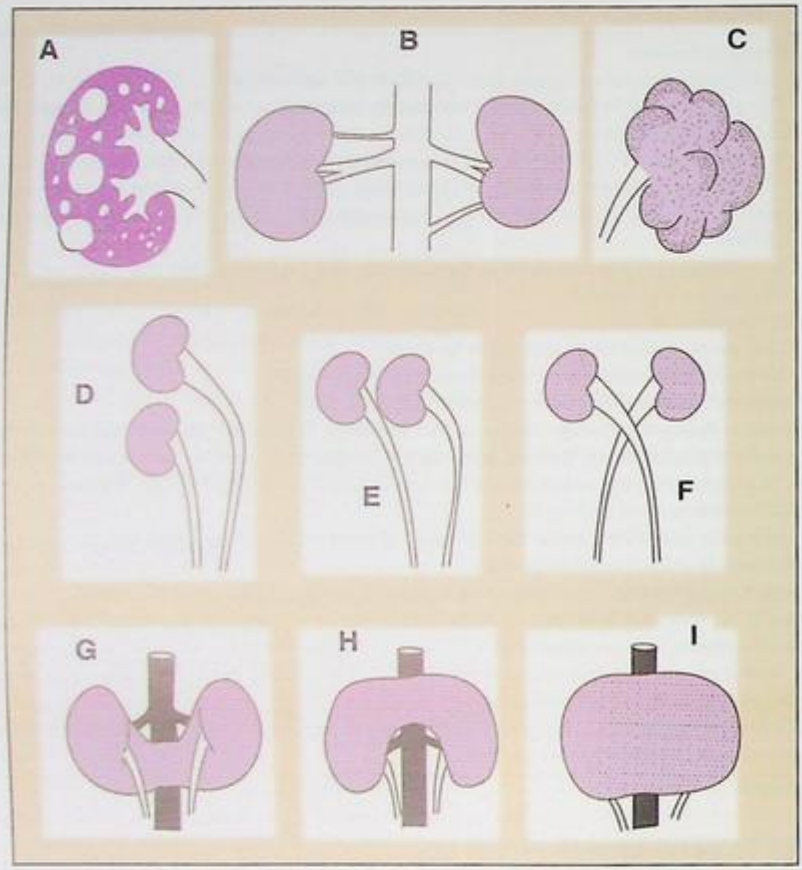

Fig. 16.10: Anomalies of the kidney. (A) Congenital polycystic kidney. (B) Aberrant renal arteries. (C) Lobulated kidney. (D), (E), (F) Transposition of kidney. (G), (H) Horseshoe kidney, and (I) Pancake kidney.

DEVELOPMENT OF THE URETER

The ureter is derived from the part of the ureteric bud that lies between the pelvis of the kidney, and the vesico-urethral canal.

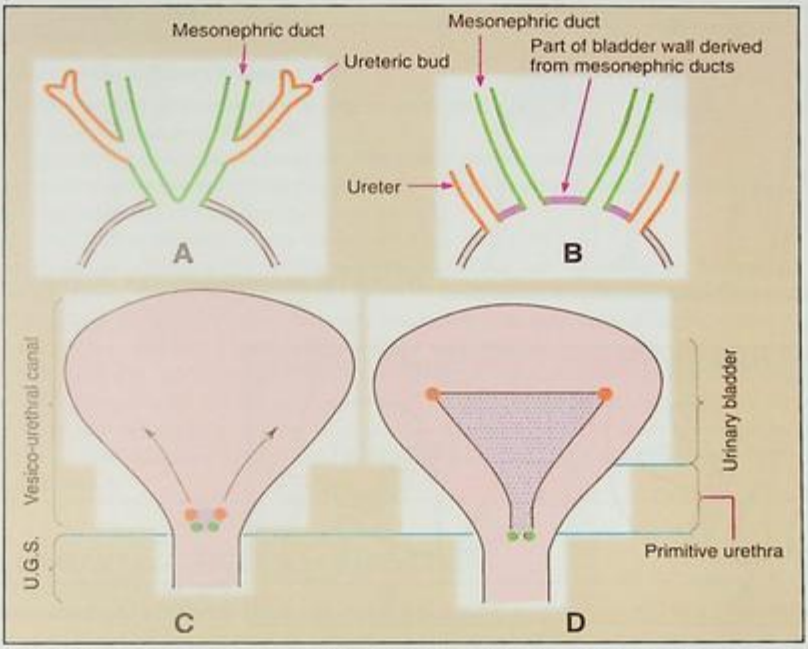

Fig. 16.11: (A) Mesonephric duct opens into primitive urogenital sinus. (B) As the sinus grows the proximal parts of mesonephric ducts are absorbed so that the mesonephric ducts and ureters now open separately. (C) The openings are at first close together. (D) Further absorption of ureters causes their opening to shift upwards and laterally. The shaded area is derived from absorbed parts of ureters and mesonephric ducts, and is mesodermal. It forms the trigone of the bladder and the posterior wall of part of the urethra.

Clinical Correlation

Anomalies of the Ureter

- The ureter may be partially or completely duplicated (Fig. 16.12). This condition may, or may not, be associated with duplication of the kidney. Very rarely, there may be more than two ureters on one, or both, sides. Of the two ureters one may open into the urinary bladder while the other may open at an abnormal site (see below).
- Instead of opening into the urinary bladder, the ureter may end in the prostatic urethra, ductus deferens, seminal vesicles, or rectum, in the male (Fig. 16.13B): and in the urethra, vagina, vestibule or rectum in the female (Fig. 16.13A).
- The upper end of the ureter may be blind, i.e. it is not connected to the kidney.
- The ureter may be dilated (***hydroureter***) because of obstruction to urine flow.
- The ureter may have valves or diverticula.
- The right ureter may pass behind the inferior vena cava. It then hooks around the left side of the vena cava; this may result in kinking and obstruction of the ureter. The real defect is in the development of the vena cava as described in Chapter 15.

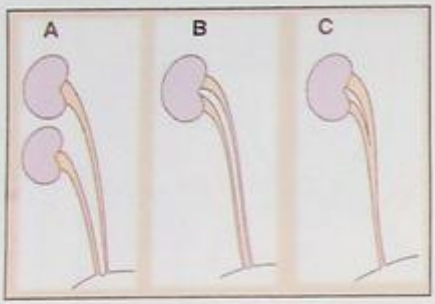

Fig. 16.12: Anomalies of ureters. Also see Fig. 16.10.

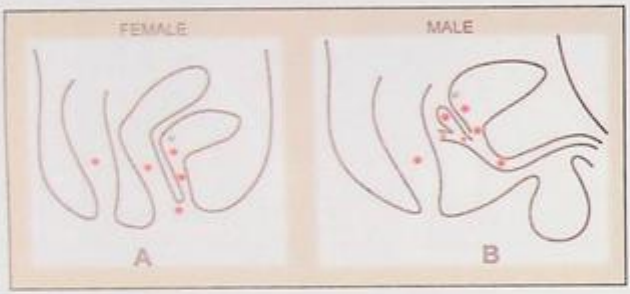

Fig. 16.13: Abnormal sites at which the ureter may open.

DEVELOPMENT OF THE URINARY BLADDER

The epithelium of the urinary bladder develops from the cranial part of the vesicourethral canal (endoderm). The epithelium of the trigone of the bladder is derived from the absorbed mesonephric ducts. (mesoderm) (However, it is later overgrown by the surrounding endodermal cells). The muscular and serous walls of the organ are derived from splanchnopleuric mesoderm.

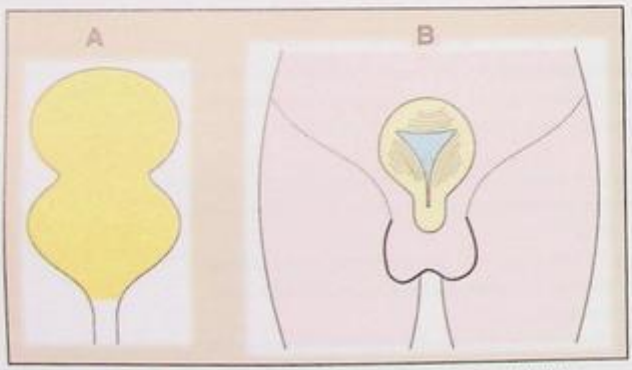

Fig. 16.14: Anomalies of the bladder. (A) Hourglass bladder. (B) Ectopia vesicae. The ureteric openings and the trigone are seen on the surface of the body.

The developing bladder is continuous cranially with the allantois. It is uncertain whether the allantois contributes to the formation of the bladder. The allantois atrophies, and is seen in postnatal life as a fibrous band, the ***urachus***, extending from the apex of the bladder to the umbilicus.

Clinical Correlation

Anomalies of the Urinary Bladder

- The urinary bladder may be absent, or may be duplicated.
- The sphincter vesicae may be absent.
- The lumen of the urinary bladder may be divided into compartments by septa.
- The bladder may be divided into upper and lower compartments (***hourglass bladder***) because of a constriction in the middle of the organ (Figs. 16.14A).
- The bladder may communicate with the rectum (Figs. 13.25A, H).
- ***Ectopia vesicae:*** The lower part of the anterior abdominal wall, as well as the ventral wall of the bladder, may be missing. As a result, the cavity of the bladder may be exposed on the surface of the body (Fig. 16.14B). This defect is usually associated with epispadias. Ectopia vesicae is caused by failure of mesoderm to migrate into the lower abdominal wall (between umbilicus and genital tubercle). Failure of migration may be due to excessive development of the cloacal membrane. The ectoderm of the anterior abdominal wall and the endoderm of the ventral wall of the urinary bladder remain unsupported and thin. Their rupture leads to the exposure of the cavity of the urinary bladder.
- Congenital diverticula may be present. These are found at the junction of the trigone with the rest of the bladder.

DEVELOPMENT OF THE FEMALE URETHRA

The female urethra is derived from the caudal part of the vesico-urethral canal (endoderm). We have seen that the posterior wall of this canal is derived from the mesonephric ducts and is, therefore, mesodermal in origin. The female urethra may receive a slight contribution from the pelvic part of the urogenital sinus (Fig. 16.15).

DEVELOPMENT OF THE MALE URETHRA

- The part of the male urethra extending from the urinary bladder up to the openings of the ejaculatory ducts (original openings of mesonephric ducts), is derived from the caudal part of the vesico-urethral canal (endoderm). The posterior wall of this part is derived from absorbed mesonephric ducts (mesoderm). (It may later be overgrown by endoderm).
- The rest of the prostatic urethra, and the membranous urethra, are derived from the pelvic part of the definitive urogenital sinus.
- The penile part of the urethra (except the terminal part) is derived from the epithelium of the phallic part of the definitive urogenital sinus (see 'Development of Penis').
- The terminal part of the penile urethra, that lies in the glans, is derived from ectoderm (Fig. 16.15).

From the above it will be clear that the female urethra corresponds to the prostatic part of the male urethra.

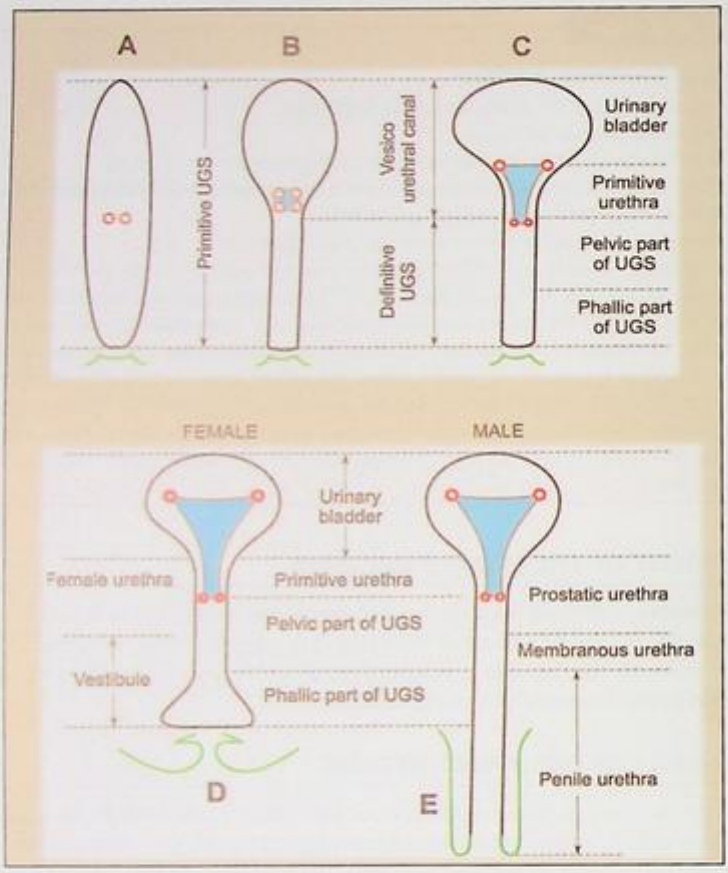

Fig. 16.15: Development of urethra. (A) Primitive UGS showing opening of mesonephric ducts. (B) Primitive UGS divided into vesico-urethral canal and definitive UGS. Mesonephric ducts and ureters open separately at the junction of the two parts. (C) Vesico-urethral canal subdivided into urinary bladder and primitive urethra. The definitive UGS divides into pelvic and phallic parts. (D) The female urethra is formed from the primitive urethra and from part of the pelvic portion of UGS. The rest of the pelvic part of UGS forms the vestibule. (E) In the male the prostatic urethra is formed in the same way as the female urethra. The membranous urethra is derived from the pelvic part of UGS. The penile urethra is derived from the phallic part of UGS. Red circles = openings of mesonephric ducts and ureters. Blue = part derived from mesoderm. Green = ectoderm.

Clinical Correlation

Anomalies of the Urethra

- There may be obstruction to the urethra at its junction with the bladder.
- The urethra may show diverticula.
- It may be duplicated in whole or in part.
- The urethra may have abnormal communications with the rectum (Figs. 13.23B, C), the vagina (Fig. 16.22) or the ureter (Fig. 16.13).
- Hypospadias and epispadias.

DEVELOPMENT OF THE PROSTATE

This gland develops from a large number of buds that arise from the epithelium of the prostatic urethra, i.e. from the caudal part of the vesico-urethral canal, and from the pelvic part of the definitive urogenital sinus. These buds form the secretory epithelium of the gland. The buds that arise from the mesodermal part of the prostatic urethra (i.e. posterior wall, above the openings of the ejaculatory ducts) form the ***inner glandular zone*** of the prostate. Buds arising from the rest of the prostatic urethra (endoderm) form the ***outer glandular zone***.

The outer zone differentiates earlier than the inner zone. In later life the outer zone is frequently the site of carcinomatous change, while the inner zone is affected in senile hypertrophy of the organ.

The muscle and connective tissue of the gland are derived from the surrounding mesenchyme which also forms the capsule of the gland.

The secretory elements of the prostate are rudimentary at birth. They undergo considerable development at puberty. The organ undergoes progressive atrophy in old age, but in some men it undergoes benign hypertrophy.

The prostate may, rarely, be absent.

Female Homologues of Prostate

Endodermal buds, similar to those that form the prostate in the male, are also seen in the female. The buds that arise from the caudal part of the vesico-urethral canal give rise to the ***urethral glands***, whereas the buds arising from the urogenital sinus form the ***paraurethral glands of Skene***.

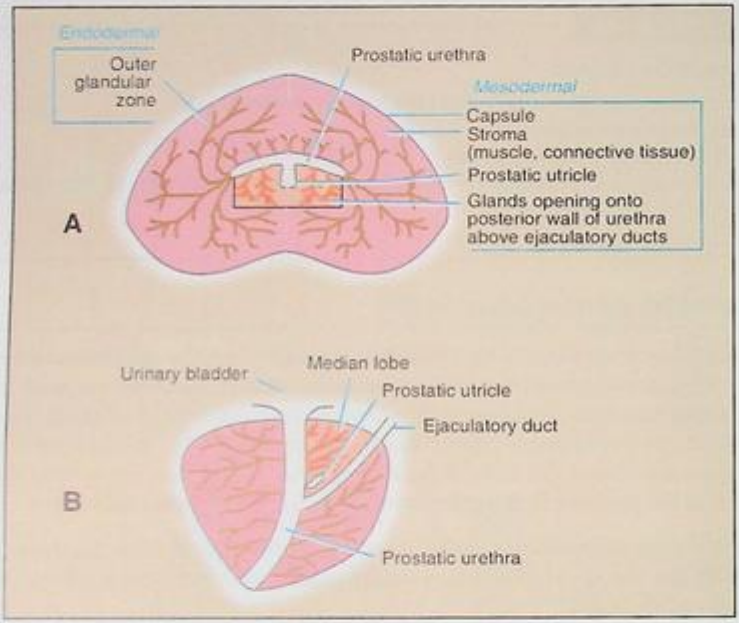

Fig. 16.16: Mesodermal and endodermal derivatives of the prostate. The glands of the median lobe, which open onto the posterior wall of the prostatic urethra (above the opening of the ejculatory ducts), are mesodermal. Fig. A shows a transverse section above the level of the opening of ejaculatory ducts. Fig. B is a sagittal section.

PARAMESONEPHRIC DUCTS

We have seen that these ducts are present in the intermediate mesoderm. They are formed by invagination of coelomic epithelium (Fig. 16.17). They lie lateral to the mesonephric ducts in the cranial part of the nephrogenic cord (Fig. 16.18A).

When traced caudally, they cross to the medial side of the mesonephric ducts. Here the ducts of the two sides meet and fuse in the middle line to form the ***utero-vaginal canal*** (or ***uterine canal***) (Fig. 16.18B). The caudal end of this canal comes in contact with the dorsal wall of, the definitive urogenital sinus. We have already seen that, in the female, this part of the sinus gives rise to the vestibule. In the female, the paramesonephric ducts give origin to the uterine tubes, the uterus, and part of the vagina (Fig. 16.19A).

DEVELOPMENT OF UTERUS AND UTERINE TUBES

The epithelium of the uterus develops from the fused paramesonephric ducts (uterovaginal canal: 1 in Fig. 16.19A). The myometrium is derived from surrounding mesoderm (3).

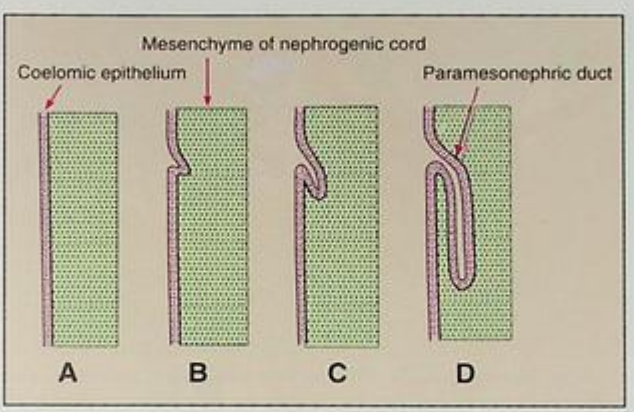

Fig. 16.17: Formation of paramesonephric ducts by invagination of coelomic epithelium.

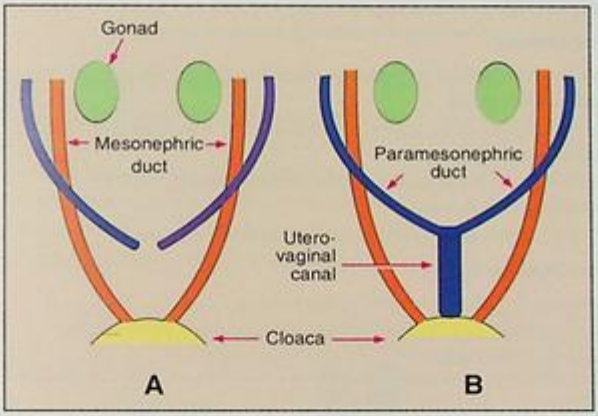

Fig. 16.18: Formation of uterovaginal canal by fusion of the caudal parts of paramesonephric ducts.

As the thickness of the myometrium increases, the unfused horizontal parts of the two paramesonephric ducts come to be partially embedded within its substance, and help to form the fundus of the uterus (2). The cervix can soon be recognised as a separate region. In the fetus the cervical part is larger than the body of the uterus.

The uterine tubes develop from the unfused parts of the paramesonephric ducts. The original points of invagination of the ducts into the coelomic epithelium remain as the abdominal openings of the tubes. Fimbria are formed in this situation.

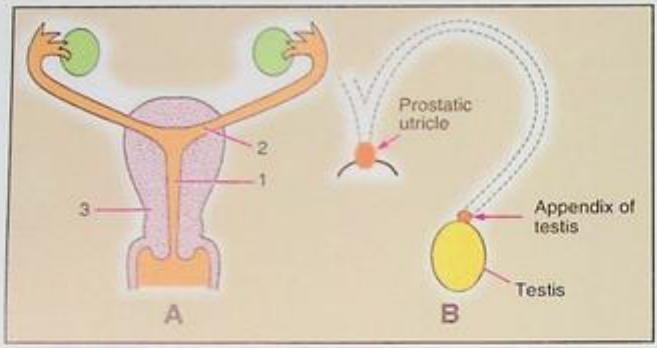

Fig. 16.19: Fate of paramesonephric ducts. (A) In the female they form the uterine tubes, the uterus, and part of the vagina. (B) In the male most of the duct disappears. Remnants are seen as the appendix of the testis and the prostatic utricle.

Clinical Correlation

Anomalies of the Uterus

- The uterus may be completely, or partially, duplicated (Figs. 16.20A, B). Complete duplication is referred to as ***uterus didelphys***.
- The lumen may be partially, or completely, subdivided by a septum (Fig. 16.20C).
- The entire uterus may be absent.
- One half of the uterus may be absent (***unicornuate uterus***) (Fig. 16.20D).
- The uterus may remain rudimentary.
- There may be atresia of the lumen either in the body or in the cervix.

Anomalies of the Uterine Tubes

- The uterine tubes may be absent, on one or both sides.
- The tubes may be partially, or completely, duplicated on one or both sides.
- There may be atresia of the tubes.

DEVELOPMENT OF VAGINA

We have noted that the lower end of the uterovaginal canal comes in close contact with the dorsal wall of the phallic part of the urogenital sinus (Fig. 16.21A). However, the uterovaginal canal and the urogenital sinus are soon separated from each other by the formation of a solid plate of cells called the ***vaginal plate***. The vagina is formed by the development of a lumen within the vaginal plate (Fig. 16.21D).

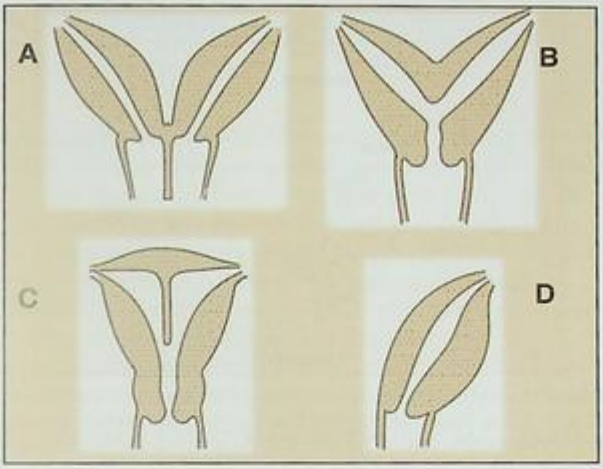

Fig. 16.20: Anomalies of the uterus. (A) Duplication of uterus and vagina.(B) Bicornuate uterus. (C) Septum in uterus. (D) Unicornuate uterus.

The vaginal plate is formed as follows:

Endodermal cells of the urogenital sinus proliferate to form two swellings called the ***sinovaginal bulbs*** (Fig. 16.21B). These bulbs soon fuse to form one mass. Most of the vaginal plate is formed from these sinovaginal bulbs (Fig. 16.21C). The part of the vaginal plate near the future cervix is derived from mesodermal cells of the uterovaginal canal.

The hymen is situated at the junction of the lower end of the vaginal plate with the urogenital sinus. Both surfaces of the hymen are lined by endoderm.

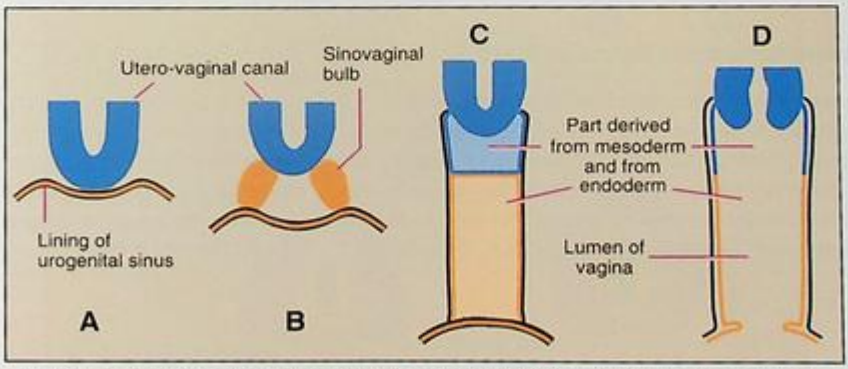

Fig. 16.21: (A) Uterovaginal canal (mesoderm) in contact with lining of UGS (endoderm). (B) Sinovaginal bulbs are formed by proliferation of endodermal lining. (C) Solid vaginal plate derived partly from mesoderm of uterovaginal canal and partly from endoderm of sinovaginal bulbs. (D) Vagina formed by canalisation of vaginal plate.

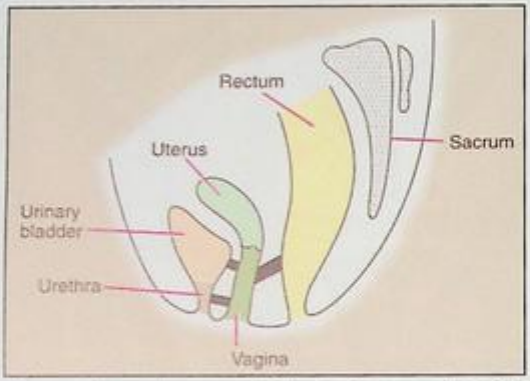

Fig. 16.22: Vaginal fistulae are abnormal communications between vagina and surrounding cavities. The fistulae are shown in solid black. They may connect the vagina to the rectum (rectovaginal fistula); to the urinary bladder (vesico-vaginal fistula) or to the urethra (ureterovaginal fistula).

Clinical Correlation

Anomalies of Vagina

- The vagina may be duplicated. This condition is usually associated with duplication of the uterus (Fig. 16.20A).
- The lumen may be subdivided longitudinally, or transversely, by a septum.
- The vagina may be absent. This condition may or may not be associated with absence of the uterus.
- The hymen may be imperforate.
- The vagina may have abnormal communications with the rectum (***rectovaginal fistula***) or with the urinary bladder (***vesico-vaginal fistula***) (Fig. 16.22).

Paramesonephric Ducts in Male

The paramesonephric ducts remain rudimentary in the male. The greater part of each duct eventually disappears (Fig. 16.19B). The cranial end of each duct persists as a small rounded body attached to the testis (***appendix of testis***) that may occasionally give rise to cysts. It has generally been considered that the prostatic utricle represents the uterovaginal canal and is, therefore, a homologue of the uterus. However, it is now believed to correspond mainly to the vagina (and possibly part of the uterus).

