Aids to embryology / by J.S. Baxter.

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FOURTH EDITION

BAILLIÈRE, TINDALL & COX

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BY

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FOURTH EDITION

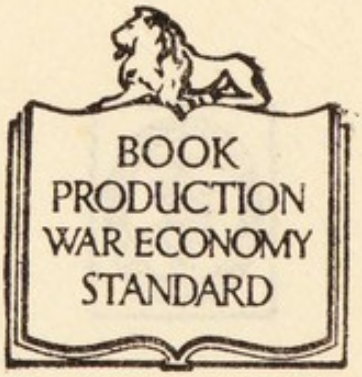
LONDON

BAILLIÈRE, TINDALL AND COX

7 & 8, HENRIETTA ST., COVENT GARDEN, W.C. 2

1948

First Edition, May, 1928
Reprinted, March, 1933
Second Edition, October, 1934
Third Edition, April, 1938
Fourth Edition, February, 1948



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PRINTED IN GREAT BRITAIN

PREFACE TO THE FOURTH EDITION

THIS book owes its inception to Dr. R. H. Hunter of Queen's University, Belfast, and the first three editions came from his pen. He has now retired from active teaching and when a fourth edition was called for, I, as one of his former students, was asked to take over the work. I have not altered the plan of the book and it is still intended primarily for the medical student preparing for the Second Professional Examinations of Universities and Colleges. Nevertheless, it is hoped that it may perhaps have a wider appeal, and that those reading for other examinations requiring a knowledge of human development may benefit from a study of its pages.

The many advances in our knowledge of human embryology since 1938, when the last edition of this book was published, necessitated a drastic revision, and the opportunity was taken almost completely to re-write it. Several new illustrations have been inserted and others re-drawn.

The index is the work of Mrs. W. B. Howell, to whom I express my sincere thanks, not only for this, but also for her care in reading the proofs.

J. S. BAXTER.

UNIVERSITY OF BRISTOL,
November, 1947.

CONTENTS

INTRODUCTION

EMBRYOLOGY is the study of the changes undergone by the living organism from the time of fertilisation (*i.e.*, union of the male and female germ cells) until adult life and maturity are reached. Such a mature individual possesses the necessary organs for the formation of new germ cells—spermatozoa in the case of the male, and ova in the case of the female—so that the species may be perpetuated.

The more dramatic and important developmental changes occur before birth, and so, in the restricted sense, the study of embryology is often confined to this period, the pre-natal period. But we must not forget that important changes, more particularly in histogenesis and growth, continue after birth and constitute the post-natal phase of development.

A knowledge of embryology is essential to the student of medicine for several reasons. The form and relations of many adult structures are explicable only in terms of their development. Abnormalities and deviations from the normal, which may be encountered in clinical work, likewise owe their explanation to a knowledge of normal embryology. The anatomy and physiology of reproduction and the formation of the fœtal membranes and placenta bear closely on the work of the obstetrician and gynæcologist, while the endocrinologist also finds interest in the subject of human development.

AIDS TO EMBRYOLOGY

CHAPTER I

THE GERM CELLS

The Male Organs of Reproduction.—The male genital glands are known as the testes. They are concerned with the production of male germ cells or spermatozoa. Also, certain cells of the testes elaborate an important internal secretion. The spermatozoa are conveyed to the exterior by a system of genital ducts with which are associated several accessory glands.

Each testis is enclosed in a strong fibro-elastic capsule, the tunica albuginea. This is covered by a serous membrane, the tunica vaginalis testis, which permits considerable mobility of the organ within the scrotum. From the capsule, septa pass inwards subdividing the testis into a number of lobules. Posteriorly the septa converge to a fibrous thickening, the mediastinum testis. Each lobule of the testis contains one or more seminiferous tubules, in the walls of which development of the male germ cells or spermatogenesis takes place. The seminiferous tubule is coiled up when in the lobule; when unravelled it measures from 1 to 2 feet in length. In between the tubules are found blood vessels, connective tissue and groups of interstitial cells of Leydig, which elaborate male sex hormone. The seminiferous tubules terminate by straight tubules in a system of channels in the mediastinum known as the rete testis; these are continued in turn into

the efferent ductules of the epididymis. The latter connect with the canal of the epididymis and this passes into the ductus deferens. Near its termination the ductus is joined by the duct of the seminal vesicle and the canal so formed, the common ejaculatory duct, perforates the upper posterior part of the prostate to end in the prostatic urethra.

Each seminiferous tubule has an outer fibrous coat. It is lined by several layers of cells, and these are of

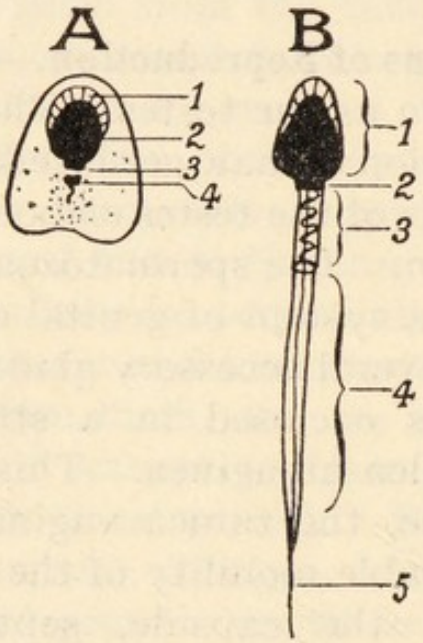

FIG. 1.—TWO STAGES IN THE DEVELOPMENT OF THE SPERMATOZOON.

A.—1, Acrosome; 2, nucleus; 3, proximal centriole; 4, distal centriole. B.—1, Perforatorium; 2, neck; 3, body; 4, tail; 5, terminal filament.

two kinds—sustentacular cells of Sertoli and male germ cells in various stages of development. The sustentacular cells are elongate, columnar elements projecting from the basement membrane towards the lumen of the tubule. They are in close relation with the developing spermatozoa, and probably provide nourishment for them.

Spermatogenesis.—The series of changes through which the male germ cells pass from the immature to the fully formed state is termed spermatogenesis. It

may readily be studied in any adult male animal, since every tubule of an active testis contains several stages of the process, and these changes occur in orderly rhythm along the length of the tubule.

The primitive germ cells lie next to the basement membrane and are known as spermatogonia. They are rounded cells with a large