DEVELOPMENT OF EXTERNAL GENITALIA

Introduction

We have seen that, with the formation of the uro-rectal septum, the cloacal membrane comes to be subdivided into a ventral, urogenital membrane, and a caudal anal membrane (Figs. 16.23A, B). The urogenital membrane becomes elongated in a cranio-caudal direction. The mesoderm on either side of it is soon heaped up to form two longitudinal elevations called the ***primitive urethral folds*** (Figs. 16.23D, 16.24A). In addition to these folds, three other elevations of mesoderm are soon apparent. These are:

- the ***genital tubercle*** which is situated in the midline between the urogenital membrane and the lower part of the anterior abdominal wall; and
- the right and left ***genital swellings*** (Fig. 16.23C).

Development of Female External Genitalia (Figs. 16.23, 16.24)

- The genital tubercle becomes cylindrical and forms the ***clitoris***.
- The genital swellings enlarge to form the ***labia majora***. Their posterior ends fuse across the midline to form the ***posterior commissure***.
- The urogenital membrane breaks down, so that continuity is established between the urogenital sinus (which forms the vestibule) and the exterior. The primitive urethral folds now form the ***labia minora***. It will be obvious that they are lined on the outside by ectoderm and on the inside by endoderm (Fig. 16.24).

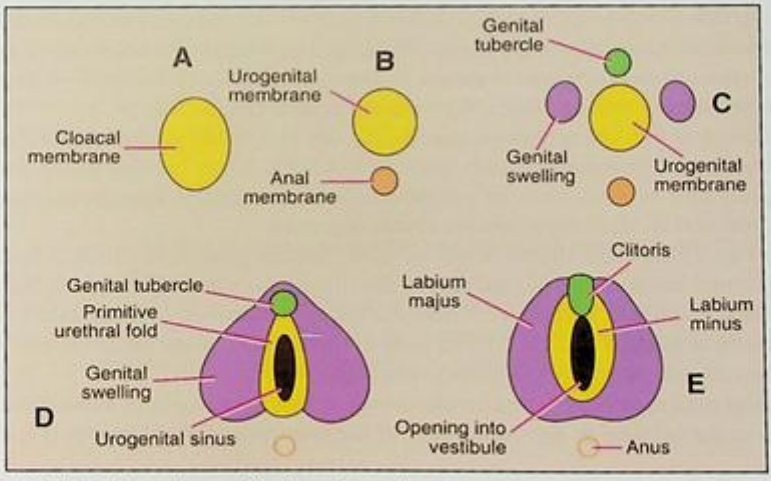

Fig. 16.23: (A). Cloacal membrane. (B). Cloacal membrane divides into urogenital membrane and anal membrane. (C) Right and left genital swellings, and a median genital tubercle appear. (D) Urogenital membrane breaks down. Its edges form the primitive urethral folds. (E) Genital tubercle becomes the clitoris. The genital swellings become the labia majora, and the primitive urethral folds become the labia minora.

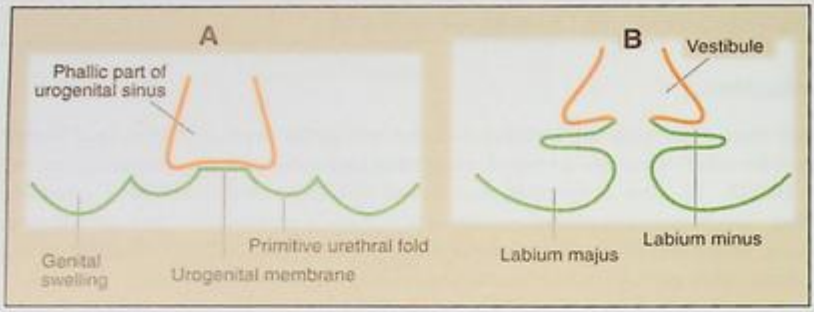

Fig. 16.24: Development of female external genitalia. Ectoderm is shown in solid line and endoderm in dotted line. Compare with Fig. 16.23.

Clinical Correlation

Anomalies of Female External Genitalia

- The clitoris may be absent, may be bifid, or may be double. It may be enlarged in hermaphroditism.
- The labia minora may show partial fusion.
- The urethra may open on the anterior wall of the vagina; this is the female equivalent of male hypospadias.

Development of Male External Genitalia

- The genital tubercle becomes cylindrical and is now called the ***phallus***. It undergoes great enlargement to form the ***penis***. As the phallus grows, the ***glans*** becomes distinguishable by the appearance of a ***coronary sulcus***. Still later, the ***prepuce*** is formed by reduplication of the ectoderm covering the distal part of the phallus (Fig. 16.25).
- We have seen that the urogenital membrane lies in a linear groove, flanked on either side by the primitive urethral folds (Figs. 16.26A to C). As the phallus grows, this groove elongates and extends onto its undersurface (Fig. 16.26B). This groove is lined by ectoderm and is called the ***primitive urethral groove***.
- From Figs. 16.26C and 16.26D it will be clear that the phallus is closely related to the endodermal lining of the phallic part of the urogenital sinus. The endodermal cells of this lining proliferate, and grow into the phallus, in the form of a solid plate of cells called the ***urethral plate*** (Fig. 16.26C). The cells of the urethral plate are in contact with the ectodermal cells lining the primitive urethral groove.
- The urogenital membrane soon breaks down, so that the urogenital sinus (phallic part) opens to the outside, in the caudal part of the primitive urethral groove (Fig. 16.26D).

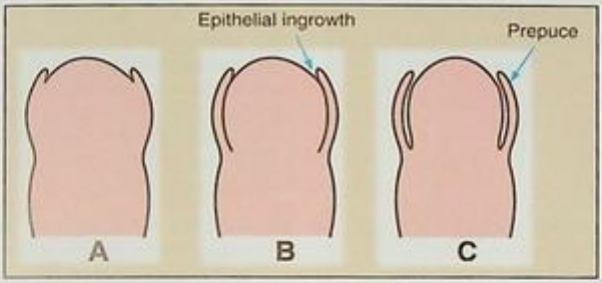

Fig. 16.25: Formation of the prepuce of the penis.

At the same time, the cells forming the core of the urethral plate degenerate, along with the ectodermal cells lining the primitive urethral groove. In this way, a deeper groove (called the ***definitive urethral groove***) lined by endodermal cells, is now formed on the undersurface of the phallus (Fig. 16.26F). At the base of the phallus this groove is continuous with the cavity of the urogenital sinus (Fig. 16.26F). The margins of this groove are called the ***definitive urethral folds***.

These folds now approach and fuse with each other. The fusion begins posteriorly in the region of the urogenital sinus and extends forwards onto the phallus (Figs. 16.26G, H). The penile urethra is formed as a result of this fusion. It will now be apparent that the wall of the penile urethra is made up of:

(1) the original endodermal lining of the phallic part of the urogenital sinus, and (2) the endodermal cells of the urethral plate.

The penile urethra formed in this way extends only up to the glans penis. The distalmost part of the urethra is of ectodermal origin, and is formed by canalisation of a solid mass of ectodermal cells (Figs. 16.26G, H).

- The genital swellings fuse with each other, in the midline, to form the ***scrotal sac*** into which the testes later descend.

Prenatal Diagnosis of Sex

The sex of a baby can be determined before birth by ultrasound examination. The penis can be seen in a male child.

In this connection it has to be noted that in fetuses about three to four months old, the genital tubercle is equally developed in both the male and female. Ultrasound examination at this stage can be misleading as the clitoris can be mistaken for a penis.

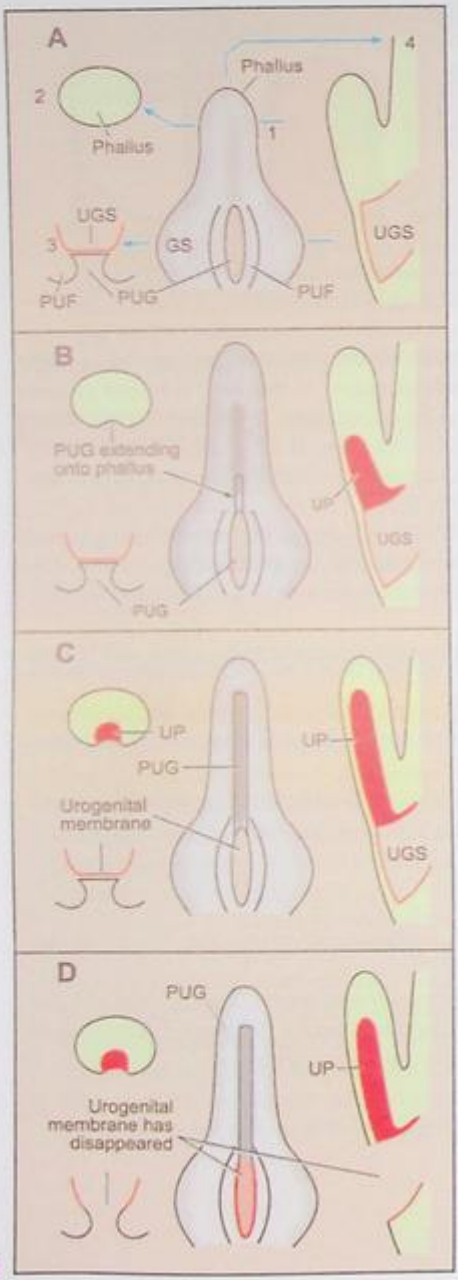

Fig. 16.26 A to D: Stages in the development of male genitalia and of penile urethra. In each set (A to H), the central figure (1) shows the genital region from the ventral aspect; (2) and (3) are transverse sections at the levels indicated; and (4) is a median section through the region. In sections ectoderm is depicted in black line, and endoderm is red. Mesoderm is green.

A. Note the following. The phallus is formed by enlargement of the genital tubercle. Caudal to the phallus there is a median, longitudinal depression, the primitive urethral groove (PUG) bounded by primitive urethral folds (PUF). Lateral to these folds we see the genital swellings (GS). In the depth of the primitive urethral groove there is the urogenital membrane which separates the groove from the urogenital sinus

B. The phallus has enlarged. The primitive urethral groove (PUG) is beginning to extend onto it. A solid mass of endodermal cells derived from the urogenital sinus, extends into the phallus. This mass is the urethral plate (UP)

C. The primitive urethral groove is now fully formed. The urethral plate has enlarged and extends deeper into the phallus

D. The urogenital membrane has broken down so that endoderm of the urogenital sinus (UGS) can now be seen from outside

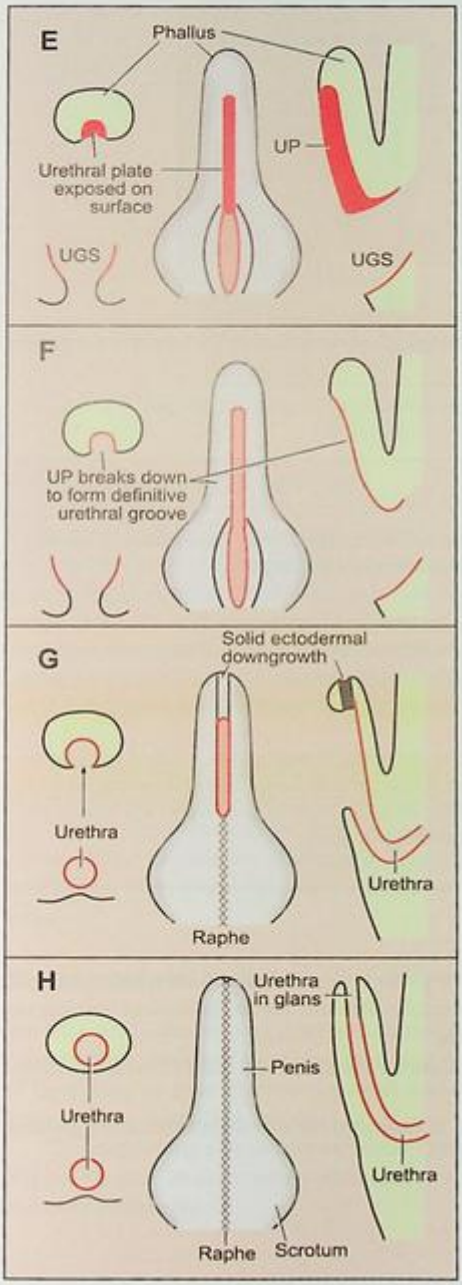

Fig. 16.26 (Continued) E to H:
First see A to D on previous page.

E. Ectoderm overlying the urethral plate has disappeared. As a result endoderm of the plate is seen on the surface

F. Cells in the centre of the urethral plate now break down and convert the plate into a groove that is seen on the surface. This is the definitive urethral groove, and the folds forming its edges are the definitve urethral folds

G. The definitve urethral folds grow towards each other and fuse to form a median raphe. In this way the definitive urethral groove is converted into a tube, which is the urethra. This process of fusion starts caudally and progresses cranially

H. In this figure and in 'G' note that the urethra formed as described above does not extend into the glans. The part of the urethra lying in the glans is derived from ectoderm which first forms a solid cord that is later canalized

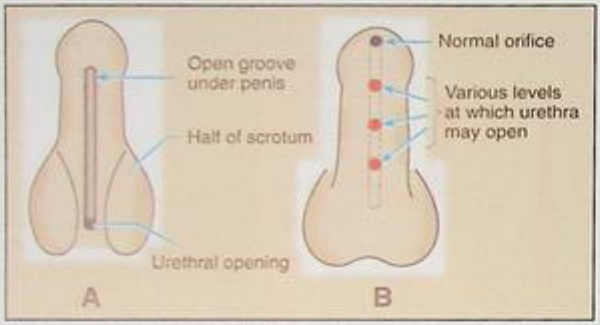

Fig. 16.27: (A) Cleft scrotum. (B) Hypospadias. The urethra opens onto the ventral aspect of the penis.

Clinical Correlation

Anomalies of Male External Genitalia

- The entire penis may be absent. Alternatively, the corpora cavernosa, or the prepuce, may be missing. The opening of the prepuce may be too narrow to allow retraction (***phimosis***).
- The penis may be double or bifid.
- Rarely, the penis may lie posterior to the scrotum.
- The urethral folds may fail to fuse, partially, or completely. When failure to fuse is complete the scrotum is in two halves and the genitals look like those of the female (Fig. 16.27A). If the defect is confined to the anterior part of the phallus, the urethra opens on the undersurface of the penis. This condition is called hypospadias (Fig. 16.27B).
- The urethra sometimes opens on the dorsal aspect of the penis. The condition is called ***epispadias***, and is usually associated with ectopia vesicae. In such cases it is believed that the genital tubercle is formed caudal to the urogenital membrane instead of being ventral to it. When the membrane ruptures, the urogenital sinus opens cranial to the developing penis.

Other anomalies of the penile urethra have been described earlier.

Primordial Germ Cells (Fig. 16.28)

The cells of the ovaries and the testes, from which germ cells are formed, are believed to be segregated early in the life of the embryo. They probably differentiate in the wall of the yolk sac and migrate to the region of the developing gonads.

All spermatozoa and ova that are formed throughout the life of the individual are believed to arise from these ***primordial germ cells***.

Migration of primordial germ cells into them is essential for development of the gonads. These cells have an inducing effect on the gonad.

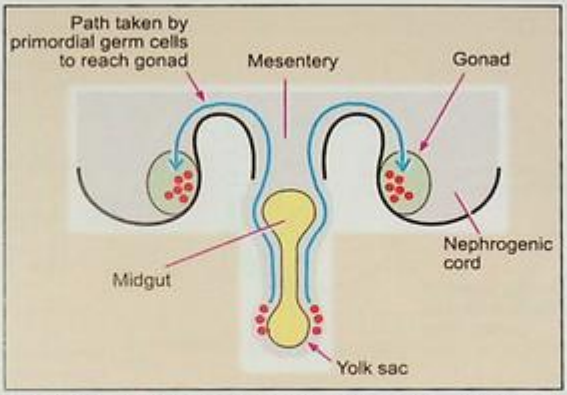

Fig. 16.28: Migration of primordial germ cells from the neighbourhood of the yolk sac to the developing gonad.

DEVELOPMENT OF TESTES

Each testis develops from the coelomic epithelium, that covers the medial side of the mesonephros, of the corresponding side (Fig. 16.29). In the region where the testis is to develop, this germinal epithelium becomes thickened. This thickening is called the ***genital ridge***. The cells of the germinal epithelium proliferate and form a number of solid ***sex cords***, that grow into the underlying mesenchyme. They reach deep into the gonad and are called ***medullary cords***. They are soon canalised to form the ***seminiferous tubules***. Meanwhile, the primordial germ cells migrate to the region of the developing testis and get incorporated in the seminiferous tubules.

The ***interstitial cells*** of the testis are derived from sex cords that are not canalised. Some of them are also derived from the surrounding mesenchyme.

The mesenchymal cells, surrounding the developing testis, form a dense layer of fibrous tissue. This is the ***tunica albuginea***. It completely separates the sex cords from the germinal epithelium and, thereafter, this epithelium can make no further contribution to testicular tissue.

Duct System of Testes

We have seen, above, that the testis develops in close proximity to the mesonephros, and the mesonephric duct. We have also seen that most of the mesonephric tubules degenerate. Some of them that lie near the testis persist and, along with the mesonephric duct, form the duct system of the testis (Fig. 16.30).

The ends of the seminiferous tubules anastomose with one another to form the ***rete-testes***. The rete-testes, in turn, establishes contact with persisting mesonephric tubules which form the ***vasa efferentia***.

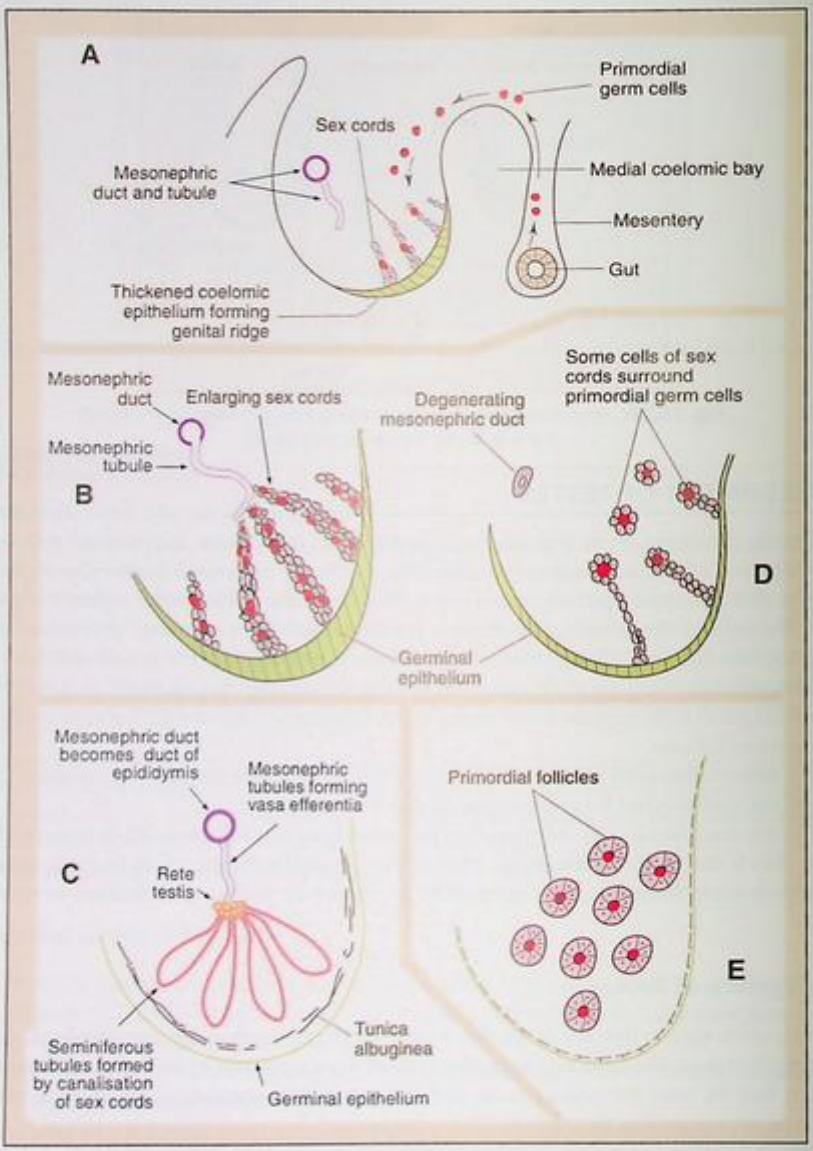

Fig. 16.29: Development of gonads. (A) Indifferent stage. (B) and (C) Testis. (D) and (E) Ovary.

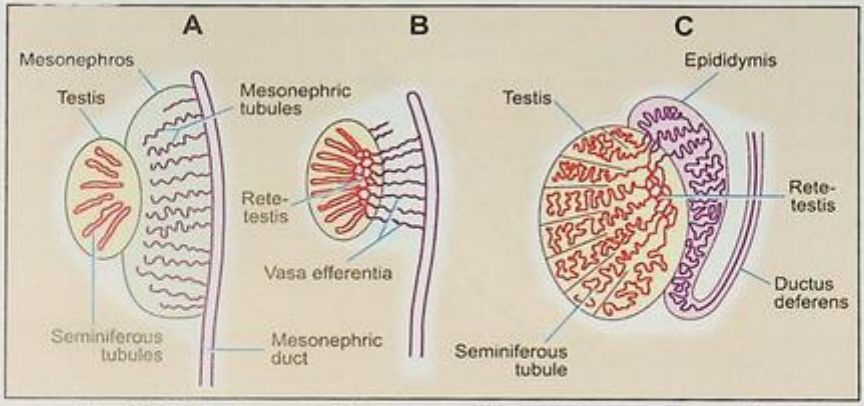

Fig. 16.30: Development of duct system of the testis. Structures derived from sex cords are shown in grey.

The cranial part of the mesonephric duct becomes highly coiled on itself to form the ***epididymis*** while its distal part becomes the ***ductus deferens***. The ***seminal vesicle*** arises, on either side, as a diverticulum from the lower end of the mesonephric duct. The part of the mesonephric duct between its opening into the prostatic urethra, and the origin of this diverticulum, forms the ***ejaculatory duct***.

Descent of Testes

The testes develop in relation to the lumbar region of the posterior abdominal wall. During fetal life, they gradually descend to the scrotum. They reach the iliac fossa during the third month, and lie at the site of the deep inguinal ring up to the seventh month of intrauterine life. They pass through the inguinal canal during the seventh month, and are normally in the scrotum by the end of the eighth month (Fig. 16.31).

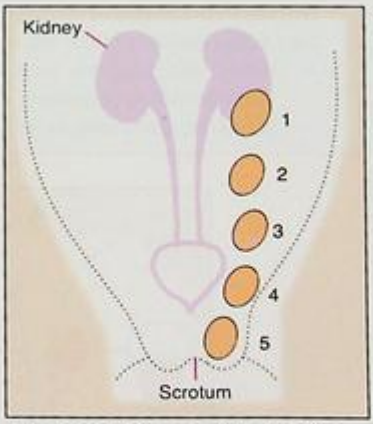

Fig. 16.31: Descent of the testis (from the lumbar region to the scrotum).

The descent of the testes is caused or assisted by several factors. These are:

- Differential growth of the body wall.
- ***Formation of inguinal bursa:*** About the sixth month of intrauterine life, the various layers of the abdominal wall, of each side, show an outpouching towards the scrotum (Fig. 16.32). This pouch progressively increases in size, and depth, and

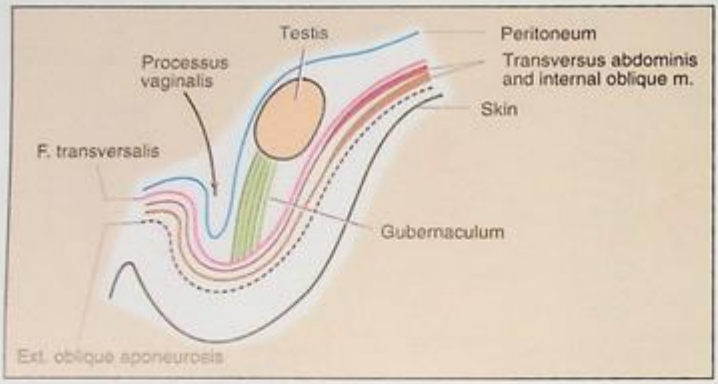

Fig. 16.32: The gubernaculum, which helps in descent of the testis.

eventually reaches the bottom of the scrotal sac. The descending testis enters this pouch to reach the scrotum. Note that the pouch is formed before the testis enters it. The cavity of the inguinal bursa becomes the ***inguinal canal***, while the various layers of its wall form the coverings of the testis and spermatic cord.

- ***The gubernaculum:*** This is a band of mesenchyme which extends from the lower pole of the testis to the scrotum. For many years it was believed that descent of the testis was caused by shortening of the gubernaculum. However, we now know that this is not possible because the gubernaculum does not contain any contractile tissue. According to some authorities the gubernaculum does not reach the scrotum but reaches the bottom of the inguinal bursa. In spite of this, the gubernaculum does play an important part in the descent of the testis as follows:
  - When the embryo increases in size, the gubernaculum does not undergo a corresponding increase in length. There is thus a relative shortening of the gubernaculum and, as a result, the testis assumes a progressively lower position.

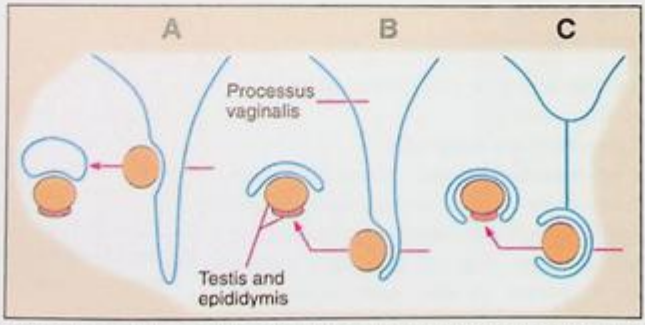

Fig. 16.33: Relation of descending testis to processus vaginalis. Note that as the testis descends it progressively invaginates the processus vaginalis.

- The gubernaculum helps to dilate the inguinal bursa.
- It provides a continuous pathway for the descending testis.

- ***Processus vaginalis:*** This is a diverticulum of the peritoneal cavity. It actively grows into the gubernacular mesenchyme of the inguinal canal and of the scrotum (Fig. 16.32). As the testis descends, it invaginates the processus vaginalis from behind. After the descent of the testis is completed, the processus vaginalis loses all connection with the peritoneal cavity and becomes the ***tunica vaginalis*** (Fig. 16.33).
- The descent of the testis is greatly influenced by hormones secreted by the pars anterior of the hypophysis cerebri.

Clinical Correlation

Anomalies of Testis

- The testis may be absent, on one or both sides.
- The testis may be duplicated.
- The two testes may be fused together.
- ***Anomalies of descent (Cryptorchidism):*** Descent of the testis may fail to occur, or may be incomplete. The organ may lie in the lumbar region, in the iliac fossa, in the inguinal canal, or in the upper part of the scrotum. Some interesting facts about this condition are as follows:
  - The testis may complete its descent after birth.
  - Spermatogenesis often fails to occur in an undescended testis.
  - An undescended testis is more likely to develop a malignant tumour than a normal testis.
  - The condition can be surgically corrected.
- ***Abnormal positions (Ectopia):*** The testis may lie (Fig. 16.34):
  - Under the skin of the lower part of the abdomen.
  - Under the skin of the front of the thigh.
  - In the femoral canal.
  - Under the skin of the penis.
  - In the perineum behind the scrotum.
- Also see hermaphroditism.

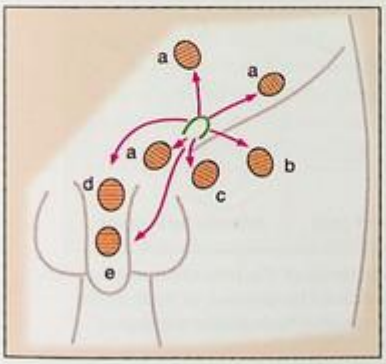

Fig. 16.34: Ectopic positions of the testis. A = under skin of the abdomen. B = over front of thigh. C = in femoral canal. D = under skin of penis. E = in perineum.

Clinical Correlation ***contd...***

Anomalies of Duct System of Testis

- The seminiferous tubules may fail to establish connection with the vasa efferentia.
- The ductus deferens may be absent, in whole or in part, on one or both sides.
- The ductus deferens may have no connection with the epididymis.

Anomalies of the Processus Vaginalis

We have seen that the part of the processus vaginalis, that extends from the deep inguinal ring up to the tunica vaginalis, normally disappears. This may persist in whole, or in part. Abdominal contents may enter it to produce various forms of ***inguinal hernia***. Alternatively, fluid may accumulate in it producing the condition called ***hydrocoele***. Various forms of hernia and of hydrocoele are shown in Fig. 16.35.

Vestigial Structures in the Region of the Testis

A number of vestigial structures are to be seen in the neighbourhood of the testis. Their importance lies in the fact that any one of them may enlarge to form a cyst.

These structures are:

- Appendix of testis (also called hydatid of Morgagni).
- Appendix of epididymis.
- Superior aberrant ductules.
- Inferior aberrant ductules.
- Paradidymis.

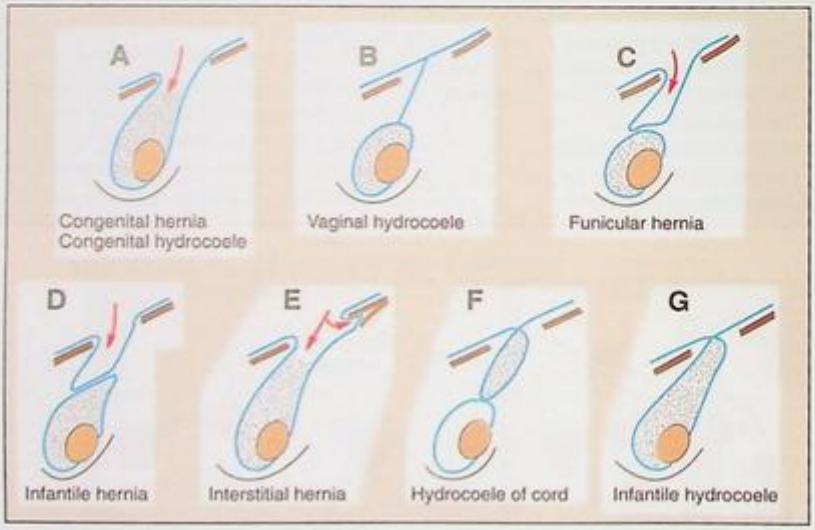

Fig. 16.35: Anomalies of processus vaginalis. Abnormal persistence of the processus vaginalis can lead to hernia (passage into it of abdominal contents, indicated by arrows); or hydrocoele (collection of fluid, shown as dots). Various types of hernia and hydrocoele are shown.

DEVELOPMENT OF THE OVARY

The early stages in the development of the ovary are exactly the same as in the testis (Figs. 16.29A, C, E).

- The coelomic epithelium on the medial side of the mesonephros becomes thickened to form genital ridges.
- Cords of cells (sex cords or medullary cords) proliferate from this germinal epithelium, and grow into the underlying mesoderm.
- Primordial germ cells, that are formed in relation to the yolk sac, migrate to the region of the developing ovary, and give rise to oocytes.
- The sex cords become broken up into small masses. The cells of each mass surround one primordial germ cell, or oocyte, to form a ***primordial follicle***.

According to some authorities the original (medullary) sex cords undergo regression in the ovary, and are replaced by a new set of ***cortical cords*** arising from coelomic epithelium. Follicular cells are derived from these cortical cords.

- ***Interstitial gland cells*** differentiate from mesenchyme of the gonad.
- As no tunica albuginea is formed, the germinal epithelium may contribute to the ovary even in postnatal life.

Descent of the Ovary

The ovary descends from the lumbar region, where it is first formed, to the true pelvis. A gubernaculum forms, as in the male, and extends from the ovary to the labium majus. It becomes attached to the developing uterus at its junction with the uterine tube. The part of the gubernaculum that persists between the ovary and the uterus, becomes the (round) ***ligament of the ovary***. The part between the uterus and the labium majus, becomes the ***round ligament of the uterus***.

CLINICAL CORRELATION

Anomalies of Ovary

- The ovary may be absent on one or both sides.
- The ovary may be duplicated.
- The ovary may descend into the inguinal canal or even into the labium majus.
- Adrenal or thyroid tissue may be present in the ovary. The ovary sometimes contains cells that are capable of differentiating into various tissues like bone, cartilage, hair, etc., and the growth of these cell rests can give rise to a peculiar tumour called a ***teratoma***.

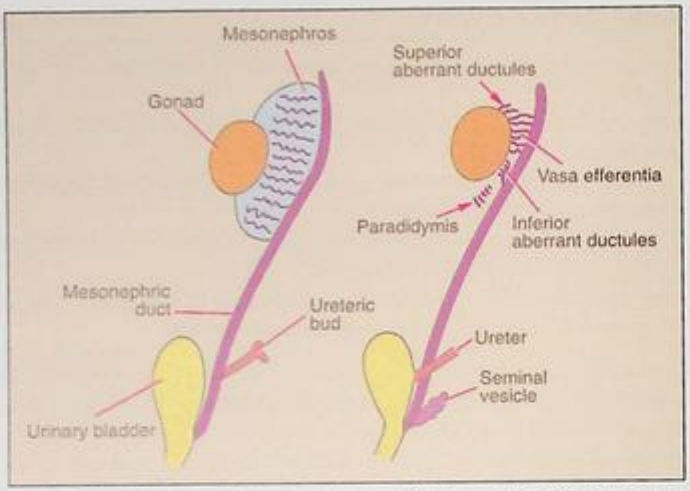

Fig. 16.36: (A) Mesonephric duct, early stage. (B) Mesonephric duct in the male, before descent of the testis.

FATE OF MESONEPHRIC DUCT AND TUBULES IN THE MALE

The mesonephric ducts give rise to the following structures (Figs. 16.36, 16.37):

- Ureteric buds from which the ureters, pelves, calyces and collecting tubules of the kidneys are derived.
- Trigone of the urinary bladder.
- Posterior wall of the part of the prostatic urethra, cranial to the openings of the ejaculatory ducts.
- Epididymis.
- Ductus deferens.
- Seminal vesicles.
- Ejaculatory ducts.
- Mesodermal part of prostate.
- ***Appendix of epididymis:*** This is a small rounded structure attached to the head of the epididymis (Fig. 16.37A). It represents the cranial end of the mesonephric duct. Occasionally it may give rise to a cyst. This is not to be confused with the appendix of the testis, which is a remnant of the paramesonephric duct.

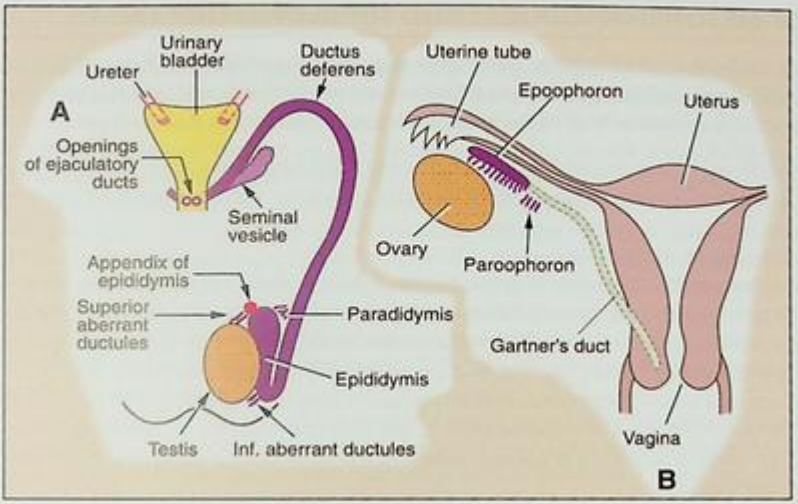

Fig. 16.37: Some structures derived from the mesonephric ducts. (A) In the male these are the epididymis, the ductus deferens, the seminal vesicles and ejaculatory ducts. The appendix of the epididymis is a vestigeal remnant. (B) In the female most of the duct disappears, Some remnants are seen as the epoophoron. For complete list of derivatives of the mesonephric ducts see text.

Remnants of Mesonephric Tubules

We have seen that most of the mesonephric tubules disappear. Some persist to form the ***vasa efferentia***. Other mesonephric tubules persist to form some vestigial structures that are seen near the testes. Their only importance is that they sometimes give rise to cysts. These remnants are as follows:

- The ***superior aberrant ductules*** (or ***epigenital tubules***) lie cranial to the vasa efferentia. They are connected to the testis but not to the epididymis.
- The ***inferior aberrant ductules*** lie caudal to the vasa efferentia. They are connected only to the epididymis.
- The ***paradidymis*** consists of tubules that lie between the testis and the epididymis (***paragenital tubules***) but are not connected to either of them.

FATE OF MESONEPHRIC DUCTS AND TUBULES IN THE FEMALE

As in the male, the mesonephric ducts give rise to the ureteric bud from which the ureter, pelvis, calyces and collecting tubules of the kidneys are derived, and give rise to the trigone of the bladder. The posterior wall of the female urethra, is also derived from them.

The mesonephric ducts and tubules do not establish any connection with the developing ovary. However, they give rise to some vestigial structures seen in the broad ligament near the ovary.

These are (Fig. 16.37B):

- ***Epoophoron:*** This consists of a longitudinal duct running parallel to the uterine tube, and a number of transverse ductules that open into the longitudinal duct. It corresponds to the epididymis and vasa efferentia of the male (Note that the word 'epoophoron' means 'above egg basket': ep = above, oo = egg, and phoron = basket).
  In some cases the longitudinal duct is unusually long. It runs along the side of the uterus, and lower down, becomes embedded in the wall of the cervix. It, however, never opens into the uterine lumen. It is the equivalent of the male ductus deferens and is also called *Gartner's duct.*
  Paroophoron: This consists of small blind tubules lying between the ovary and the uterus, and is the female equivalent of the paradidymis. The word paroophoron means 'near egg basket.'

Table 16.1: Summary of Male and Female Homologues derived from Undifferentiated Genital System

Structure	Male Derivative	Female Derivative
Gonad	Testis	Ovary
Sex cords	Sertoli cells (seminiferous tubules)	Granulose cells
Primordial germ cells	Spermatozoa	Ova
Paramesonephric duct	Appendix of testis	Uterine tube, uterus
	Utricle of prostate	Upper vagina
Mesonephric duct	Appendix of epididymis,	Appendix of ovary
	Epididymis,	Gartner's duct
	Ductus deferens,	
	Ejaculatory duct	
	Seminal vesicle	
Mesonephric tubules	Vasa efferentia	Epoophoron
	Paradidymis	Paroophoron
Genital tubercle	Penis	Clitoris
Genital swellings	Scrotum	Labia majora
Urethral folds	Floor of penile urethra	Labia minora

CONTROL OF DIFFERENTIATION OF GENITAL ORGANS

From the account of the development of the gonads and genitalia, it is seen that these organs are derived from the same primordia in both sexes. The male and female genital systems are identical till the beginning of seventh week of intrauterine life. The factors that determine whether these organs will develop as in the male, or as in the female are as follows:

- The most important factor is the chromosomal sex of the individual, which is determined at the time of fertilisation. We have already seen that individuals with two X-chromosomes are female, while those with one X-chromosome and one Y-chromosome are male.
- The Y-chromosome bears a gene that is responsible for production of a ***testis determining factor***. This factor plays a vital role in causing the developing gonad to become a testis. Apart from a direct action on the gonad, this factor influences other genes that play a role in the process. Under the influence of these genes, supporting (Sertoli) cells are formed from cells of the sex cords and interstitial (Leydig) cells are formed from mesenchymal cells of the gonadal ridge.
- Once the testis is formed, interstitial cells in it begin to produce testosterone (under the influence of gonadotropins produced in the placenta). This testosterone influences the differentiation of genital ducts, and external genitalia. By the end of eignteenth week of intrauterine life fetal interstitial cells disappear to reappear only at the time of puberty.
- Supporting cells in the fetal testis) produce a ***Mullerian inhibiting substance***. This substance causes regression of paramesonephric ducts. The sertoli cells also secrete an ***androgen binding factor*** that helps in formation of spermatozoa from spermatogonia.

As the Y-chromosome is missing in a female fetus, none of the processes described above take place. The oestrogens (derived from maternal and placental sources) influence the formation of internal and external genital organs.

Clinical Correlation

Hermaphroditism

Abnormal development of the gonad and the genitalia gives rise to various types of hermaphroditism. A hermaphrodite is really a person who is both a male and a female at the same time. Such a person has never been known to exist. However, persons having both testes and ovaries have been reported and such individuals are referred to as ***true hermaphrodites***. The word ***pseudohermaphrodite*** is used for a person whose external genitalia look like those of one sex, whereas the gonad is of the other sex.

Some forms of hermaphroditism are as follows:

True Hermaphroditism

The person has at least one testis and one ovary in the body. The external genitalia may be male, or female, or midway between the two. The chromosomal sex may be either male or female.

Pseudohermaphroditism

Gonads are of one sex, while genitalia (internal, external or both) are of opposite sex. A patient having a testis is described as a ***male hermaphrodite***; and one having an ovary is described as a ***female hermaphrodite***.

Female pseudohermaphroditism is caused by excess of androgens produced by the fetal suprarenal gland (adrenogenital syndrome). It may also be caused by administration of progestins to the mother during pregnancy.

TIMETABLE OF SOME EVENTS DESCRIBED IN THIS CHAPTER

Age	Developmental Events
3rd week	Formation of intermediate mesoderm External genitalia begin to form.
4th week	Pronephric tubules begin to form and have regressed by the end of the same week. Mesonephric tubules start forming. Urorectal septum begins to form.
5th week	The metanephros is formed.
6th week	Mesonephros is well developed. The cloacal membrane divides into the urogenital and the anal membrane.
7th week	Urogenital sinus is established.
3rd month	Urethral folds fuse with each other. At the end of the month, prostate begins to develop.
12th week	The definitive kidney (metanephros) becomes functional.
5th month	Vagina gets canalised.

The external genitalia are most susceptible to teratogens between the seventh and ninth weeks; but they can be affected later in pregnancy as well.

Chapter 17

The Nervous System

HIGHLIGHTS

- Ectoderm overlying the notochord becomes thickened to form the ***neural plate***.
- Neural plate is converted to ***neural groove***, and then to ***neural tube***.
- Neural tube has an enlarged cranial part that forms the ***brain***, and a narrow caudal part that becomes the ***spinal cord***.
- The cranial part of neural tube shows three dilatations: ***prosencephalon***, ***mesencephalon***, and ***rhombencephalon***. The prosencephalon divides into ***diencephalon*** and ***telencephalon***. The rhombencephalon divides into ***metencephalon*** and ***myelencephalon***.
- The telencephalon forms most of the ***cerebral hemisphere*** including the corpus striatum. The ***lateral ventricle*** is the cavity of the telencephalon.
- The diencephalon forms the ***thalamus***, ***hypothalamus*** and related structures. Its cavity is the ***third ventricle***.
- The mesencephalon forms the ***midbrain***. Its cavity forms the ***cerebral aqueduct***.
- The metencephalon forms the ***pons***. It also forms the ***cerebellum***.
- The myelencephalon forms the ***medulla oblongata***. The ***fourth ventricle*** is the cavity of the rhombencephalon.
- The ***neural crest*** is made up of cells that lie along the lateral edges of the neural plate. Its most important derivatives are cells of ***sensory ganglia***, ***parasympathetic ganglia*** and of ***sympathetic ganglia***. It also forms the cells of the ***adrenal medulla*** and ***Schwann cells*** that form sheaths for peripheral nerve fibres.
- The wall of the neural tube at first has a single layer of cells. They multiply and form three layers, ***ependymal mantle*** and ***marginal***. Neurons develop in the mantle layer.
- The mantle layer divides into a ventral part, the ***basal lamina***, and a dorsal part, the ***alar lamina***. These are separated by a groove, the ***sulcus limitans***.
- In the spinal cord the alar lamina forms the ***posterior grey column***, and the basal lamina forms the ***ventral grey column***. The marginal layer becomes white matter.
- In the medulla, pons and midbrain, ***efferent cranial nerve nuclei*** develop in the basal lamina and ***afferent nuclei*** in the alar lamina.
- The alar lamina of the mylencephalon also forms the ***olivary nuclei*** (which migrate ventrally), and the ***pontine nuclei*** which migrate into the pons. The ***cerebellum*** is derived from the alar lamina of the metencephalon.
- The alar lamina of the mesencephalon forms the ***colliculi***, the ***red nucleus*** and the ***substantia nigra***.

INTRODUCTION

The formation of neural tissue has been considered in chapter 7, where we have seen that the ependymal (or neuroepithelial) cells of the neural tube give rise both to neurons and to neuroglia. We have also studied the formation of myelin sheath. We shall now consider the development of individual parts of the nervous system.

The Neural Tube and Its Subdivisions

Apart from its blood vessels and some neuroglial elements, the whole of the nervous system is derived from ectoderm. The part of the ectoderm that is destined to give origin to the brain and spinal cord, can be distinguished while the embryo is still in the form of a three-layered embryonic disc. This ectoderm is situated on the dorsal (amniotic) aspect of the embryonic disc, in the midline, and overlies the notochordal process (Figs. 17.1A, B). It soon becomes thickened to form the ***neural plate*** (Fig. 17. 1B).

The neural plate becomes depressed along the midline as a result of which the ***neural groove*** is formed (Fig. 17. 1C). This groove becomes progressively deeper. At the same time, the two edges of the neural plate come nearer each other, and eventually fuse, thus converting the neural groove into the ***neural tube*** (Fig. 17.1D).

These stages in the formation of the neural tube do not proceed simultaneously all over the length of the neural plate. The middle part is the first to become tubular, so that for some

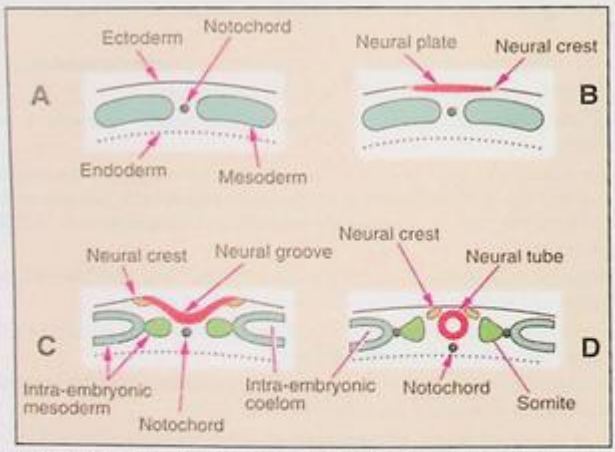

Fig. 17.1: Formation of neural tube. (A) Embryonic disc before formation of neural plate. (B) Neural plate formed by thickening of ectoderm. (C) Neural plate is converted to a groove. (D) The groove is converted to a tube. Note the neural crest which lies along the edges of the neural plate (B), or neural groove (C). After formation of the neural tube the neural crest lies dorsal to it (D).

Prosencephalon	Telencephalon	Cerebral cortex Corpus striatum	Cerebral hemisphere
	Diencephalon	Thalamus Hypothalamus Optic stalk Pars nervosa of hypophysis cerebri	
Mesencephalon		Midbrain	
Rhombencephalon	Metencephalon	Pons and cerebellum	
	Myelencephalon	Medulla oblongata	

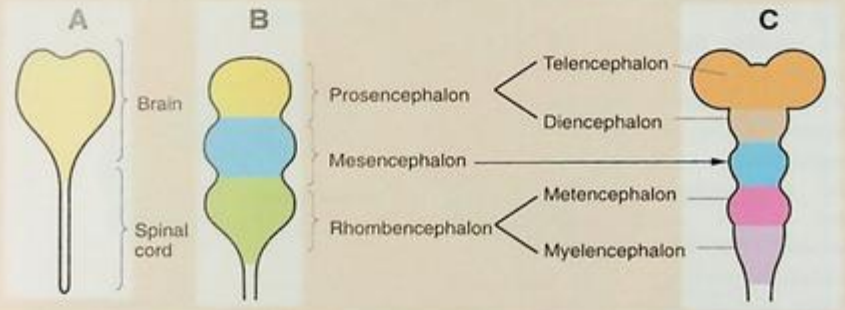

Fig. 17.2: Primary brain vesicles and their subdivisions.

time the neural tube is open cranially and caudally. These openings are called the ***anterior*** and ***posterior neuropores***, respectively. The fusion of the two edges of the neural plate extends cranially, and caudally, and eventually the neuropores disappear leaving a closed tube.

Even before the neural tube has completely closed, it is divisible into an enlarged cranial part and a caudal tubular part (Fig. 17.2A). The enlarged cranial part forms the brain. The caudal tubular part forms the spinal cord: it is at first short, but gradually gains in length as the embryo grows. The cavity of the developing brain soon shows three dilatations (Fig. 17.2B). Cranio-caudally, these are the ***prosencephalon***, ***mesencephalon***, and ***rhombencephalon***. The prosencephalon becomes subdivided into the ***telencephalon*** and the ***diencephalon*** (Fig. 17.2C). The telencephalon consists of right and left ***telencephalic vesicles***. The rhombencephalon also becomes subdivided into a cranial part, the ***metencephalon***, and a caudal part, the ***myelencephalon***. The parts of the brain that are developed from each of these divisions of the neural tube are shown in Fig. 17.2.

The prosencephalon, mesencephalon and rhombencephalon are at first arranged craniocaudally (Fig. 17.3A). Their relative position is greatly altered by the appearance of a number of flexures. These are:

- the ***cervical flexure***, at the junction of the rhombencephalon and the spinal cord (Fig. 17.3B);
- the ***mesencephalic flexure*** (or ***cephalic flexure***), in the region of the midbrain (Fig. 17.3C);
- the ***pontine flexure***, at the middle of the rhombencephalon, dividing it into the metencephalon and myelencephalon (Fig. 17.3D); and
- the ***telencephalic flexure***, that occurs much later, between the telencephalon and diencephalon.

These flexures lead to the orientation of the various parts of the brain as in the adult (Fig. 17.4).

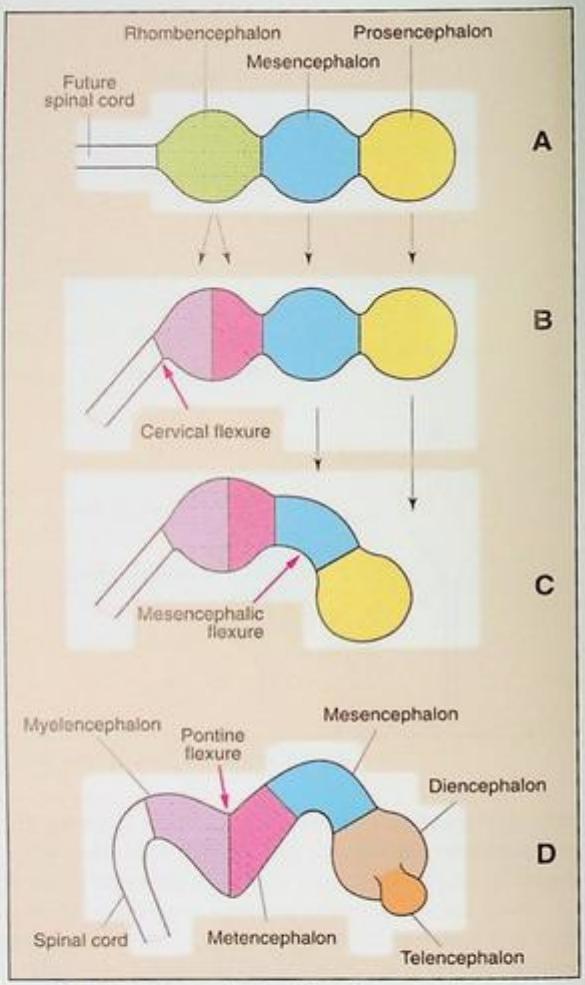

Fig. 17.3: (A) Neural tube before formation of flexures. (B) Cervical flexure formed. (C) Mesencephalic flexure formed. (D) Pontine flexure formed.

Each of the subdivisions of the developing brain encloses a part of the original cavity of the neural tube (Fig. 17.5). The cavity of each telencephalic vesicle becomes the ***lateral ventricle***, and that of the diencephalon (along with the central part of the telencephalon), becomes the ***third ventricle***. The cavity of the mesencephalon remains narrow, and forms the ***aqueduct***, while the cavity of the rhombencephalon forms the ***fourth ventricle***. Its continuation in the spinal cord is the ***central canal***.

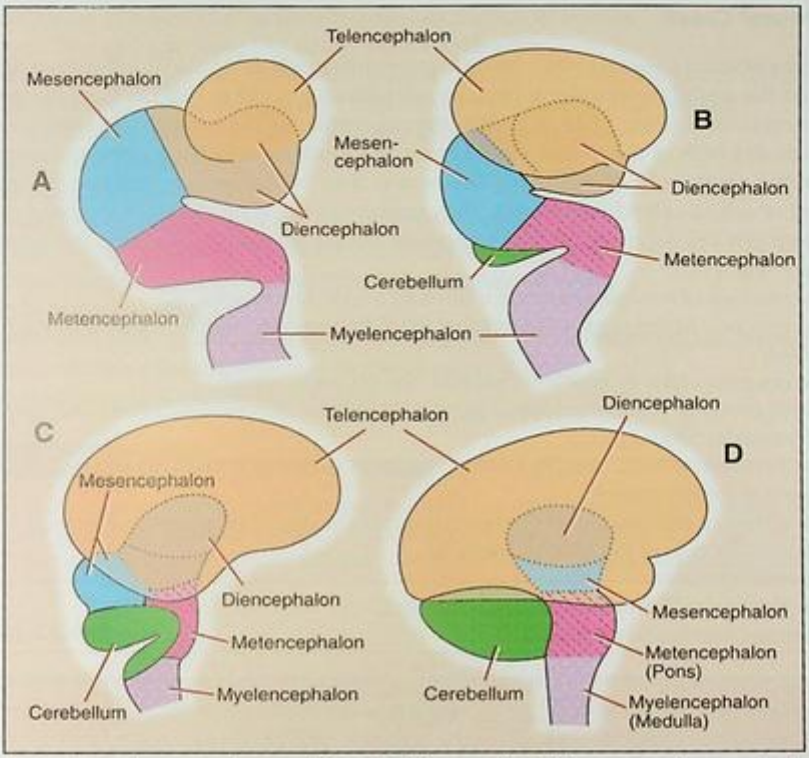

Fig. 17.4: Development of external form of the human brain. Note progressive overlapping of diencephalon and mesencephalon by the expanding telencephalon.

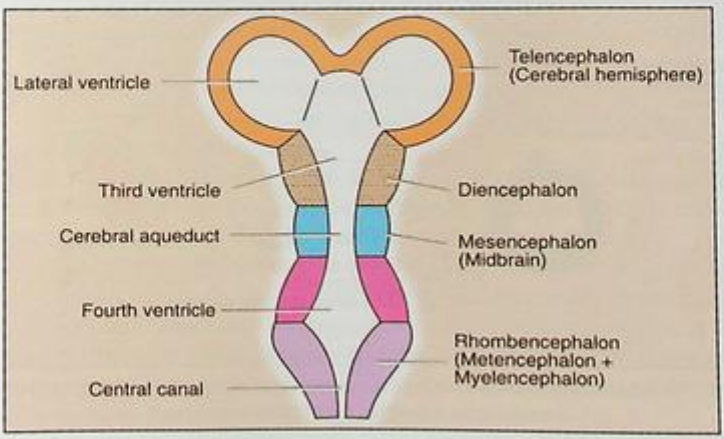

Fig. 17.5: Development of ventricles of the brain.

The Neural Crest

At the time when the neural plate is being formed, some cells at the junction between the neural plate and the rest of the ectoderm become specialised (on either side) to form the primordia of the neural crest (Figs. 17.1B, C). With the separation of the neural tube from the surface ectoderm, the cells of the neural crest appear as groups of cells lying along the dorsolateral sides of the neural tube (Fig. 17.1D). The neural crest cells soon become free (by losing the property of cell to cell adhesiveness). They migrate to distance places throughout the body. In subsequent development, several important structures are derived from the neural crest. These are (Fig. 17.6):

- The neurons of the spinal posterior (dorsal) nerve root ganglia.
- The neurons of the sensory ganglia of the fifth, seventh, eighth, ninth and tenth cranial nerves.
- The neurons of the sympathetic ganglia. The preaortic ganglia.
- The neurons of parasympathetic ganglia of cranial nerves (i.e., ciliary, submandibular, sphenopalatine and otic).
- The parasympathetic ganglia (enteric ganglia) of the gastrointestinal tract and ganglia related to pelvic viscera.
- The Schwann cells that form the neurolemmal sheaths of all peripheral nerves.
- The specific cells of the adrenal medulla.
- Chromaffin tissue..
- The pigment cells (melanoblasts) of the skin.
- Piamater and arachnoidmater

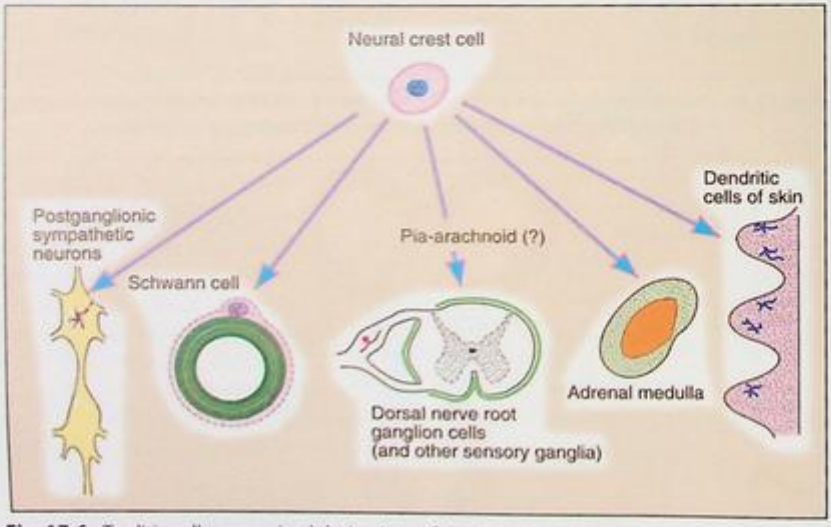

Fig. 17.6: Traditionally recognised derivatives of the neural crest. Some additional derivatives are now recognised (as mentioned in the text).

Other structures believed to arise from the neural crest are as follows.

- Mesenchyme of dental papilla, odontolasts and dentine.
- Bones of the face and part of the vault of skull. (frontal, parietal, squamous temporal, part of the sphenoid, maxilla, zygomatic, nasal, vomer, palatine and mandible).
- Dermis, smooth muscle and fat of face and ventral aspect of neck.
- Muscles of the ciliary body.
- Sclera and choroids of eye (?).
- Substantia propria and posterior epithelium of cornea.
- Connective tissues of thyroid, parathyroid, thymus and salivary glands.
- Derivatives of the first, second and third pharyngeal cartilages.
- C cells of the thyroid gland.
- Cardiac semilunar valves, and conotruncal septum (spiral septum plus bulbar septum).
- Smooth muscle of blood vessels of the face and of forebrain.
- The satellite cells of all sensory ganglia.

Clinical Correlation

Several diseases and syndromes are associated with the disturbances of the neural crest e.g. Hirschsprung's disease (aganglionic megacolon), aorticopulmonary septal defects of heart, cleft lip, cleft palate, frontonasal dysplasia, neurofibromatosis, tumor of adrenal medulla and albinism and others.

SPINAL CORD

The spinal cord is developed from the caudal cylindrical part of the neural tube.

When this part of the neural tube is first formed, its cavity is in the form of a dorsoventral cleft. The lateral walls are thick, but the roof (dorsal), and the floor (ventral), are thin (Fig. 17.7A). The wall of the tube subdivides into the matrix cell or ependymal layer, the mantle layer and the marginal layer (Fig. 17.7B) as already described.

The mantle zone grows faster in the ventral part of the neural tube, and becomes thicker, than in the dorsal part. As a result, the ventral part of the lumen of the neural tube becomes compressed. The line separating the compressed ventral part, from the dorsal part, is called the ***sulcus limitans*** (Fig. 17.7C). With its formation, the lateral wall of the developing spinal cord can be divided into a dorsal part, called the dorsal or ***alar lamina***, and a ventral part, called the ventral or ***basal lamina***.

This division is of considerable functional importance. The basal lamina develops into structures that are motor in function, and the alar lamina into those that are sensory. The alar and basal laminae are also called the ***alar and basal plates*** respectively.

With continued growth in thickness of the mantle layer, the spinal cord gradually acquires its definitive form (Figs. 17.7D, E). With growth of the alar lamina, the dorsal part of the cavity within the cord becomes obliterated: the posterior median septum is formed in this situation. The ventral part of the cavity remains as the ***central canal.*** Further enlargement of the basal lamina causes it to project forwards on either side of the midline, leaving a furrow, the ***anterior median fissure***, between the projecting basal laminae of the two sides.

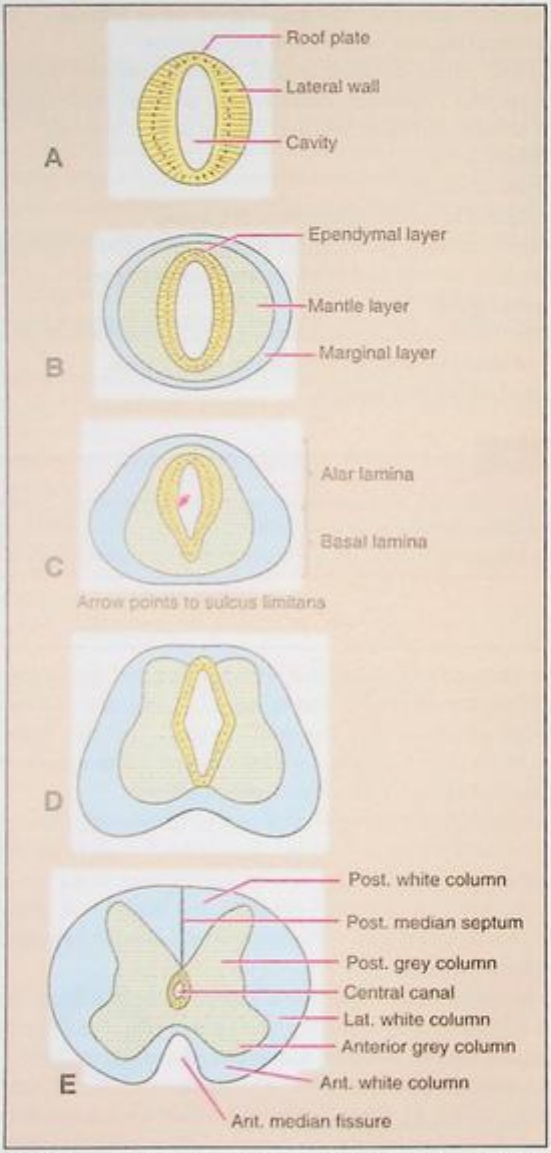

Fig. 17.7: Development of spinal cord. (A) Single layered neural tube. (B) ependymal, mantle and marginal layers established. (C) & (D) Mantle layer divided into alar and basal laminae. (E) Ventral and dorsal grey columns established. The dorsal part of the cavity of the neural tube disappears. The ventral part persists as the central canal.

The nerve cells that develop in the mantle zone of the basal lamina become the ***neurons of the anterior grey column*** (Fig. 17.8). The axons of these cells grow out of the ventrolateral angle of the spinal cord to form the ***anterior nerve roots*** of the spinal nerves. The nerve cells that develop in the mantle layer of the alar lamina form the ***neurons of the posterior grey column***. These are sensory neurons of the second order. Their axons travel predominantly upwards in the marginal layer to form the ***ascending tracts*** of the spinal cord. Many of these cells form ***interneurons.***

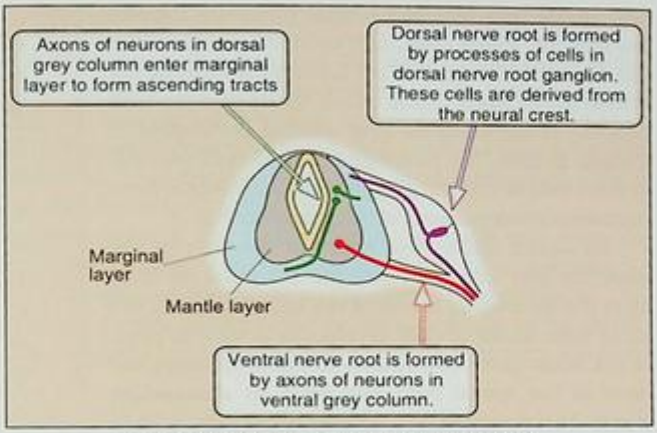

Fig. 17.8: Development of spinal nerve roots.

The ***dorsal nerve roots*** are formed by the axons of cells that develop from the neural crest (Figs. 17.6, 17.8). Groups of these cells collect on the dorsolateral aspect of the developing spinal cord to form the ***dorsal nerve root ganglia*** (or ***spinal ganglia***). The axons of these

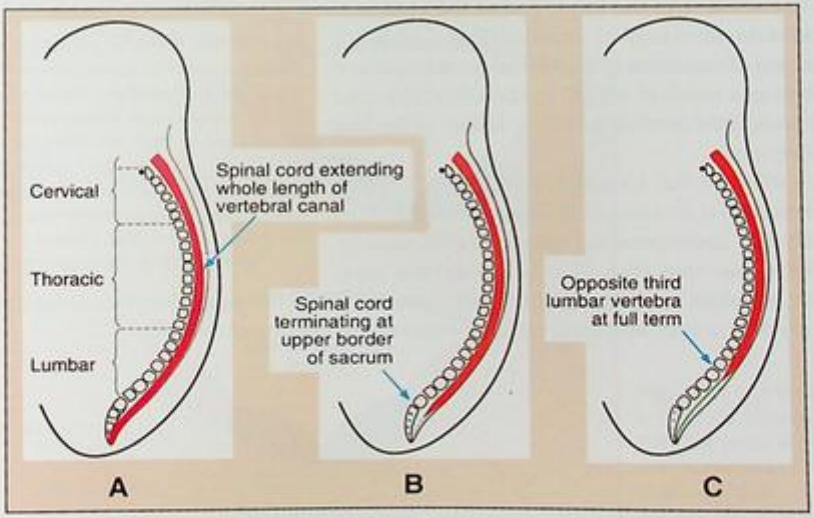

Fig. 17.9: Recession of spinal cord. Note that the lower end of the cord gradually move cranially, relative to the vertebrae.

cells divide into two. The central processes migrate towards the spinal cord, and establish contact with the dorsolateral aspect of the latter, thus forming the ***dorsal nerve roots***. These axons finally synapse with neurons of the posterior grey column developing in the alar lamina. The peripheral processes of the cells of the dorsal nerve root ganglia grow outwards to form the sensory components of the spinal nerves.

As stated above, the axons of neurons in the posterior grey column enter the marginal layer, to form the ***ascending tracts*** of the spinal cord. At the same time, axons of cells developing in various parts of the brain grow downwards to enter the marginal layer of the spinal cord and form its ***descending tracts.*** These ascending and descending tracts form the ***white matter*** of the spinal cord. As the mantle layer takes on the shape of the anterior and posterior ***grey columns,*** the white matter becomes subdivided into anterior, lateral and posterior ***white columns.***

The spinal cord at first extends throughout the length of the developing vertebral canal (Fig. 17.9 A). Subsequently, however, the vertebral column becomes much longer than the spinal cord with the result that at full term the lower end of the cord is at the level of the third lumbar vertebra (Figs. 17.9 B, C). This process of ***recession of the spinal cord*** continues after birth as a result of which, in the adult, the cord usually ends at the level of the lower border of the first lumbar vertebra.

One effect of this recession (of the cord) is that the intervertebral foramina no longer lie at the level at which the corresponding spinal nerves emerge from the spinal cord (Fig. 17.10). The nerves have, therefore, to follow an oblique downward course to reach the foramina. This obliquity is least for the cervical nerves, and greatest for the sacral and coccygeal nerves.

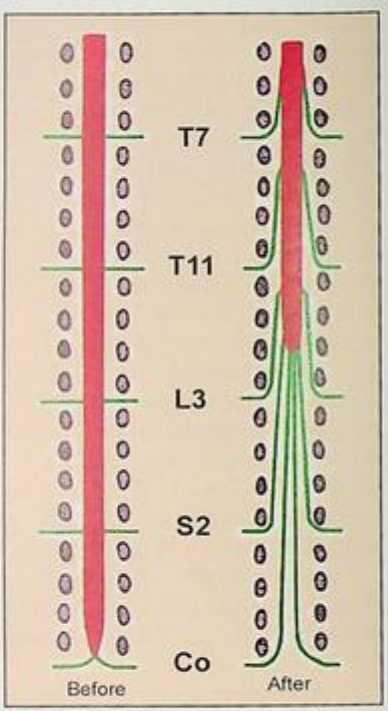

Fig. 17.10: Effect of recession of spinal cord on course of spinal nerves. (A) shows the condition before recession begins. Spinal nerves pass horizontally from the spinal cord to their exit from the vertebral canal. (B) shows the condition after recession has occurred. The nerves now have to run obliquely downwards to reach the points of exit. The obliquity is greatest in the case of the lowest nerves.

MEDULLA OBLONGATA

The medulla oblongata develops from the myelencephalon. The early development of the medulla is similar to that of the spinal cord. The appearance of the sulcus limitans divides each lateral wall into a dorsal or alar lamina, and a ventral or basal lamina (Fig. 17.11A). Subsequently, the thin ***roof plate*** becomes greatly widened as a result of which the alar laminae come to lie dorso-lateral to the basal laminae. Thus, both these laminae are now in the floor of the developing fourth ventricle (Fig. 17.11B).

Cells developing in the lateral part of each alar lamina migrate ventrally, and reach the marginal layer overlying the ventrolateral aspect of the basal lamina. These cells constitute the caudal part of the ***bulbo-pontine extension***, and develop into the ***olivary nuclei*** (Figs. 17.11C, 17.14). The remaining cells of the alar lamina develop into the sensory nuclei of the cranial nerves related to the medulla. The motor nuclei of these nerves are derived from the basal lamina (Fig. 17.12).

The nerve cells of the alar and basal laminae are at first grouped in accordance with their function, and are arranged as illustrated in Fig. 17.12. Subsequently, some of these nuclei migrate ventrally, from their primitive position in the floor of the fourth ventricle. Their ultimate position is indicated in Fig. 17.13.

The ***gracile and cuneate nuclei*** are derived from the lowermost part of the somatic afferent column.

The ***white matter*** of the medulla is predominantly extraneous in origin, being composed of fibres constituting the ascending and descending tracts that pass through the medulla.

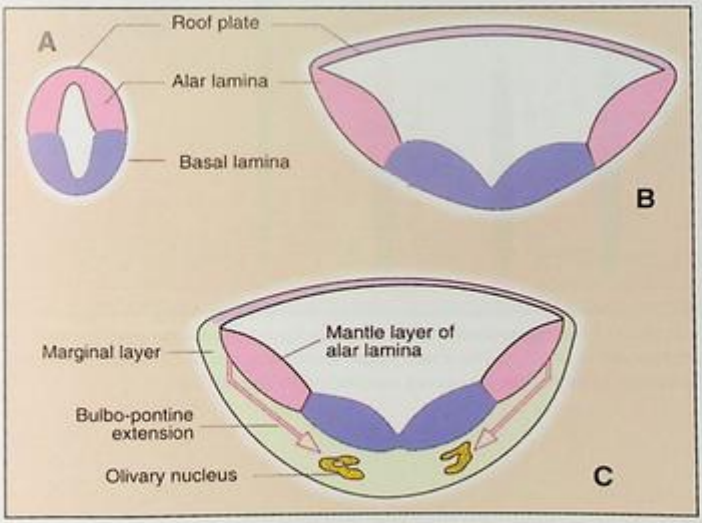

Fig. 17.11: Development of medulla oblongata. In 'B', note the great widening of the roof plate. In 'C', note the bulbo-pontine extension and the olivary nuclei.

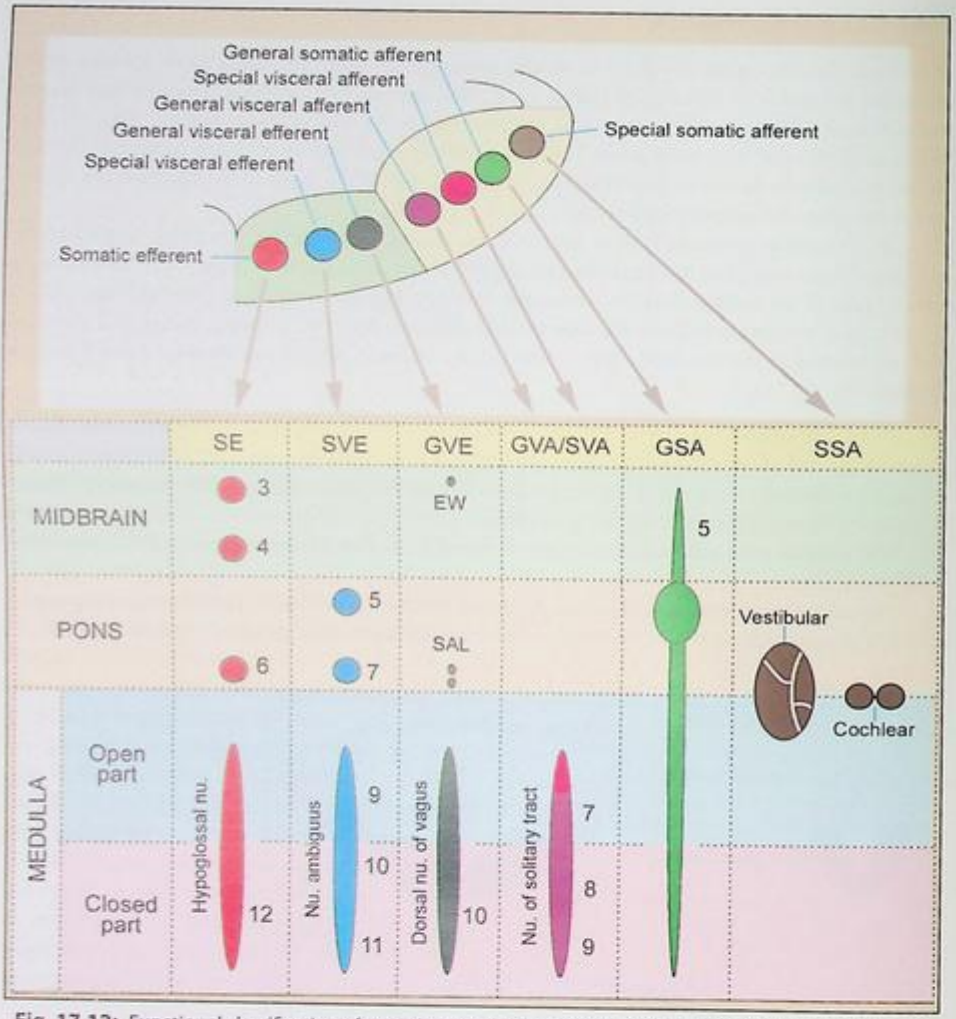

Fig. 17.12: Functional classification of cranial nerve nuclei. The upper figure shows the arrangement of nuclear columns in the brainstem of the embryo. The lower figure shows the nuclei derived from each column. Numbers indicate cranial nerves connected to the nuclei.

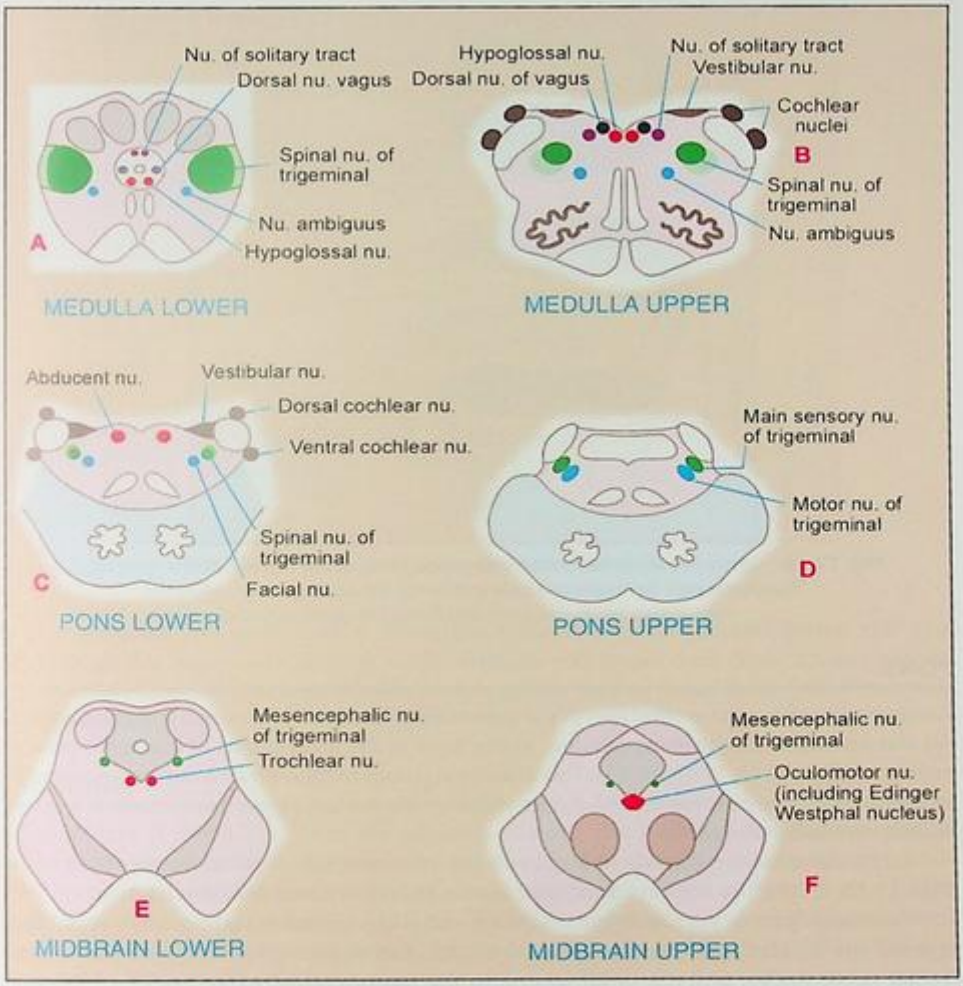

Fig. 17.13: Location of cranial nerve nuclei as seen in transverse sections at various levels of the brainstem.

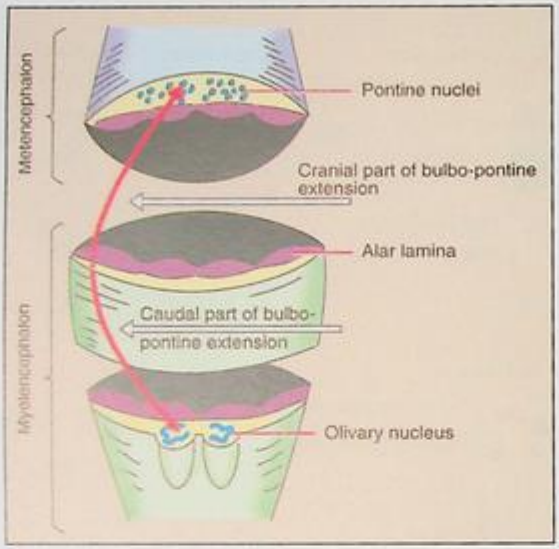

Fig. 17.14: Scheme to show the cranial and caudal parts of the bulbo-pontine extension. The caudal part lies in the medulla and forms the olivary nuclei, while the cranial part lies in the pons and forms the pontine nuclei.

PONS

The pons arises from the ventral part of the metencephalon. It also receives a contribution from the alar lamina of the myelencephalon, in the form of the cranial part of the bulbo-pontine extension (Figs. 17.12, 17.13, 17.15). This extension comes to lie ventral to the metencephalon, and gives rise to the ***pontine nuclei***. Axons of cells in these nuclei grow transversely to form the ***middle cerebellar peduncle***.

As in the myelencephalon, the roof of the metencephalon becomes thin and broad (Figs. 17.12, 17.13). The alar and basal laminae are thus orientated as in the medulla.

The lateral part of each alar lamina (often called the ***rhombic lip***) becomes specialised to form the cerebellum. The ventral part of the alar lamina gives origin to the sensory cranial nerve nuclei, and the basal lamina to the motor cranial nerve nuclei, of the pons (Figs. 17.12, 17.13). Their derivation is illustrated in Figs. 17.12 and 17.13.

The nuclei derived from the basal, and alar, laminae lie in the dorsal or tegmental part of the pons. The ventral part of the pons is constituted by:

- Cells of the bulbo-pontine extension (derived from the alar lamina of the myelencephalon), that form the pontine nuclei. Axons of the cells in these nuclei grow transversely and form the ***middle cerebellar peduncle***.

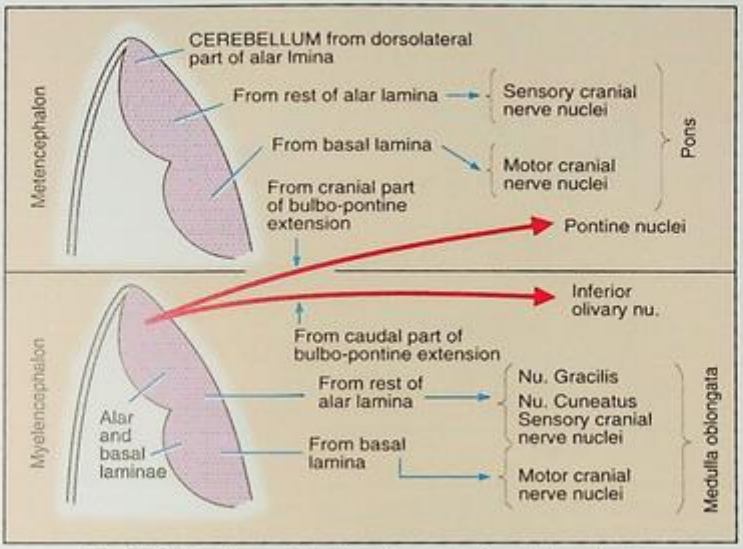

Fig. 17.15: Scheme of the development of medulla and pons.

- Corticospinal and corticobulbar fibres that descend from the cerebral cortex, and pass through this region on their way to the medulla and spinal cord. Some fibres from the cerebral cortex terminate in relation to the pontine nuclei. These are the corticopontine fibres.

MIDBRAIN

The midbrain is developed from the mesencephalon. The cavity of the mesencephalon remains narrow and forms the aqueduct. As described in the case of the spinal cord, the mantle layer becomes subdivided into a dorsal or alar lamina and a ventral or basal lamina by the appearance of the sulcus limitans (Fig. 17.16). The nuclei which develop from the basal lamina are: (1) the oculomotor nerve nucleus, (2) the trochlear nerve nucleus, and (3) the Edinger Westphal nucleus (GVE).

The alar lamina gives rise to the cells of the colliculi. At first, these form one mass which later becomes subdivided by a transverse fissure. Some cells of the alar lamina migrate ventrally to form the ***red nucleus*** and the ***substantia nigra*** (Fig. 17.16).

The marginal layer of the ventral part of the mesencephalon is invaded by downward growing fibres of the corticospinal, corticobulbar and corticopontine pathways. This region, thus, becomes greatly expanded, and forms the ***basis pedunculi*** (crus cerebri).

	FROM ALAR LAMINA	FROM BASAL LAMINA
MIDBRAIN	Colliculi Substantia nigra Red nucleus Mesencephalic nu. of trigeminal n.	Oculomotor nu. Edinger Westphal nu. Trochlear nu.
PONS	Pontine nuclei Vestibular nu. Cochlear nu. Main sensory nu. of trigeminal n. Nu. of spinal tract of trigeminal n. Nu. of tractus solitarius	Motor nu. of trigeminal n. Motor nu. of facial n. Nucleus of abducent n. Sup. salivatory nu. Lacrimatory nu.
MEDULLA	Inf. salivary nu. Vestibular nu. Nu. of spinal tract of trigeminal n. Nu. of tractus solitarius Part of dorsal nu. of vagus n.	Part of dorsal nucleus of vagus n. Inf. salivatory nu. Nu. ambiguus Hypoglossal nu.

Fig. 17.16: Structures of the midbrain derived from alar and basal laminae.

CEREBELLUM

The cerebellum develops from the dorsolateral part of the alar lamina of the metencephalon (Fig. 17.17A). Obviously, there are at first two primordia of the cerebellum, right and left. These extend medially in the roof plate of the metencephalon to eventually fuse across the midline (Figs. 17.17B, C). As the cerebellum increases in size, fissures appear on its surface. The lateral lobes and vermis can soon be distinguished, as a result of differential growth.

The developing cerebellum can be divided into: (a) an ***intraventricular part*** that bulges into the cavity of the developing fourth ventricle, and (b) an ***extraventricular part*** that is seen as a bulging on the surface (Fig. 17.17C). At first the intraventricular part is the larger of the two, but at a later stage, the extraventricular part becomes much larger than the intraventricular part and constitutes almost the whole of the organ (Fig. 17.17D).

The cerebellum, at first, consists of the usual matrix cell, mantle and marginal layers. Some cells of the mantle layer migrate into the marginal layer to form the cerebellar cortex. The cells of the mantle layer that do not migrate into the cortex, develop into the ***dentate, emboliform, globose*** and ***fastigal nuclei***.

The ***superior cerebellar peduncle*** is formed chiefly by the axons growing out of the dentate nucleus. The ***middle cerebellar peduncle*** is formed by axons growing into the cerebellum from the cells of the pontine nuclei, while the ***inferior cerebellar peduncle*** is formed by fibres that grow into the cerebellum from the spinal cord and medulla.

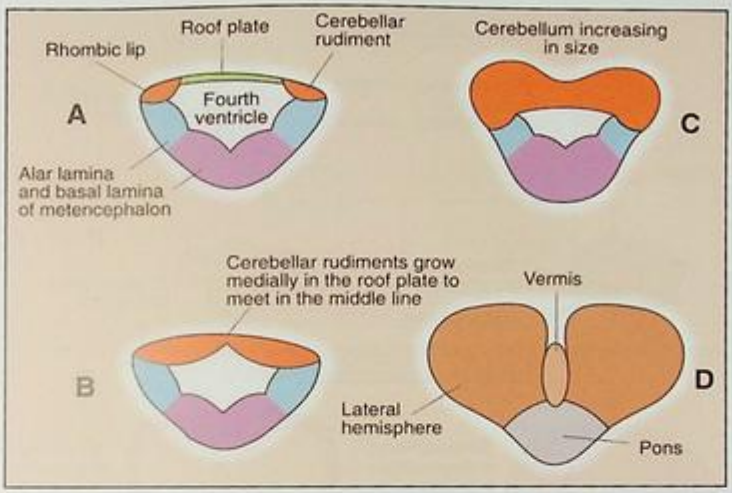

Fig. 17.17: Some stages in the development of the cerebellum. (A) Cerebellar rudiments appear from alar lamina of metencephalon. (B) They grow into the roof plate of the metencephalon to meet in the midline. (C) Cerebellum enlarges and bulges out of the fourth ventricle. (D) Lateral hemispheres and vermis can be distinguished.

CEREBRAL HEMISPHERE

The cerebrum is a derivative of the prosencephalon. We have seen that the prosencephalon is divisible into a median diencephalon and two lateral telencephalic vesicles (Fig. 17.2C). The telencephalic vesicles give origin, on either side, to the ***cerebral cortex*** and the ***corpus striatum***. The diencephalon gives rise to the ***thalamus***, ***hypothalamus*** and related structures. The telencephalic vesicles are at first small (Figs. 17.18B, F), but rapidly increase in size extending upwards, forwards and backwards (Figs. 17.18, 17.19). As a result of this enlargement, the telencephalon comes to completely cover the lateral surface of the diencephalon (Figs. 17.18D, H) and eventually fuses with it (Fig. 17.19). Thus, the cerebral cortex and corpus striatum come to lie lateral to the thalamus and hypothalamus.

With further upward, forward and backward extension of the telencephalic vesicles, the vesicles of the two sides come into apposition with each other above, in front of, and behind the diencephalon (Figs. 17.18H, 17.19).

The cavity of the diencephalon forms the ***third ventricle***, while the cavities of the two telencephalic vesicles form the ***lateral ventricles*** (Fig. 17.5).

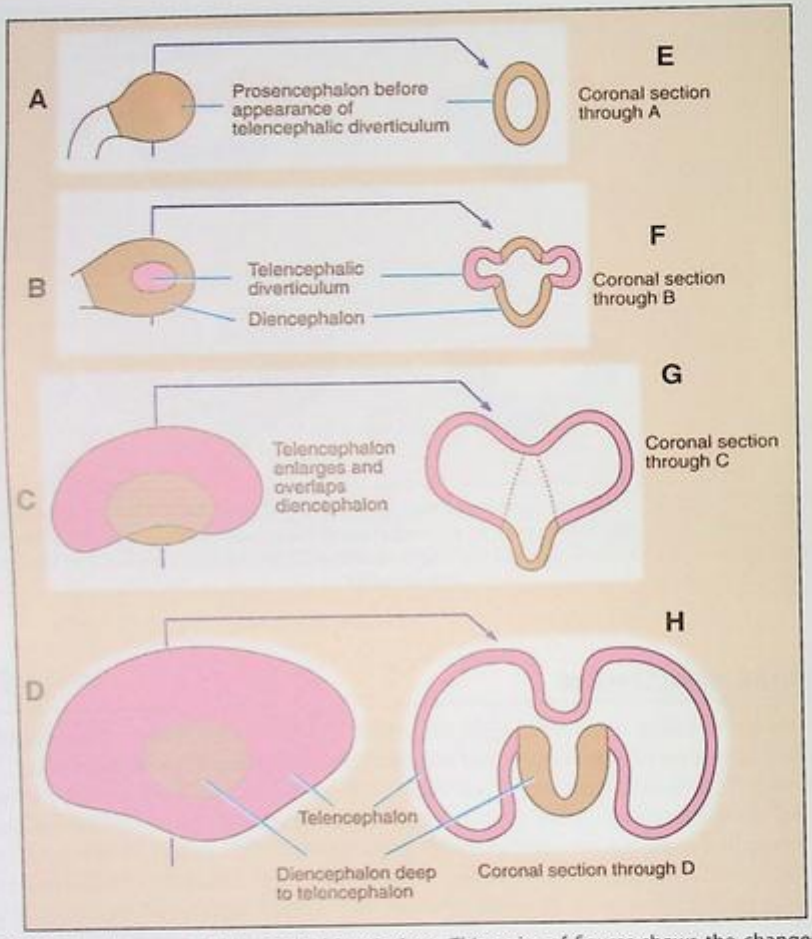

Fig. 17.18: Development of the cerebral hemisphere. This series of figures shows the changes in the relative size and position of the diencephalon and the telencephalic vesicles. Figures (A), (B), (C) and (D) are lateral views. Figures (E), (F), (G) and (H) are corresponding coronal sections along the axes indicated. (A), (E) Prosencephalon before appearance of telencephalic vesicles. (B), (F) Telencephalic vesicles appear. (C), (G) Telencephalic vesicles enlarge and partially cover diencephalon. (D), (H) Telecephalon much larger than diencephalon and completely overlapping it.

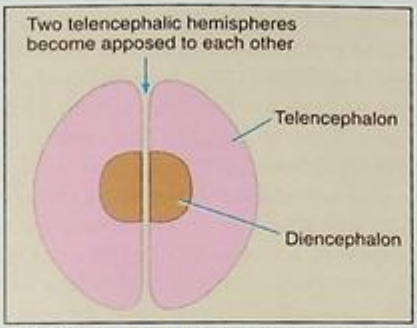

Fig. 17.19: Figure to show that the two telencephalic vesicles come to be apposed to each other in front of and behind the diencephalon.

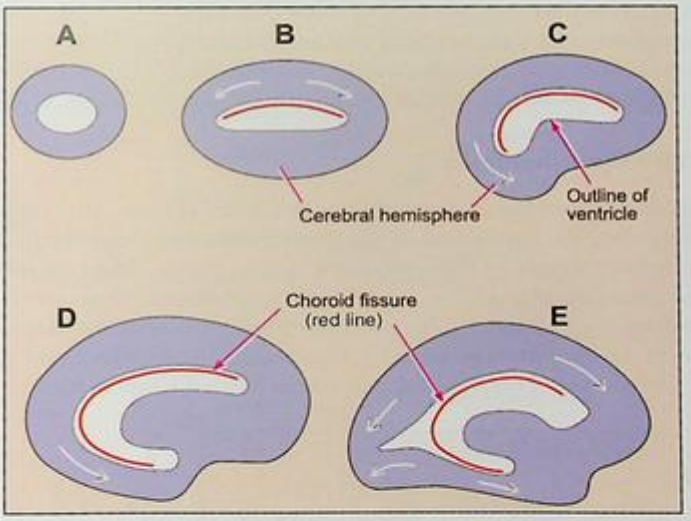

Fig. 17.20: Establishment of the form of the cerebral hemisphere and of the lateral ventricle. Arrows indicate direction of growth. The choroid fissure is shown in dotted line.

Each lateral ventricle is at first a spherical space within the telencephalic vesicle (Fig. 17.20A). With the forward and backward growth of the vesicle, the ventricle becomes elongated anteroposteriorly (Fig. 17.20B). The posterior end of the telencephalic vesicle now grows downwards and forwards, to form the temporal lobe, and the cavity within it becomes the ***inferior horn*** (Figs. 17.20C, D). The ventricle thus becomes C-shaped. Finally, as a result of backward growth, the occipital pole of the hemisphere becomes established, the part of the ventricle within it becoming the ***posterior horn*** (Fig. 17.20E).

From Fig. 17.18H, it will be seen that, with the enlargement of the telencephalic vesicles, their medial walls become apposed to each other. In this way a groove bounded by the two medial surfaces is formed, these surfaces being continuous with each other in the floor of the groove. Note that the floor of this groove forms the roof of the third ventricle. Just above the floor of this groove, the medial wall is invaginated laterally into the cavity of the lateral ventricle. The cavity of the invagination is the ***choroid fissure*** (Fig. 17.21). A fold of pia mater extends into this fissure and forms the ***telachoroidea***. A bunch of capillaries is formed within this fold and forms the ***choroid plexus*** (Fig. 17.22). The original wall of the ventricle lining the choroid plexus, remains very thin and forms the ependymal covering of the plexus (Fig. 17.22). Note that the telachoroidea is in intimate relationship to both lateral ventricles and also to the roof of the third ventricle (Fig. 17.22).

With the establishment of the temporal pole and the formation of the inferior horn of the lateral ventricle, the choroid fissure becomes C-shaped (Fig. 17.20). The inferior part of the fissure now invaginates into the inferior horn of the lateral ventricle (Fig. 17.20E).

Thalamus and Hypothalamus

The thalamus and hypothalamus develop from the diencephalon. After the establishment of the telencephalon, the lateral wall of the diencephalon becomes thickened. It is soon subdivided into three regions by the appearance of two grooves, called the ***epithalamic*** and ***hypothalamic sulci*** (Fig. 17.23A). The central part, lying between these two sulci, enlarges to form the ***thalamus*** (Figs. 17.23B, C). The part above the epithalamic sulcus remains relatively small and forms the ***epithalamus***, which is represented by the ***habenular nuclei*** and the ***pineal body***. The part below the hypothalamic sulcus forms the hypothalamus.

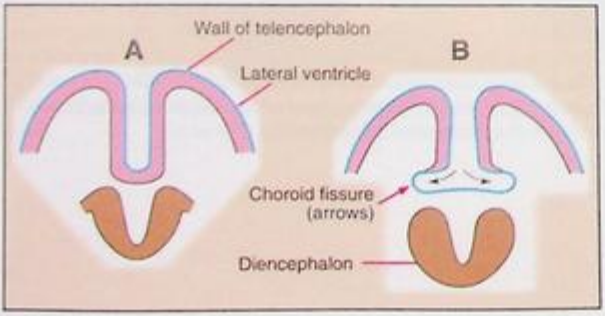

Fig. 17.21: Formation of the choroid fissure. The wall of the telencephalon remains thin at this site.

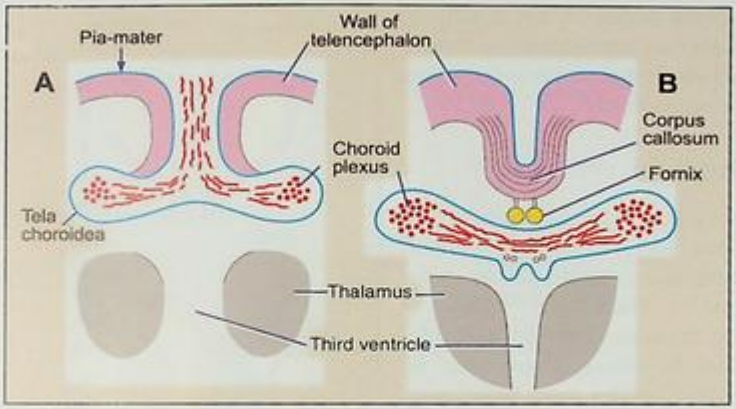

Fig. 17.22: Formation of telachoroidea (fold of piamater) and choroid plexus (bunch of capillaries).

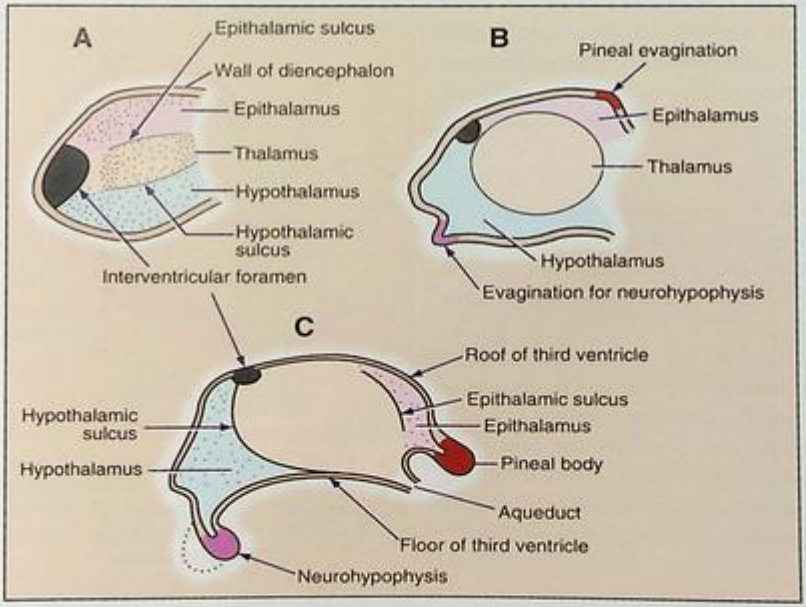

Fig. 17.23: Development of thalamus and hypothalamus. The appearance of the epithalamic and hypothalamic sulci divides the diencephalon into thalamus, epithalamus and hypothalamus. The pineal body is formed in relation to the epithalamus, and the neurohypophysis in relation to the hypothalamus.

The various nuclei of the thalamus and hypothalamus are formed by multiplication of cells in the mantle layer of the wall of the diencephalon.

Corpus Striatum

The corpus striatum is a derivative of the telencephalon. Early in its development each telencephalic vesicle can be subdivided into a basal part which is thick, and a superior part which is thin (Figs. 17.24A, B). Some of the cells, in the mantle layer of the thick basal part, migrate into the overlying marginal layer to form part of the cerebral cortex. The remaining cells of the mantle layer of this region form the corpus striatum.

The developing corpus striatum soon becomes subdivided into medial and lateral subdivisions, which increase in thickness (Fig. 17.24C). Meanwhile, the cerebral cortex is developing and numerous axons, that are growing downwards from it, or are growing towards it, pass through the region of the corpus striatum and divide it into a deeper and a superficial part. These fibres constitute the ***internal capsule*** (Fig. 17.25).

The part of the corpus striatum that comes to lie deep to the internal capsule, becomes the ***caudate nucleus***, and the superficial part becomes the ***lentiform nucleus*** (Fig. 17.26). The lentiform nucleus later becomes subdivided into the ***putamen***, and the ***globus pallidus***.

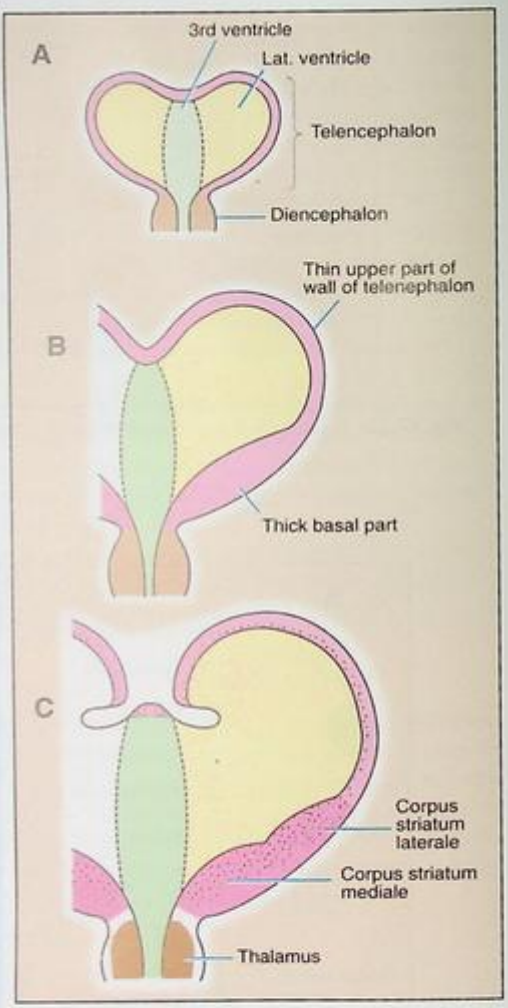

Fig. 17.24: Early development of corpus striatum as seen in coronal sections. (A) Telencephalon before appearance of corpus striatum. (B) Wall of basal part thickened. (C) Thickening divides into medial and lateral parts.

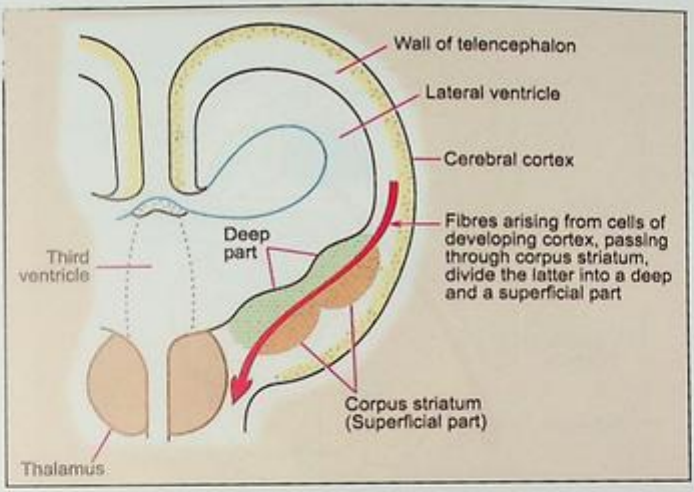

Fig. 17.25: Wall of telencephalon at a stage somewhat later than that shown in Fig. 17.31C. The region of the developing corpus striatum is divided (longitudinally) into deep and superficial parts (by nerve fibres growing downwards through it).

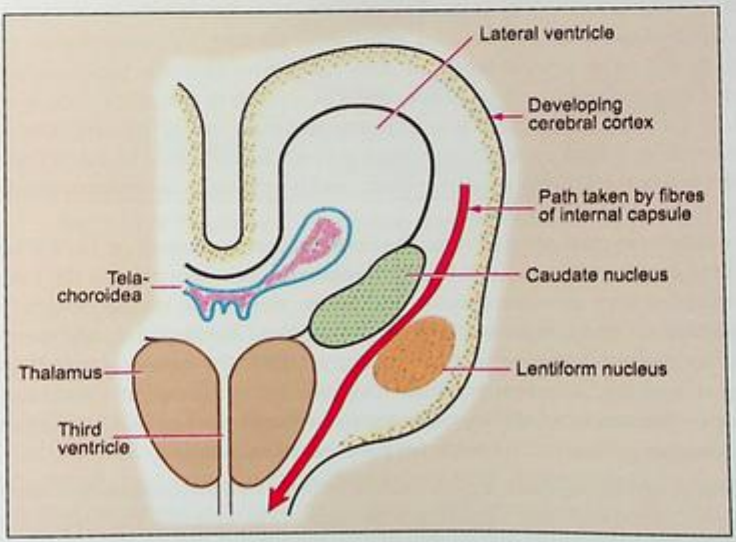

Fig. 17.26: Deep part of corpus striatum becomes the caudate nucleus. Superficial part becomes the lentiform nucleus. Note relation of these to the thalamus developing in the diencephalon.

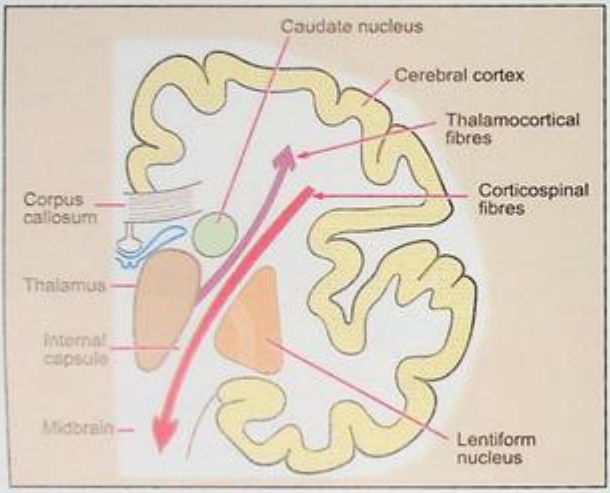

Fig. 17.27: With enlargement of the telencephalon the lentiform nucleus comes to lie lateral to the thalamus. The internal capsule passes through the interval between the lentiform nucleus laterally and the caudate nucleus and thalamus medially.

Cerebral Cortex

The cerebral cortex is formed by migration of cells from the mantle layer into the overlying marginal layer. These cells divide, and subdivide, leading to considerable thickening of the cortex. By full term, several layers of cells can be recognised. Simultaneously, there is considerable side to side expansion of the cortex as a result of which its surface area is greatly increased. As the surface expansion is at a greater rate than that of the hemisphere as a whole, the cortex becomes folded on itself. Sulci and gyri are formed as a result of this folding. The region of the insula is relatively slow in growth, and is gradually overgrown by adjacent areas, which form the opercula of the insula.

From a developmental point of view, the cerebral cortex consists of: (a) the ***hippocampal cortex***, (b) the ***pyriform cortex***, and (c) the ***neocortex***. The neocortex is the most important part. It undergoes very great expansion and forms the whole of the cerebral cortex seen on the superolateral and medial surfaces of the cerebral hemisphere, and the cortex of the inferior surface excluding the pyriform area (Fig. 17.29B). The hippocampal cortex forms the hippocampus, and the indusium griseum. The piriform cortex gives rise to the part of the cerebral cortex that receives olfactory sensations. It forms the ***uncus***, the anterior part of the ***parahippocampal gyrus***, and the ***anterior perforated substance***.

The developing telencephalon has a medial wall (apposed to its counterpart of the opposite side), a superolateral wall, and a basal striatal region (Fig. 17.24C). The hippocampal cortex develops in the medial wall, the pyriform cortex in the marginal layer superficial to the corpus striatum, and the neocortex in the superolateral region (Fig. 17.29A).

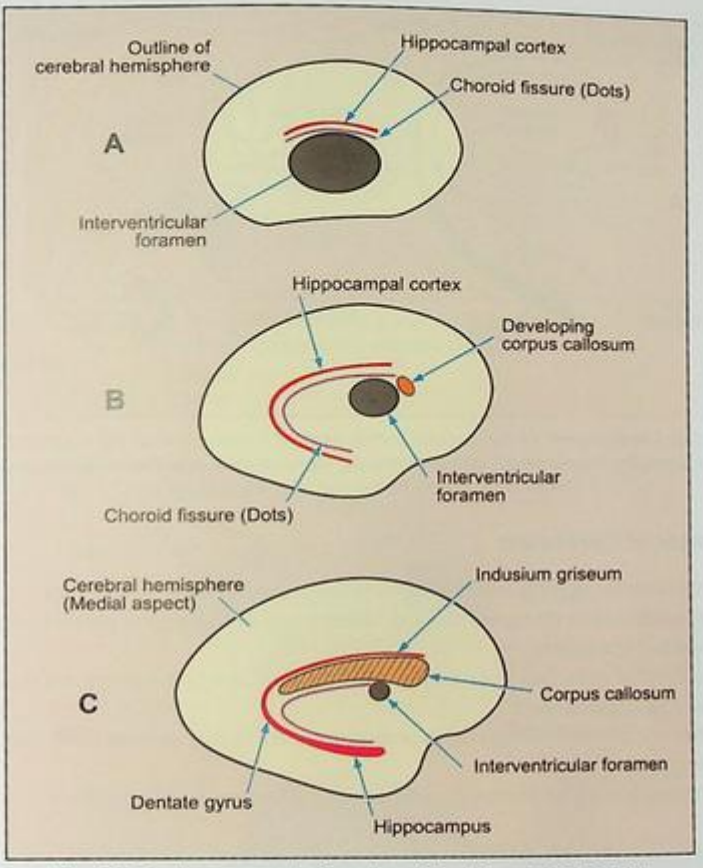

Fig. 17.28: Three stages in formation of the hippocampal cortex.

From Figs. 17.28, 17.29A, it will be seen that the hippocampal cortex is closely related to the choroid fissure. With the establishment of the inferior horn of the lateral ventricle, the hippocampal cortex follows the curve of the choroid fissure and thus assumes a ring-like configuration (Fig. 17.28B). However, the superior part of the hippocampal cortex is soon separated from the fissure by the formation of the corpus callosum. This part of the cortex remains rudimentary and forms the ***indusium griseum***. The lower part of the hippocampal cortex undergoes relatively greater development and becomes the ***hippocampus*** and the dentate gyrus (Fig. 17.28C). With the expansion of the neocortex (see below), these structures are pushed into the cavity of the inferior horn of the lateral ventricle (Fig. 17.29B).

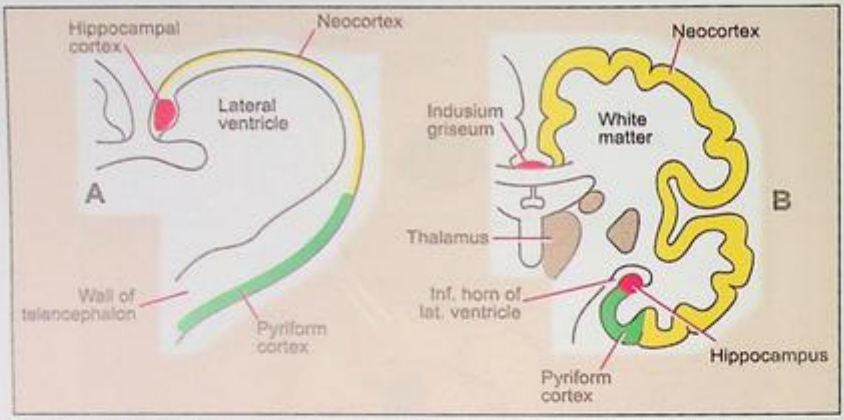

Fig. 17.29: Development of the cerebral cortex. Most of the cerebral cortex is derived from the neocortex. The hippocampal cortex forms the hippocampus and the indusium griseum. The piriform cortex forms part of the limbic system.

White Matter of Cerebrum

The bulk of the cerebrum is constituted by its white matter. This is made up of:

- axons of cortical cells that grow towards other areas of the cortex, either in the same or in the opposite hemisphere;
- axons of cortical cells that grow downwards through the hemisphere, on their way to the brain stem and spinal cord;
- axons that connect the thalamus, hypothalamus and basal ganglia to one another and to the cortex; and
- axons that grow into the hemisphere from the brainstem and spinal cord.

Cerebral Commissures

The part of the wall of the neural tube that closes the cranial end of the prosencephalon is called the ***lamina terminalis*** (Figs. 17.30, 17.31A). After the appearance of the telencephalic vesicles, the lamina terminalis lies in the anterior wall of the third ventricle. Reference to Fig. 17.30 will show that any neuron growing from one hemisphere to the other must pass through this lamina. To facilitate this passage, the lamina terminalis becomes thickened to form the ***commissural plate*** (Fig. 17.31B).

The first commissural fibres to develop form the ***anterior commissure***. This is followed by the formation of the ***hippocampal commissure***. The ***corpus callosum*** appears later. It, at first, lies anterior to the diencephalon, but because of rapid increase in its size it extends backwards and roofs over this region (Fig. 17.31C).

Other commissures that appear are the ***optic chiasma***, the ***habenular commissure*** and the ***posterior commissure***.

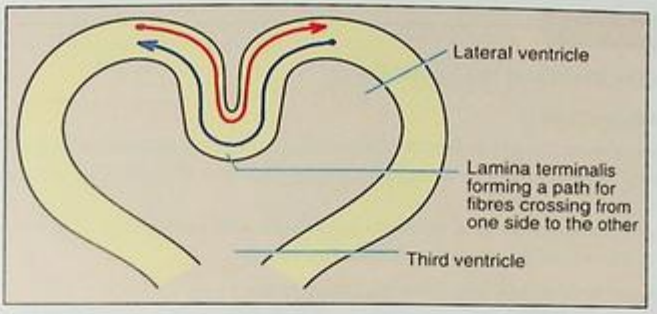

Fig. 17.30: Diagram to show how the lamina terminalis serves as a path for nerve fibres passing from one cerebral hemisphere to the other.

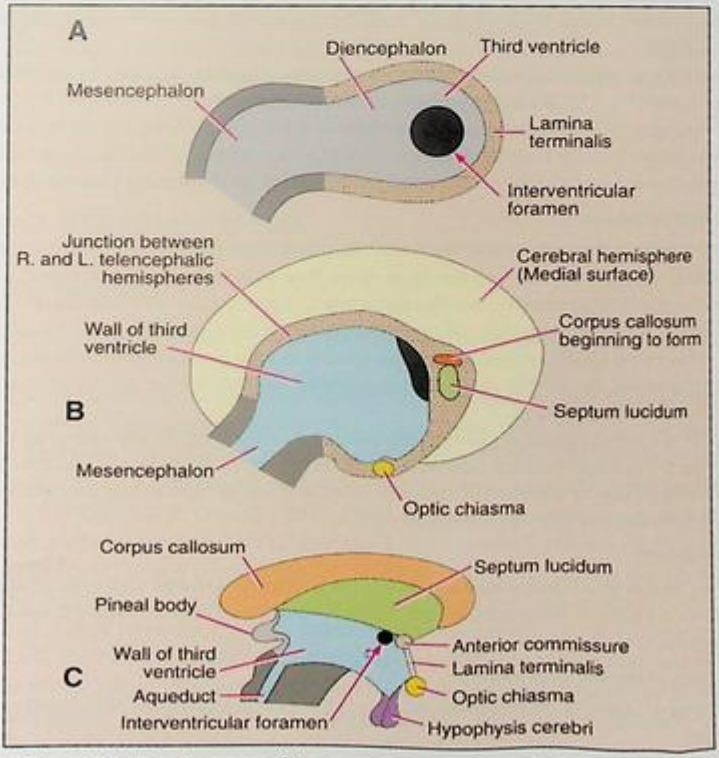

Fig. 17.31: Development of the corpus callosum and other commissures.

Clinical Correlation

Anomalies of the Brain and the Spinal Cord

Non-closure of Neural Tube

- ***Posterior rachischisis:*** The whole length of the neural tube remains unclosed (Figs. 17.32A).
- ***Anencephaly:*** The neural tube remains open in the region of the brain. The exposed brain tissue degenerates.
- Non-fusion of the neural tube is of necessity associated with non-closure of the cranium (***cranium bifidum***) or of the vertebral canal (***spina bifida***, Fig. 17.32A).

Outward Bulging of Neural Tube and Covering Membranes

As a result of non-fusion of the neural tube, or of overlying bones (e.g. spina bifida), neural tissue may lie outside the cranial cavity or vertebral canal. When this happens in the region of the brain the condition is called ***encephalocoele***, and when it occurs in the spinal region it is called ***myelocoele*** (Figs. 17.32B, C).

- When the condition is due to non-closure of the neural tube, nervous tissue is exposed on the surface, as in anencephaly, and in rachischisis (Fig. 17.32A).
- When the neural tube has closed, and the outward bulging is a result of a defect in the overlying bones, the neural tissue is covered by bulging skin and membranes (***meningo-mylocoele***) (Figs. 17.32B, C, E).
- Occasionally the bulging is caused by the membranes alone (***meningocoele***), the neural tissue being normally located (Fig. 17.32D). Some varieties of these conditions are illustrated in Figs. 17.32B to E.

When a meningo-myelocoele is present, the medulla oblongata, and the tonsils of the cerebellum, are displaced caudally into the foramen magnum causing obstruction to the flow of cerebrospinal fluid. This leads to hydrocephalus. These conditions together constitute the ***Arnold Chiari deformity***.

Congenital Hydrocephalus

An abnormal quantity of cerebrospinal fluid may accumulate in the ventricular system of the brain (***hydrocephalus***). This may be due to a blockage to its flow or to excessive production. The ventricles become very large and the infant is born with a large head. The pressure of the fluid causes degeneration of nervous tissue. Similar enlargement of the spinal cord is called ***hydromyelia***; the enlargement of the central canal being called ***syringocoele***. This condition may be associated with the formation of abnormal cavities near the central canal (***syringomyelia***). Destruction of nervous tissue at this site results in a characteristic syndrome.

In one form of hydrocephalus resulting from blockage of the median and lateral apertures of the fourth ventricle, the enlargement is predominantly in the posterior cranial fossa, and the cerebellum is abnormal (***Dandy Walker syndrome***). Obstruction to flow of cerebrospinal fluid may also be caused by stenosis or malformation of the cerebral aqueduct.

Faulty Development

The brain may be too small (***microcephaly***) or too large (***macrocephaly***). Gyri may be absent or may be poorly formed. Faulty development of the cerebral cortex may lead to impaired intelligence or in congenital paralysis.

Absence of Parts of the Nervous System

Parts of the nervous system may be absent. Absence of the corpus callosum, spinal cord or cerebellum is documented.

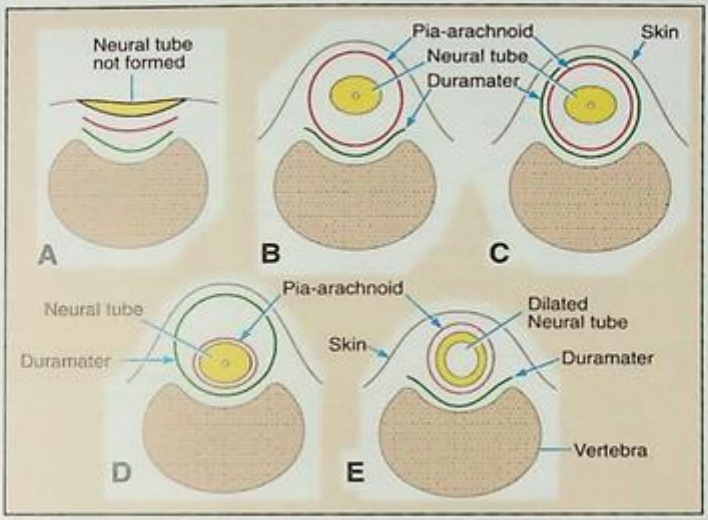

Fig. 17.32: Anomalies of the neural tube. (A) Posterior rachischisis. (B), (C) and (E) Varieties of meningo-myelocoele. (D) Meningocoele.

AUTONOMIC NERVOUS SYSTEM

Sympathetic Neurons

Any sympathetic pathway consists of two neurons, i.e. a preganglionic and a postganglionic neuron.

- The preganglionic neurons develop in the mantle layer of the thoraco-lumbar region of the spinal cord (segments T1 to L2 or L3). These cells are located near the sulcus limitans, and form the lateral horn of the cord (Fig. 17.33). The axons growing out from them are myelinated. They pass into the ventral nerve roots to enter the spinal nerves. After a very short course through the spinal nerves, they leave them and grow towards the postganglionic neurons. The postganglionic neurons form the various ganglia of the sympathetic trunk. Some postganglionic neurons come to lie near the viscera, and form visceral sympathetic ganglia. The preganglionic fibres meant for them do not relay in the sympathetic trunk but pass through branches of the trunk to reach the visceral ganglia.
- The axons of the postganglionic neurons grow towards the various viscera of the body, to innervate them. Some of them enter spinal nerves and are distributed through them to blood vessels, hair and sweat glands. Postganglionic neurons are generally believed to be derived from cells of the neural crest.

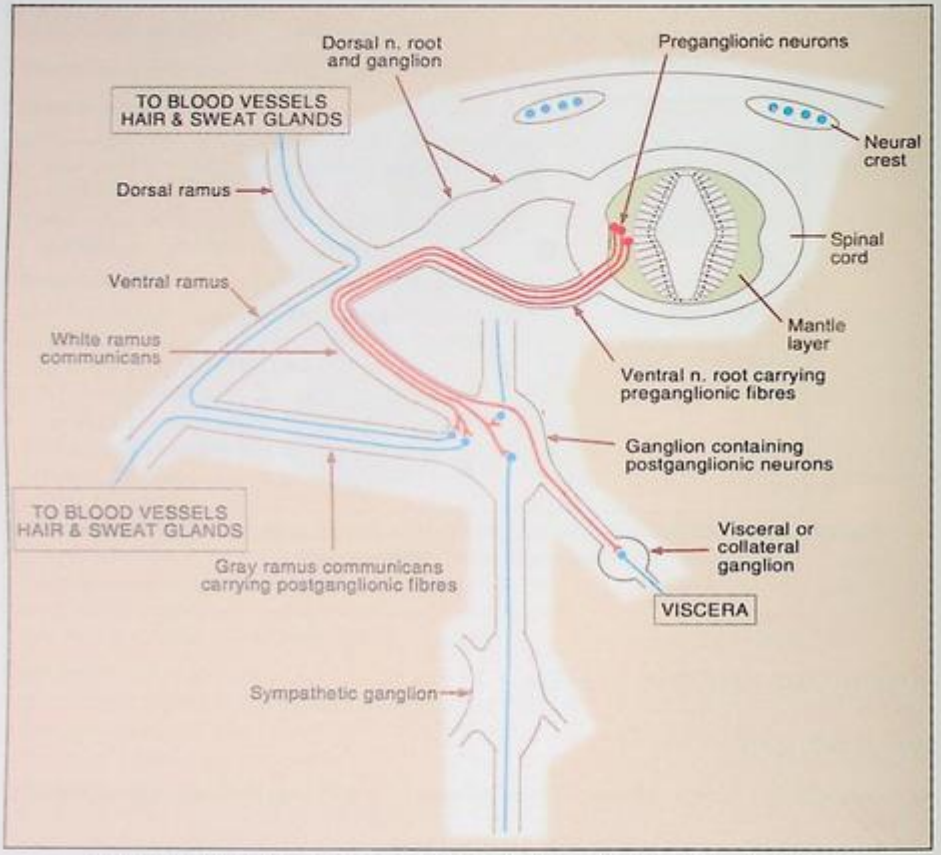

Fig. 17.33: Development of preganglionic and postganglionic sympathetic neurons.

Parasympathetic Neurons

As in sympathetic pathways, parasympathetic pathways also consist of two neurons (preganglionic and postganglionic).

The Preganglionic Neurons

The preganglionic neurons of the parasympathetic system are formed in two distinct situations.

The Cranial Parasympathetic Outflow

These neurons are formed in relation to the general visceral efferent nuclear column of the brain stem (Fig. 17.34A). They give rise to the Edinger-Westphal nucleus, salivatory and lacrimatory

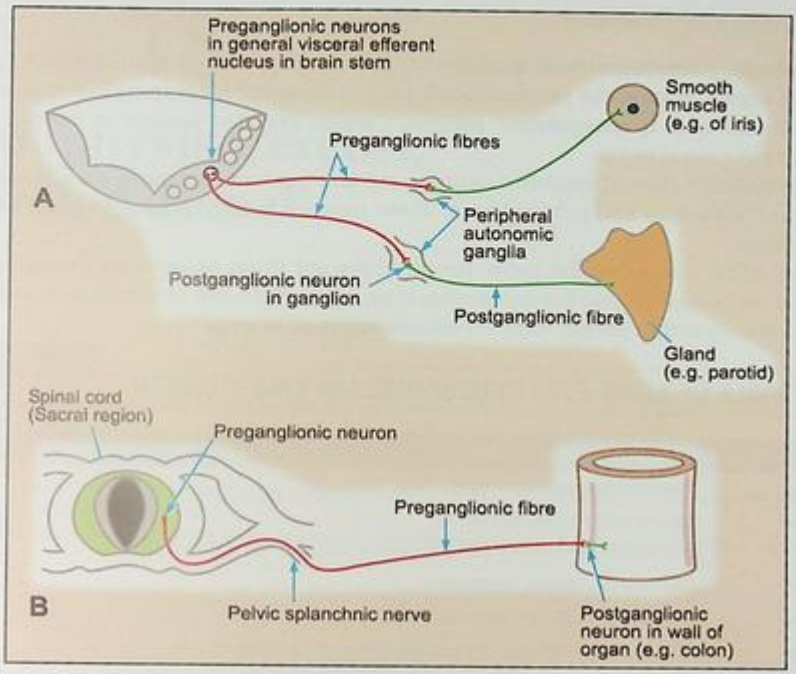

Fig. 17.34: Development of preganglionic and postganglionic parasympathetic neurons. (A) Cranial outflow. (B) Sacral outflow.

nuclei and the dorsal nucleus of the vagus. The preganglionic parasympathetic fibres taking origin from the Edinger-Westphal nucleus run in the oculomotor nerve to reach the ciliary ganglion. The superior salivatory and lacrimatory nuclei give origin to preganglionic fibres, which run in the facial nerve to reach the sphenopaltine and submandibular ganglia. The inferior salivatory nucleus give origin to the fibres which are related to the glossopharyngeal nerve and terminate in the otic ganglion. The dorsal nucleus of the vagus gives preganglionic parasympathetic fibres that terminate in various ganglia situated in the walls of viscera supplied by the vagus nerve.

The Sacral Parasympathetic Outflow

The preganglionic neurons are formed in the mantle layer of the sacral part of the spinal cord (S2 - S4). These cells lie near the sulcus limitans. Their axons constitute the preganglionic parasympathetic fibres, which terminate by synapsing with postganglionic neurons situated in the walls of pelvic viscera and hindgut.

The Postganglionic Neurons

Postganglionic parasympathetic neurons are derived from the neural crest cells.

In the cranial region, the postganglionic parasympathetic neurons form the ciliary, otic, submandibular and sphenopalatine ganglia. Ganglia are also present in various viscera supplied by the vagus nerve.

Postganglionic parasympathetic neurons are also present in various ganglia that lie in relation to the hindgut and pelvic viscera. These neurons receive preganglionic fibres of the sacral outflow.

It should be noted that the entire length of the gut (from oesophagus to anal canal) is populated by postganglionic parasympathetic neurons which are of neural crest origin. The neural crest cells within the gut form the **enteric nervous system.**

TIMETABLE OF SOME EVENTS DESCRIBED IN THIS CHAPTER

Age	Developmental Events
3rd week	Neural tube begins to form.
4th week	Neural folds begin to fuse.
	Premordia of sensory ganglia (spinal and cranial) are formed.
25th day	Closure of anterior neuropore.
27th day	Closure of posterior neuropore.
28th day	The most cranial pair of cervical spinal ganglia develops.
5th week	Formation of brain vesicle.
	Sympathetic ganglia are formed.
	Cerebral hemispheres begin to form.
6th week	Cerebellum starts forming.
10th week	The corpus callosum forms.
12th week	Cerebellar cortex and purkinje cells are formed.
15th week	The dentate nucleus is seen.
4th month	Myelination of nerve fibres begin.
Late fetal life	Sulci and gyri appear over cerebral hemispheres.

Chapter 18

Hypophysis Cerebri, Pineal, Adrenal

HIGHLIGHTS

- The pars anterior and intermedia of the ***hypophysis cerebri*** develop from Rathke's pouch. The pars nervosa develops from a downgrowth arising from the floor of the third ventricle.
- The ***pineal gland*** develops as a diverticulum from the roof of the third ventricle (diencephalon).
- The ***adrenal cortex*** is derived from coelomic epithelium. The cells of the ***adrenal medulla*** are derived from the neural crest.

In this chapter we will consider the development of three glands, the development of which is closely connected with that of the nervous system.

HYPOPHYSIS CEREBRI

The hypophysis cerebri or pituitary gland is developed from two separate sources.

- The ***anterior and intermediate parts*** of the organ develop from an ectodermal diverticulum, that grows upwards from the roof of the stomatodaeum, just in front of the buccopharyngeal membrane. The diverticulum is called ***Rathke's pouch*** (Fig. 18.1A). It later becomes cut off from the stomatodaeum (Fig. 18.1B).
- The ***pars nervosa and stalk*** of the hypophysis cerebri develop from a down-growth from the floor of the third ventricle (diencephalon) in the region of the infundibulum (Fig. 18.1C). This downgrowth comes into relationship with the posterior aspect of Rathke's pouch and fuses with it (Fig. 18.1C).

The anterior wall of Rathke's pouch proliferates greatly to form the pars anterior of the hypophysis. The posterior wall remains thin and forms the ***pars intermedia***. The original cleft of Rathke's pouch separates these two parts. Some cells of the anterior part grow upwards along the infundibular stalk to form the ***tuberal part*** of the hypophysis.

With the formation of the mouth and pharynx, the original site of attachment of Rathke's pouch to the stomatodaeum, comes to lie in the roof of the nasopharynx. Remnants of Rathke's pouch may sometimes give rise to peculiar tumours called ***craniopharyngiomas*** that are seen in relation to the sphenoid bone and the roof of the nasopharynx.

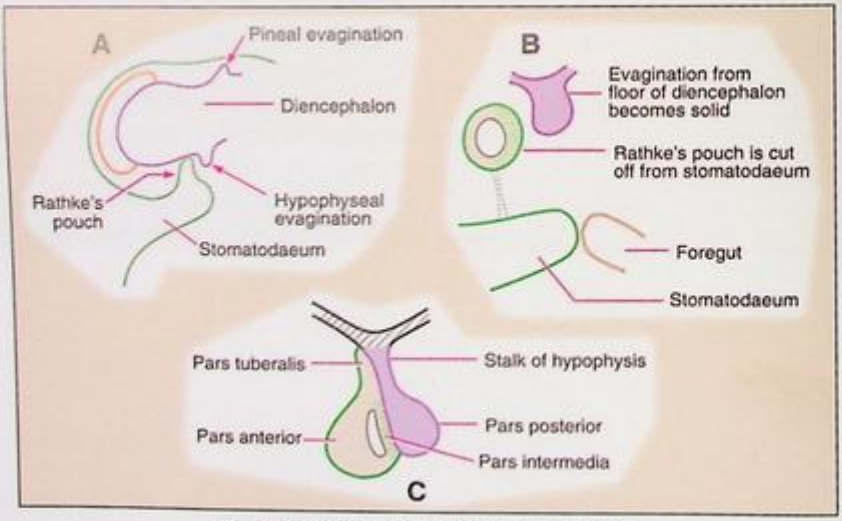

Fig. 18.1: Development of hypophysis cerebri.

Accessory anterior lobe tissue may be seen in relation to the posterior wall of the pharynx. Rarely the hypophysis may fail to develop (agenesis) or may be under developed (hypoplasia).

Rathke's pouch appears in the third week of intrauterine life. It loses contact with the surface epithelium by the second month.

PINEAL GLAND

The pineal gland, (or pineal body) arises as a diverticulum from the roof of the diencephalon (Fig. 18.1A). The outgrowth is at first hollow but later becomes solid (Fig. 18.2).

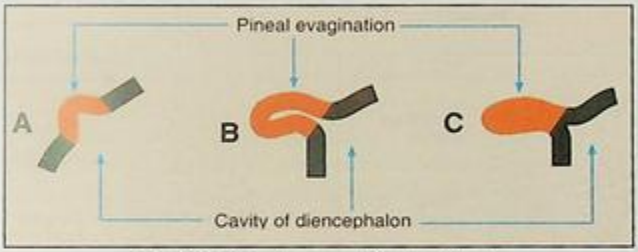

Fig. 18.2: Development of pineal body.

The specific cells of the pineal body are believed to be modified neuroglial cells. For long considered to be a vestigeal structure of no importance, the pineal gland is now known to secrete a number of hormones that have a regulatory influence on many other endocrine glands.

ADRENAL

The adrenal gland consists of a superficial cortex, and a deeper medulla. The cells of the ***cortex*** arise from coelomic epithelium (mesoderm). The cells of the ***medulla*** are derived from the neural crest (ectoderm).

The cells of the cortex arise from the coelomic epithelium, that lies in the angle between the developing gonad and the attachment of the mesentery (Figs. 18.3A). The cells arising from the coelomic epithelium may be divided into two groups:

1. The cells that are formed first are large and acidophil. They surround the cells of the medulla, and form the ***fetal cortex*** (Figs. 18.3C, D). The fetal cortex disappears after birth.
2. Subsequently, the coelomic epithelium gives origin to smaller cells that surround the fetal cortex. These smaller cells form the ***definitive cortex*** (Figs. 18.3C, D). According to some authorities the cells of the fetal cortex are incorporated into the reticular zone of the definitive cortex.

The differentiation of cortical zones (Fig. 18.3D) begins during the late fetal period. The zona glomerulosa and zona fasciculate are present at birth but the zona reticularis becomes

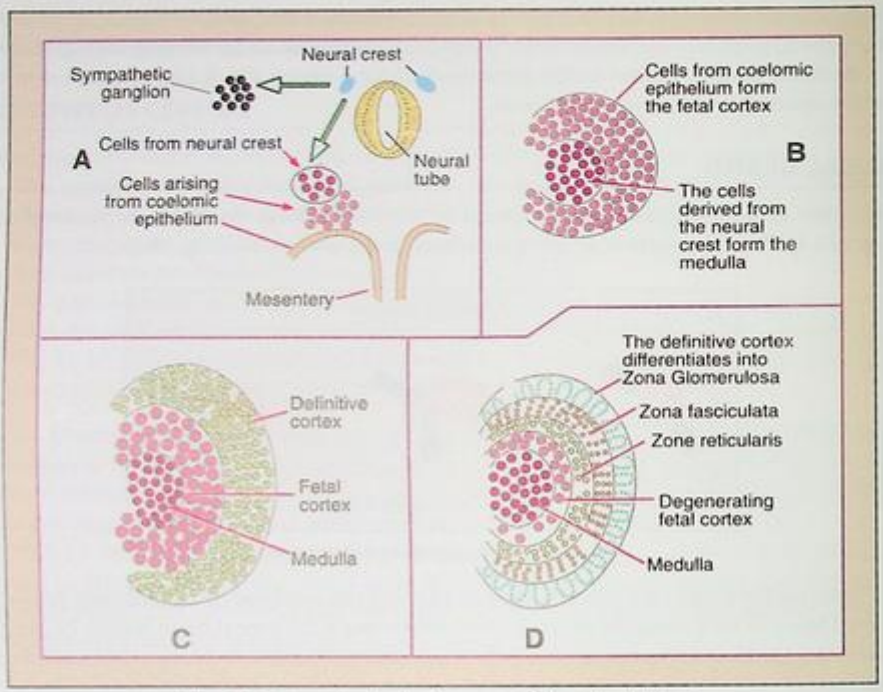

Fig. 18.3: Stages in the development of the adrenal gland.

recognisable at the end of the third year. The suprarenal of the human fetus is almost of the same size as that of the adult. It is quite large as compared to the fetal kidney. The size of the gland (particularly of fetal cortex) becomes smaller during the first year of postnatal life.

The cells of the medulla are derived from the neural crest. They are similar to the postganglionic sympathetic neurons (cells of sympathetic ganglia). Pre-ganglionic sympathetic neurons terminate in relation to them. These cells migrate to the region of the developing cortical cells and come to be surrounded by them.

The adrenal gland begins to develop in the fifth week of intrauterine life.

Clinical Correlation

Anomalies of Adrenal

- Adrenal cortical tissue may be present at various ectopic sites.
- The entire adrenal may be ectopic and may lie deep to the capsule of the kidney. It may be fused to the liver or the kidney.
- There may be congenital hyperplasia (overdevelopment) of the cortex. In the male this leads to the ***adrenogenital syndrome*** marked by very early development of secondary sexual characters. In the female, it may cause enlargement of the clitoris and the child may be mistaken for a male (***pseudohermaphroditism***).

CHROMAFFIN TISSUE

Chromaffin tissue is made up of cells similar to those of the adrenal medulla, and like the latter, is derived from the cells of the neural crest. This tissue is to be seen in relation to the abdominal aorta where it forms the para-aortic bodies. It is also seen in relation to sympathetic ganglia and plexuses and along the splanchnic nerves.

TIMETABLE OF THE EVENTS DESCRIBED IN THIS CHAPTER

Age	Developmental Events
3rd week	Infundibular diverticulum develops in the floor of 3rd ventricle.
4th week	Rathke's pouch projects from the roof of stomodeum.
5th week	Adrenal gland begins to develop.
8th week	Rathke's pouch loses its connection with the oral cavity.

Chapter 19

The Eye and Ear

HIGHLIGHTS

- The ***retina*** is formed from the ***optic vesicle***, an outgrowth of the prosencephalon. The optic vesicle is converted into the ***optic cup***.
- The ***lens*** of the eye is derived from a thickened area of surface ectoderm, the lens placode. The placode is converted into the lens vesicle which comes to lie in the optic cup.
- Other coats of the eyeball are derived from mesoderm surrounding the optic vesicle. The epithelium covering the superficial surface of the ***cornea*** is derived from surface ectoderm.
- The ***eyelids*** are formed by reduplication of surface ectoderm above and below the cornea.
- The ***lacrimal sac*** and ***nasolacrimal duct*** are derived from ectoderm buried in the naso-optic furrow.
- The ***membranous labyrinth*** (internal ear) is derived from a thickening of surface ectoderm called the ***otic placode***. The placode is converted into the ***otic vesicle*** and then to different parts of the labyrinth.
- The ***bony labyrinth*** is formed from mesenchyme surrounding the membranous labyrinth.
- The ***middle ear*** and ***auditory tube*** develop from the tubo-tympanic recess (from first and second pharyngeal pouches).
- The ***malleus*** and ***incus*** are derived from Meckel's cartilage. The ***stapes*** is derived from the cartilage of the second pharyngeal arch.
- The ***external acoustic meatus*** is derived from the first ectodermal cleft. The ***auricle*** is formed from swellings that appear around the cleft.

DEVELOPMENT OF THE EYE

The various components of the eyeball are derived from the following primordia:

1. An outgrowth from the prosencephalon called the ***optic vesicle***.
2. A specialised area of surface ectoderm (called the ***lens placode***) that gives rise to the lens.
3. The mesoderm surrounding the optic vesicle.

Formation of the Optic Vesicle

- The region of the neural plate destined to form the prosencephalon shows a linear thickened area on either side (Fig. 19.1B).
- This area soon becomes depressed to form the *optic sulcus* (Fig. 19.1C).
- Meanwhile, the neural plate becomes converted into the prosencephalic vesicle. As the optic sulcus deepens, the wall of the prosencephalon overlying the sulcus bulges outwards to form the ***optic vesicle*** (Figs.19.1D, E).
- The proximal part of the optic vesicle becomes constricted, and elongated, to form the ***optic stalk*** (Fig. 19.2).

Formation of the Lens Vesicle

- As the optic vesicle grows laterally, it comes into relation with the surface ectoderm. An area of this surface ectoderm, overlying the optic vesicle, becomes thickened to form the ***lens placode*** (Fig. 19.3A).
- The lens placode soon sinks below the surface and is gradually convened into the ***lens vesicle*** (Fig. 19.3).
- The lens vesicle becomes completely separated from the surface ectoderm.

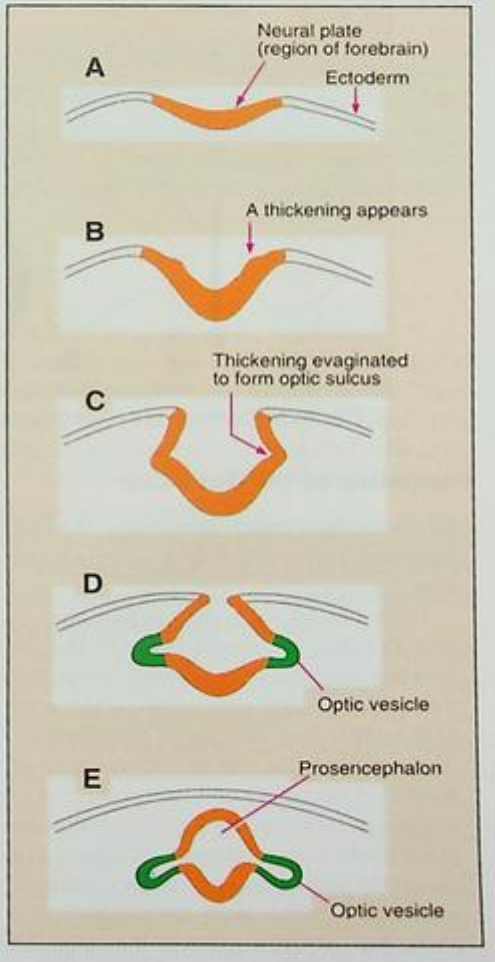

Fig. 19.1: Formation of the optic vesicle.

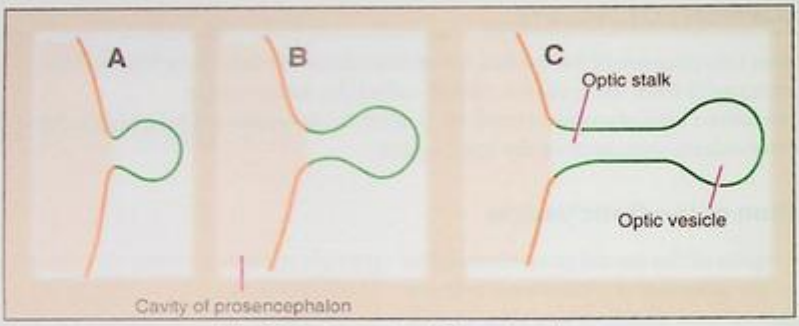

Fig. 19.2: Formation of the optic stalk.

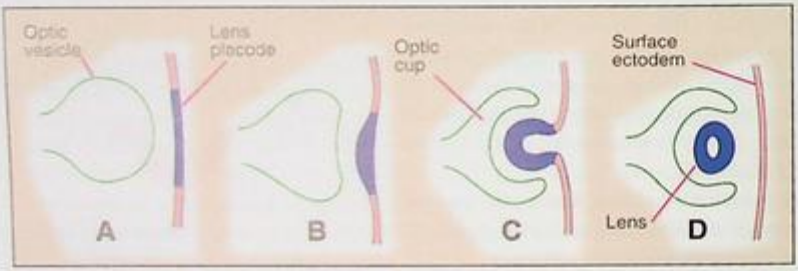

Fig. 19.3: Development of the lens vesicle and its invagination into the optic cup.

Formation of the Optic Cup

While the lens vesicle is forming, the optic vesicle becomes converted into a double-layered ***optic cup***.

From Fig. 19.3 it is easy to gain the impression that this has happened because the developing lens has invaginated itself into the vesicle. However, this is not so. The conversion of the optic vesicle, to the optic cup, is a result of differential growth of the wall of the vesicle. The margins of the cup grow over the upper and lateral sides of the lens to enclose it. However, such overgrowth does not take place on the inferior aspect of the lens, as a result of which the wall of the cup shows a deficiency in this situation. This deficiency extends for some distance along the inferior surface of the optic stalk and is called the ***choroidal or fetal fissure*** (Fig. 19.4).

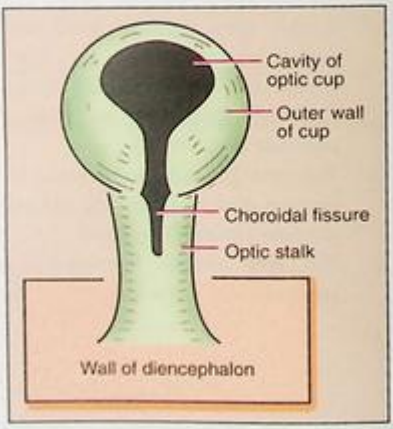

Fig. 19.4: Optic cup and stalk seen from below to show the choroidal fissure.

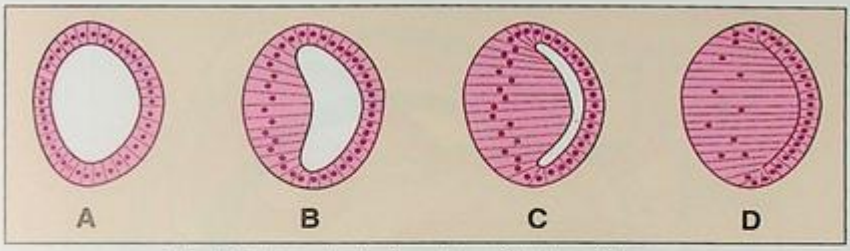

Fig. 19.5: Stages in the formation of the lens of the eye.

The developing neural tube is surrounded by mesoderm, which subsequently condenses to form the meninges. An extension of this mesoderm covers the optic vesicle. Later, this mesoderm differentiates to form a superficial fibrous layer corresponding to the dura mater, and a deeper vascular layer corresponding to the pia-arachnoid. With the formation of the optic cup, part of the inner vascular layer is carried into the cup, through the choroidal fissure (Fig. 19.6A).

Derivation of Parts of the Eyeball

The derivation of the various parts of the eyeball can now be summarised as follows:

- The ***lens*** is formed from the lens vesicle. The vesicle is at first lined by a single layer of cubical cells (Fig. 19.5A). The cells in the anterior wall of the vesicle remain cubical. Those in the posterior wall gradually become elongated (Figs. 19.5B to D). As they do so the cavity of the vesicle is encroached upon and is eventually obliterated. The elongated cells of the posterior wall lose their nuclei and are converted into the fibres of the lens. The anterior layer remains as the epithelium covering this aspect of the lens.
- The ***retina*** is derived from the layers of the optic cup. The optic cup is divisible into anterior and posterior parts..The larger posterior part, becomes thick, and forms the retina proper (***optical part of retina***). The anterior part remains thin, and forms an epithelial covering for the ciliary body and iris (***ciliary and iridial parts of retina***: Fig. 19.6B).
  The outer wall of the posterior part of the optic cup remains thin. Its cells form the pigmented layer of the retina. The inner wall of the cup differentiates into matrix cell, mantle and marginal layers as in the neural tube. After giving origin to the cells of the mantle layer, the cells of the matrix layer form the ***rods and cones***. The cells of the mantle layer form the ***bipolar cells***, the ***ganglion cells***, and other neurons of the retina, and also the supporting elements. The axons of the ganglion cells grow into the marginal layer to form the ***layer of nerve fibres***. These fibres grow into the optic stalk by passing through the choroidal fissure. The optic stalk, is thus, convened into the ***optic nerve***.
- The ***vitreous*** is believed to be derived partly from ectoderm and partly from mesoderm. The ectodermal component is derived, mainly, from the optic cup but the lens vesicle may also contribute to it. The mesodermal component comes into the optic cup through the choroidal fissure.

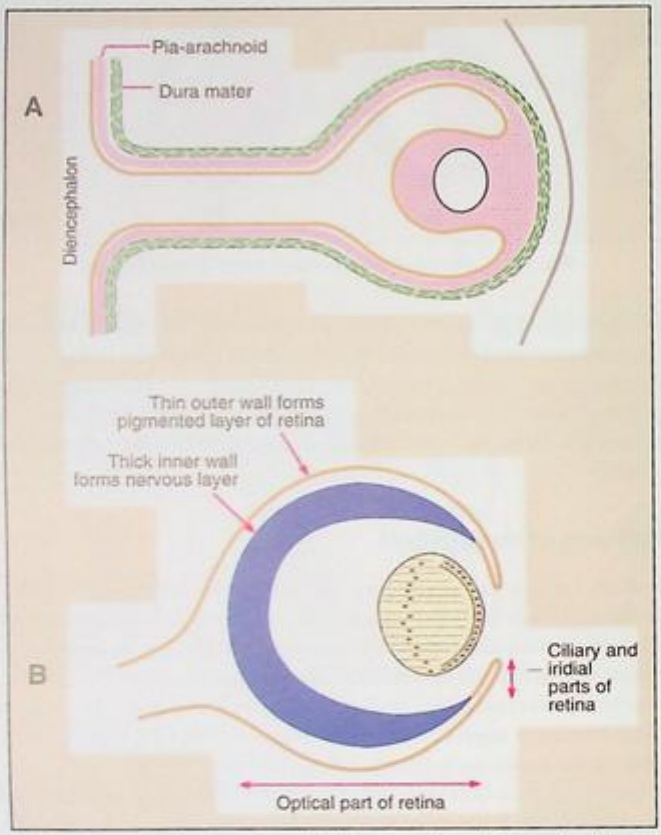

Fig. 19.6: (A) Developing optic cup surrounded by extensions of pia-arachnoid and duramater. (B) Subdivisions of the optic cup.

- The ***choroid*** is formed from the inner vascular layer of mesoderm that surrounds the optic cup (Figs. 19.6A, 19.7). According to some authorities this mesoderm contains cells derived from the neural crest.
- The mesodermal basis of the ***ciliary body and iris*** is derived from a forward prolongation of the mesoderm forming the choroid. The posterior surface of this mesoderm comes to be lined by two layers of pigmented epithelium derived from the ciliary and iridial parts of the retina. The two layers of epithelium correspond to the two layers of the optic cup (Fig. 19.7).

  The ***musculature of the iris*** (sphincter and dilator pupillae) is of ectodermal origin (optic cup). The ***ciliary muscles*** have been generally regarded as mesodermal but the present view is that they are of neural crest origin.

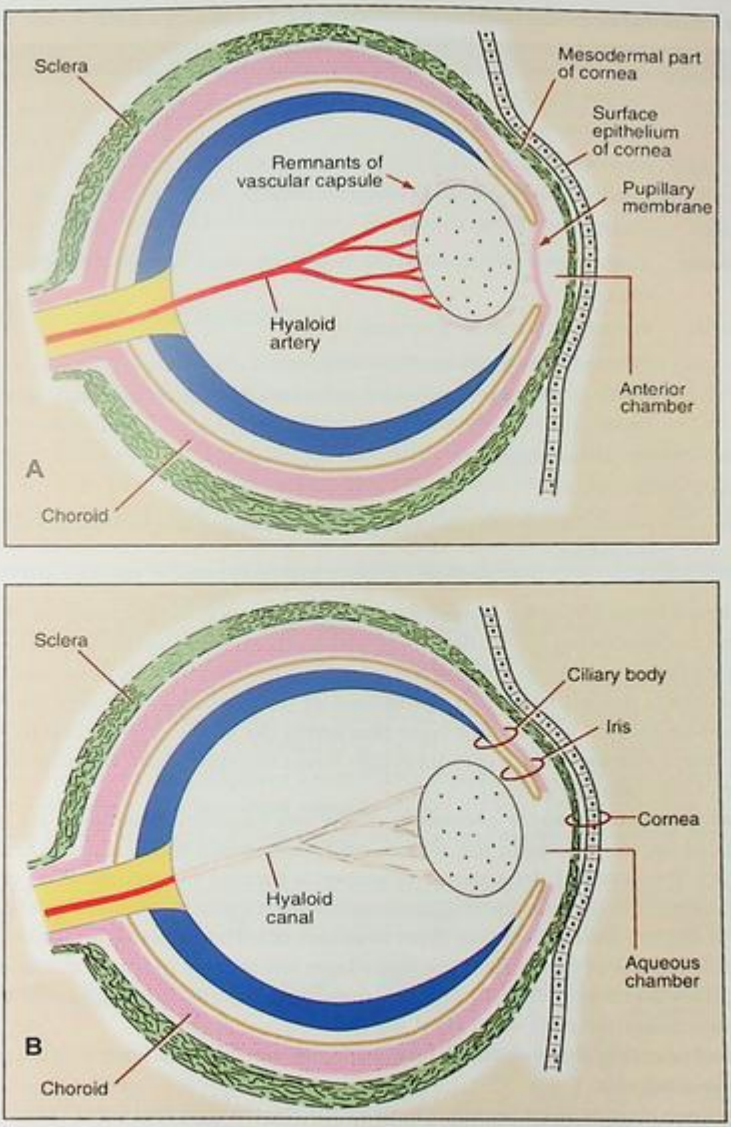

Fig. 19.7: (A) Derivation of coats of the eyeball. Note pupillary membrane and hyaloid artery. For parts of retina see Fig. 19.6. (B) The hyaloid artery and pupillary membrane have disappeared. Position of artery can be seen as the hyaloid canal.

Table 19.1: Summary of derivation of various part of the eye ball

Part	Derived from
Lens	Surface ectoderm
Retina	Neuroectoderm (optic cup)
Vitreous	Mesoderm
Choroid	Mesoderm (infiltrated by neural crest cells ?)
Ciliary body	Mesoderm
Ciliary muscles	Mesenchymal cells covering the developing ciliary body (neural crest?).
Iris	Mesoderm
Muscles of iris	Neuroectoderm (from optic cup)
Sclera	Mesoderm (infiltrated by neural crest cells?)
Cornea	Surface epithelium by ectoderm, substantia propria and inner epithelium by neural crest.
Conjunctiva	Surface ectoderm
Blood vessels	Mesoderm
Optic nerve	Neuroectoderm. its coverings (pia, arachnoid and dura) are derived from mesoderm.

- The ***sclera*** is formed from the posterior part of the layer of mesoderm surrounding the optic cup, and corresponding to the dura (Figs. 19.6A, 19.7). Some authorities believe that (like the choroid) the mesoderm forming the sclera is infiltrated by cells from the neural crest.
- The substantia propria and inner epithelium of the ***cornea*** are derived from the neural crest and are formed by the same layer that forms the sclera. The substantia propria is in close contact with the surface ectoderm that forms the epithelium covering the superficial surface of the cornea (Fig. 19.7).
- The ***anterior and posterior chambers*** of the eye (aqueous chamber) are formed by a splitting of the mesoderm in the region, and correspond to the subarachnoid space of the brain. The cavity of the anterior chamber is formed by vacuolization of mesoderm present anterior to the lens. Vacuolization splits the mesenchyme into outer (anterior) and inner (posterior) layers. The outer layer becomes continuous with the sclera and with the substantia propria of the cornea. The inner layer lies in front of lens and iris and is termed the pupillary membrane (Fig. 19.7A). The mesodermal cells lining the cavity give origin to a flattened mesothelium.
- The ***blood vessels of the eyeball*** are formed in the mesodermal layer that is a continuation of the pia-arachnoid.

We have seen already that this mesoderm forms the choroid and contributes to the ciliary body and iris. Part of this mesoderm, that gets invaginated into the optic cup, forms the retinal vessels. The central artery and vein of the retina at first lie in the choroidal fissure, but come to be buried in the fibres of the developing optic nerve. As the choroidal fissure extends for some distance along the optic stalk, the central artery of the retina runs through the substance of the distal part of the optic nerve.

Initially, the lens is completely surrounded by a vascular capsule. The posterior part of the capsule is supplied by the hyaloid artery (Fig. 19.7A). This artery is a continuation of the central artery of the retina and passes through the vitreous. Later in fetal life, the vascular capsule and the hyaloid artery disappear, but the hyaloid canal in the vitreous (through which the artery passes) persists.

The anterior part of the vascular capsule of the lens, comes to be lined posteriorly by the iridial part of the retina, and forms the iris (Fig. 19.7A,B). The pupil is for some time closed by a part of this vascular tissue, which is termed the ***iridopupillary membrane.*** This membrane normally disappears before birth.

Accessory Structures of Eyeball

The *eyelids* are formed by reduplication of the surface ectoderm above and below the cornea (Fig. 19.8). The ectodermal folds formed contain some mesoderm that gives rise to muscle and to the tarsal plates. As the folds enlarge, their margins approach each other. Ultimately, they meet and fuse together. The lids thus cut off a space called the ***conjunctival sac.*** The conjunctiva is, thus, of ectodermal origin. The lids remain united with each other until the seventh month of intrauterine life. (In many lower animals, e.g., cats, the offspring are born with fused eyelids).

The ***lacrimal gland*** is formed from a number of buds that arise from the upper angle of the conjunctival sac (Fig. 19.8D).

The ***lacrimal sac*** and ***nasolacrimal duct*** are derived from the ectoderm of the naso-optic (or nasolacrimal) furrow (Fig. 19.9). This furrow lies along the line of junction of the maxillary process and the lateral nasal process, and extends from the medial angle of the eye to the region of the developing mouth (Fig. 19.10). The ectoderm of the furrow becomes buried to form a solid cord that is subsequently canalised (Fig. 19.11). The upper part of this cord forms the ***lacrimal sac***. The lower part, acquires a secondary connection to the nasal cavity, and forms the ***nasolacrimal duct***. The ***lacrimal canaliculi*** are formed by canalisation of ectodermal buds that arise from the margin of each eyelid near its medial end and grow to the lacrimal sac.

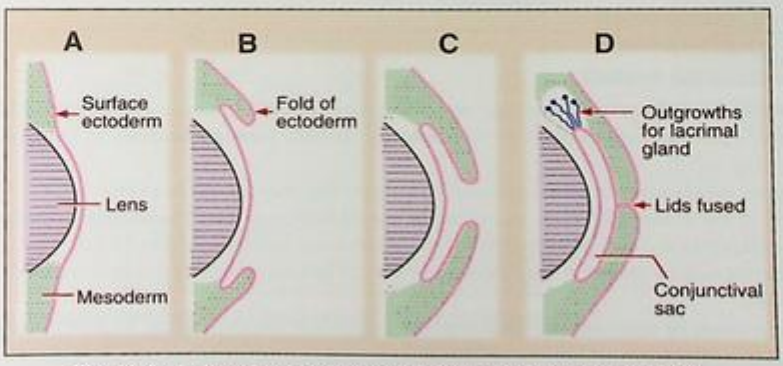

Fig. 19.8: Formation of eyelids, conjunctival sac and lacrimal gland.

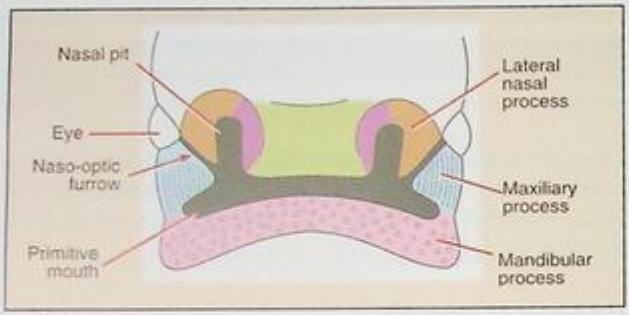

Fig. 19.9: Nasolacrimal (naso-optic) furrow. For details see Fig. 11.5.

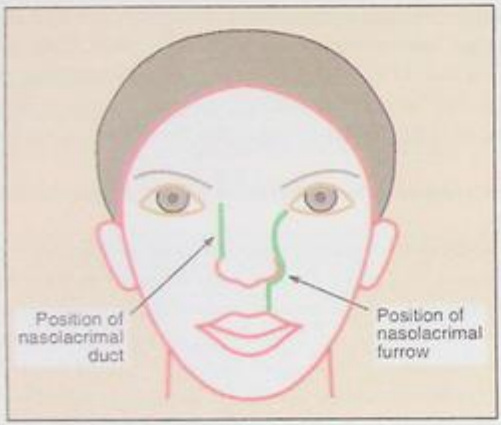

Fig. 19.10: Position of nasolacrimal furrow and of nasolacrimal duct projected on to an adult human face.

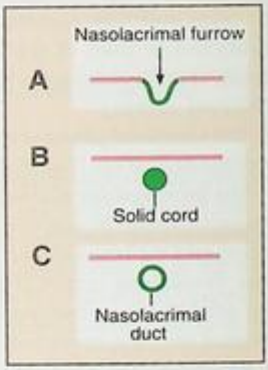

Fig. 19.11: Formation of nasolacrimal duct.

Clinical Correlation

Anomalies of the Eyeball

- The entire eyeball may fail to develop (***anophthalmos***), or may remain very small (***microphthalmos***).
- The two eyes may fuse completely (***cyclopia***), or partially (***synophthalmos***), to form one midline organ (Fig. 19.12).
- The optic vesicle may not be invaginated by the lens and may remain as a cyst.
- Failure of the choroidal fissure to obliterate completely, may lead to deficiencies (***coloboma***) of various layers of the eyeball including the iris, ciliary body and choroid (Fig. 19.13).
- The cornea may be absent. It may show anomalies of size and shape, and may also show congenital opacities.
- The sclera may be thin with the result that the pigment of the choroid can be seen through it (***blue sclera***).

Clinical Correlation ***contd...***

- In addition to various types of coloboma, the iris may show anomalies of its histological structure. Very rarely, the sphincter or dilator pupillae muscle may be absent. The pupil may be abnormal in position, shape or size.
- The lens may, very rarely, be absent or may be very small. It may be abnormal in position or shape. It may show congenital opacities (***cataract***). Congenital cataract may be due to parathyroid deficiency, to avitaminosis or to the infection, German measles, (acquired during early pregnancy). Cataract may be genetically determined.
- The hyaloid artery and the vascular capsule of the lens, or their remnants, may persist. When the capsule persists on the anterior aspect of the lens it may completely occlude the pupil (***persistent pupillary membrane***).
- The various layers of the eye may show anomalies of pigmentation. There may either be too little pigment as in ***albinism***, or too much.
- The retina may show various congenital anomalies in its structure. These may involve the macula, and may result in visual defects, including those of colour vision.

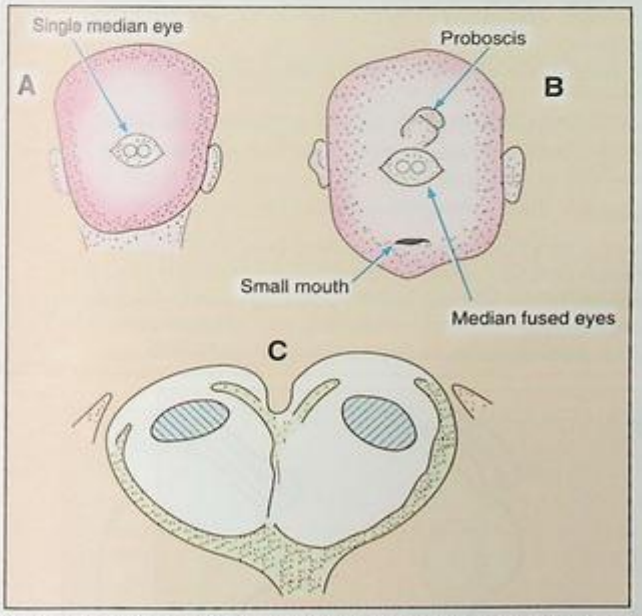

Fig. 19.12: (A) Synophthalmos (fused median eye). A section through such an eye is shown in (C). In (B) we see synophthalmos, and a proboscis above the median eye.

Fig. 19.13: Coloboma of iris.

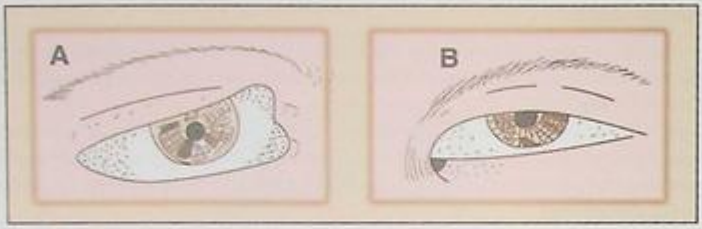

Fig. 19.14: (A) Coloboma of upper lid. (B) Epicanthic fold. Such a fold is normal in some races, e.g. Mongolian (Chinese).

Clinical Correlation ***contd...***

Anomalies of Accessory Structures of Eye

Anomalies of Eyelids and Related Structures

- The eyelids may very rarely be absent. In these cases there is no conjunctival sac. The conjunctiva and the cornea are replaced by skin.
- Part of the eyelid may be missing (***coloboma of eyelid***; Fig. 19.14A). There may be underdevelopment of the tarsus or of the Meibomian glands.
- The palpebral fissure may be abnormally wide or narrow. It may be abnormal in orientation and shape. The two lids may be completely, or partially, fused with each other.
- There may be abnormal folds of skin in relation to the lids. Similar folds, e.g., ***epicanthus*** (Fig. 19.14B) may be a normal feature in certain races.
- The lid margins may be turned inwards (***entropion***) or outwards (***ectropion***) (Fig. 19.15). Rarely, the whole lid may be everted.
- The levator palpebrae superioris may fail to develop. This leads to drooping of the lids (***ptosis***).
- The eyelashes, and eyebrows, may be missing, or may be duplicated. The eyelashes may be abnormal in direction.

Anomalies of the Lacrimal Apparatus

- The lacrimal gland may be absent or non-functional. The gland may be ectopic in position.
- The lacrimal passages may be absent in whole or in part, or there may be atresia of some part.
- The lacrimal duct may be represented by an open furrow on the face, due to non-obliteration of the naso-optic furrow (see oblique facial cleft).
- There may be supernumerary puncta, or canaliculi.

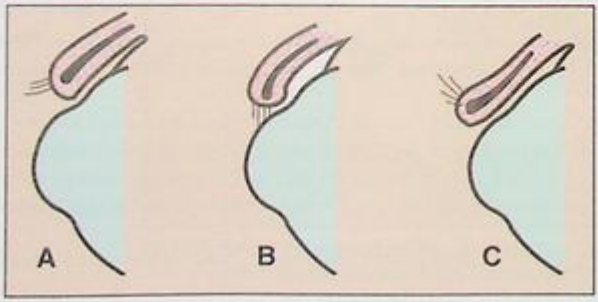

Fig. 19.15: (A) Normal lid. (B) Entropion. (C) Ectropion.

DEVELOPMENT OF THE EAR

The three morphological subdivisions of the ear (namely the external, middle and internal ear) each have a separate origin.

Internal Ear

The membranous labyrinth is derived from a specialised area of surface ectoderm overlying the developing hindbrain. This area is first apparent as a thickening called the ***otic placode*** (Fig. 19.16A). The otic placode soon becomes depressed below the surface to form the ***otic pit*** (Fig. 19.16B). The pit then becomes rounded to form the ***otic vesicle*** which separates from the surface ectoderm (Fig. 19.16C).

The otic vesicle is at first an oval structure. By differential growth of various parts of its wall, it gives rise to the structures comprising the ***membranous labyrinth***.

Some details of this process are illustrated in Fig. 19.17.

Localised areas of the epithelium of the membranous labyrinth undergo differentiation to form specialised sensory end organs of hearing, and of equilibrium (***cristae*** of semicircular ducts; ***maculae*** of utricle and saccule; ***organ of Corti*** of cochlea). These are innervated by peripheral processes of the cells of the vestibulocochlear ganglion. This ganglion is derived from the neural crest. Its cells are peculiar in that they remain bipolar throughout life (Fig. 19.18).

The ***bony labyrinth*** is formed from the mesenchyme surrounding the membranous labyrinth. (Fig. 19.19A). This mesenchyme becomes condensed to form the ***otic capsule***. The mesenchymal condensation is soon converted into cartilage. Between this cartilage and the membranous labyrinth, there is a layer of loose periotic tissue (Fig. 19.19B). The spaces of the bony labyrinth are created by the disappearance of this periotic tissue. The membranous labyrinth is filled with a fluid called ***endolymph***, while the periotic spaces surrounding it are filled with ***perilymph***.

The periotic tissue, around the utricle and saccule, disappears to form a space called the ***vestibule*** (Fig. 19.20). The periotic tissue, around the semicircular ducts also disappears to form the ***semicircular canals.*** Two distinct spaces are formed, one on either side of the cochlear duct. These are the ***scala tympani*** and the ***scala vestibuli***. The scala vestibuli communicates

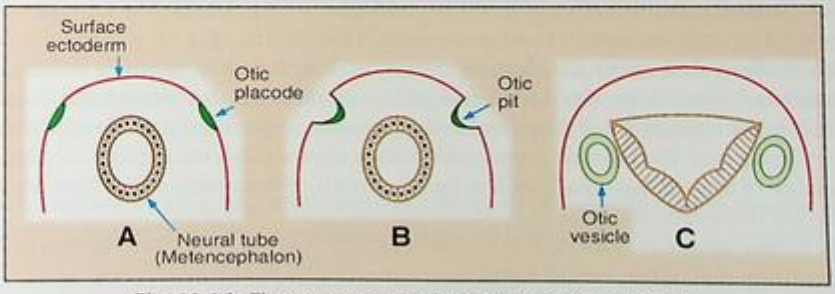

Fig. 19.16: Three stages in the formation of the otic vesicle.

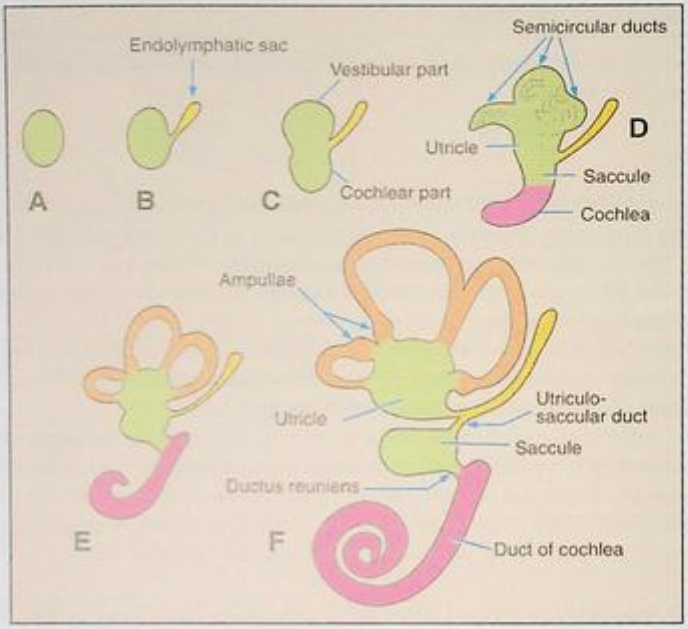

Fig. 19.17: Gradual transformation of a rounded otic vesicle to the highly complicated form of the membranous labyrinth.

with the vestibule while the scala tympani grows towards the tympanic cavity, from which it remains separated by a membrane (Fig. 19.20). The cartilaginous labyrinth is subsequently, ossified to form the bony labyrinth (Fig. 19.19D).

Middle Ear

The epithelial lining of the middle ear and of the pharyngo-tympanic tube is derived from the ***tubo-tympanic recess***. This recess develops from the dorsal part of the first pharyngeal pouch, and also receives a contribution from the second pouch (Fig. 19.21). The tympanic antrum, and mastoid air cells are formed by extensions from the middle ear.

The ***malleus*** and ***incus*** are derived from the dorsal end of Meckel's cartilage, while the ***stapes*** is formed from the dorsal end of the cartilage of the second pharyngeal arch (Fig. 19.22). The ossicles are at first outside the mucous membrane of the developing middle ear. They invaginate the mucous membrane, which covers them throughout life (Fig. 19.23). The ossicles of the ear fully ossify in the fourth month of intrauterine life. They are the first bones in the body to do so.

The ***tensor tympani*** is derived from the mesoderm of the first pharyngeal arch and the ***stapedius*** from that of the second arch.

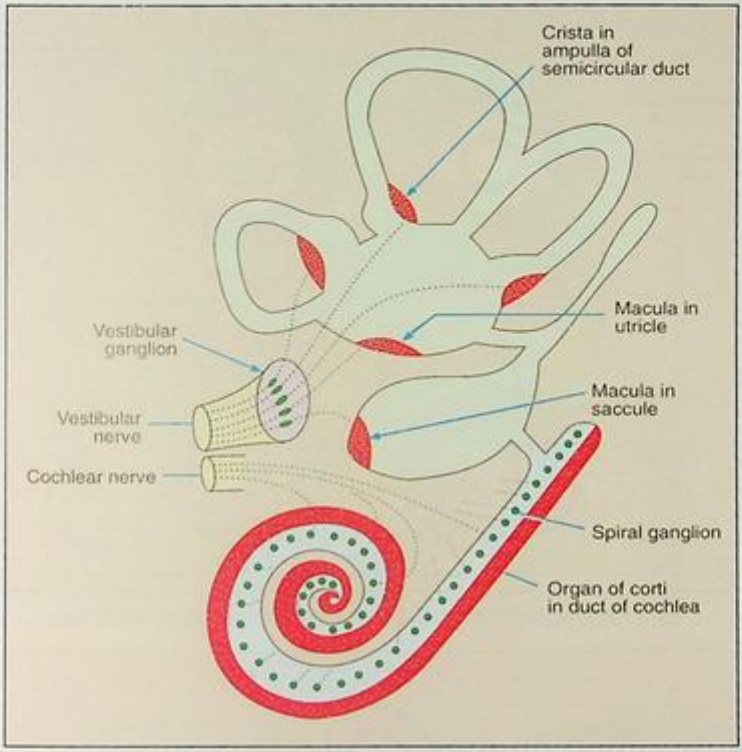

Fig. 19.18: Specialised sensory areas developing in the internal ear and their nerve supply.

External Ear

The ***external acoustic meatus*** is derived from the dorsal part of the first ectodermal cleft (Fig. 19.24A). However, its deeper part is formed by proliferation of its lining epithelium, which grows towards the middle ear (Fig. 19.24B). This proliferation is at first solid (***meatal plug***), but is later canalised (Fig. 19.24C).

The auricle, or ***pinna***, is formed from about six mesodermal thickenings (called ***tubercles*** or ***hillocks***) that appear on the mandibular and hyoid arches, around the opening of the dorsal part of the first ectodermal cleft (i.e. around the opening of the external acoustic meatus) (Fig. 19.25).

The mandibular arch forms only the tragus and a small area around it, the rest of the auricle being formed from the hyoid arch. This is consistent with the fact that the auricular muscles are supplied by the facial nerve.

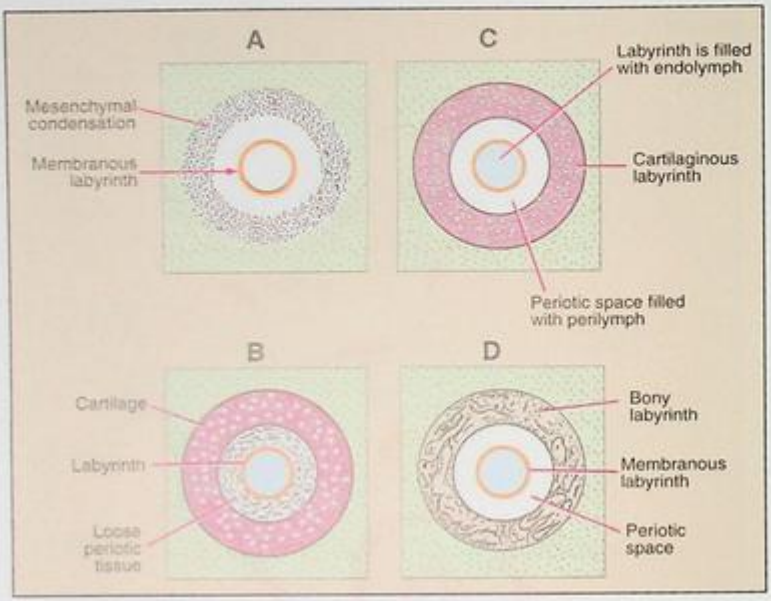

Fig. 19.19: Establishment of the basic structure of the bony labyrinth.

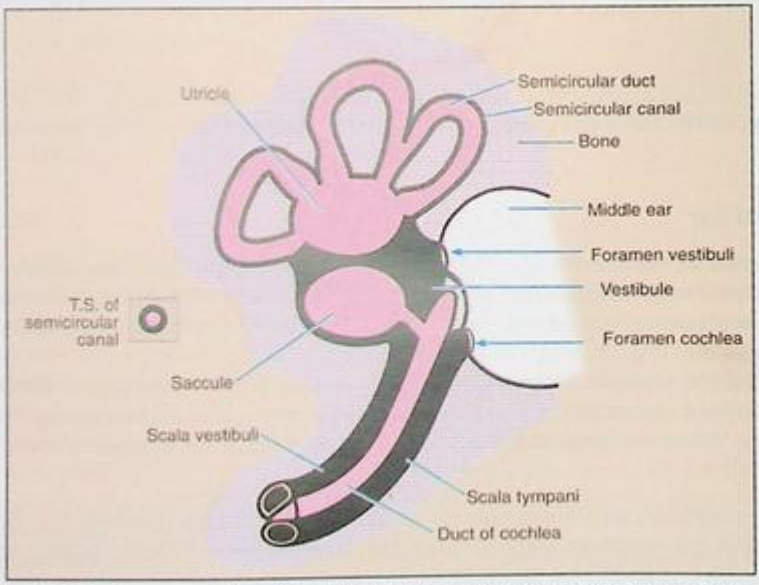

Fig. 19.20: Some parts of bony labyrinth (black), and of membranous labyrinth (pink).

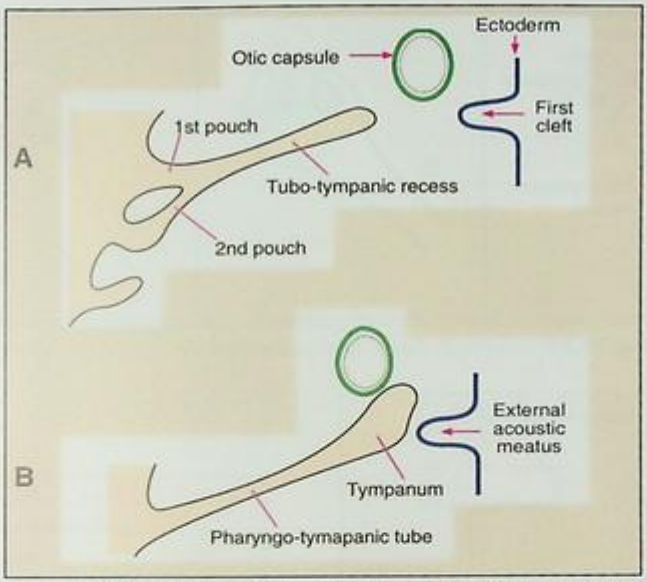

Fig. 19.21: Development of the middle ear (tympanum). Formation of tubo-tympanic recess(A), and its subdivision into the tympanum and the pharyngo-tympanic tube (B).

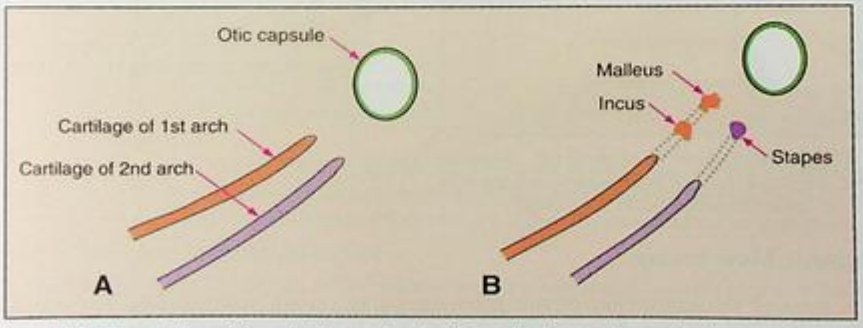

Fig. 19.22: The ossicles of the middle ear develop from the first and second pharyngeal arches.

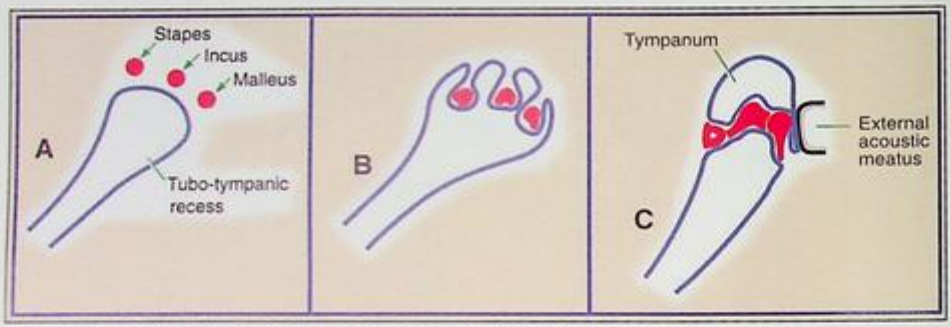

Fig. 19.23: Ossicles of the ear gradually invaginate into the tympanum.

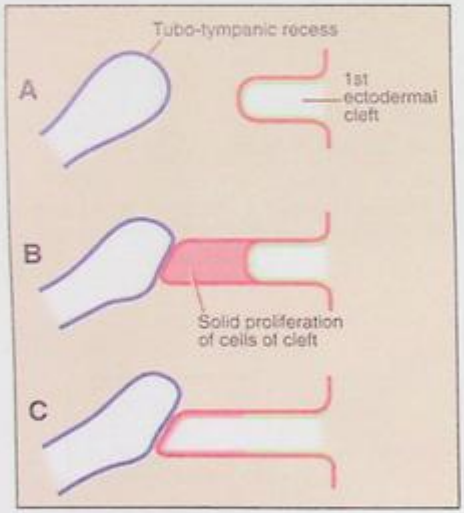

Fig. 19.24: Development of external acoustic meatus. The solid mass of ectodermal cells seen in (B) has been canalised as seen in (C).

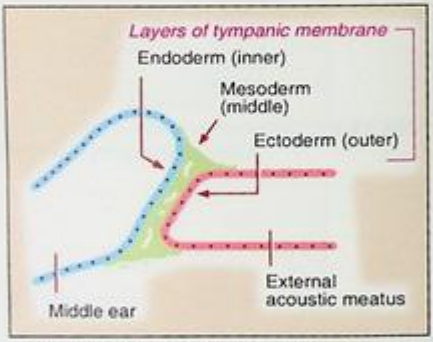

Fig. 19.25: Layers of tympanic membrane.

Tympanic Membrane

This is formed by apposition of the tubo-tympanic recess and the first ectodermal cleft, these two forming the inner (endodermal) and outer (ectodermal) epithelial linings of the membrane. The intervening mesoderm forms the connective tissue basis.

Two points worth noting are as follows:

- The handle of the malleus grows into the connective tissue from above.
- The chorda tympani nerve is at first outside the membrane but comes to lie within its layers, because of upward extension of the membrane.

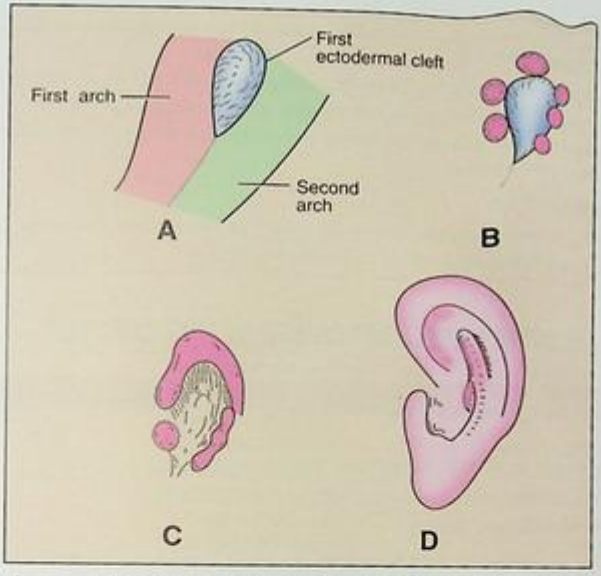

Fig. 19.26: Development of the auricle. (A) First ectodermal cleft around which the auricle develops. (B) Small swellings or hillocks appear. (C) Hillocks gradually fuse with one another to form the auricle.

Clinical Correlation

Anomalies of the Ear

Anomalies of the Auricle

- The development of the auricle may get arrested at any stage. As a result of this, it may be totally, or partially, absent; it may be represented by isolated nodules; or it may be very small. Alternatively it may be very large.
- The migration of the auricle from its primitive caudo-ventral position may remain incomplete. This migration occurs as a result of the growth of the maxillary and mandibular processes. This explains the association of caudo-ventral displacement of the auricle with mandibulofacial dysostosis.

Anomalies of the External Auditory Meatus

- There may be stenosis, or atresia, of the meatus over its whole length, or over part of it. The lumen may be closed by fibrous tissue, by cartilage, or by bone.
- The normal curvature of the meatus may be accentuated as a result of which the tympanic membrane cannot be fully seen from the outside.

Clinical Correlation ***contd...***

Anomalies of the Middle Ear

- The ossicles may be malformed. They may show abnormal fusion to one another or to the wall of the middle ear. The stapes may be fused to the margins of the fenestra vestibuli.
- The facial nerve may bulge into the middle ear and may follow an abnormal course.
- The stapedial artery may persist.

Anomalies of the Internal Ear

Various parts of the membranous labyrinth may remain underdeveloped. In some cases the cochlea alone is affected. These anomalies lead to congenital deafness.

TIMETABLE OF SOME EVENTS DESCRIBED IN THIS CHAPTER

Age	Developmental Event
Eye	
22nd day	Appearance of optic sulcus (over the neural plate).
4th week	Optic vesicle comes in contact with surface ectoderm. Lens placode is forming.
5th week	Eye primordium is completely surrounded by loose mesenchyme.
6th week	Choroid fissure is formed. Lens vesicle is seen.
7th week	A solid lens is formed.
The eyeball is most susceptible to teratogens during the 4th to 8th week, and can get affected till the end of pregnancy.	
Ear	
22nd day	Otic placode is seen.
5th week	Auricle starts forming.
6th week	The cochlea and semicircular canals starts forming.
8th week	The cochlea and semicircular canal assume their definitive external form.
10th week	Scala vestibuli and scala tympani appear .
7th month	External acoustic meatus gets canalised.
The ear is most sensitive to teratogens during the 4th to 9th weeks, and can be affected up to the 12th week.	

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HUMAN EMBRYOLOGY

This is the tenth edition of the best-selling title Human Embryology, first published in 1976. It is not only the leading textbook, but has now become an authority on the subject. It's long-standing popularity is on account of it's readability, concise and clear text, and a large number of simple but informative illustrations.

The book presents essential concepts in human development for medical students. Each chapter opens with highlights, followed by various descriptions of the normal development of particular systems in a systematic manner. All the chapters have been completely revised and edited with great care. Clinical correlations have been added and highlighted in separate boxes to enhance the clinical concepts of the students and grounding their understanding of the subject. Chapters conclude with a time-table of development events.

To avoid unnecessary details that could interrupt the flow for undergraduate students, some aspects of the subject relevant only for postgraduates are available in the accompanying CD.

Professor Inderbir Singh MBBS MS PhD FAMS has over 50 years of teaching experience. He taught Anatomy and Embryology at various medical colleges from 1952 to 1989 and retired as Professor of Anatomy, Government Medical College, Rohtak. Professor Singh has been conferred the title of Professor Emeritus by Maharishi Dayanand University, Rohtak. To his credit are a large number of research papers and books on Gross Anatomy, Histology and Neuroanatomy. He has recently been awarded with Emeritus Teacher Award by National Board of Examination for making invaluable contribution for teaching of Anatomy.

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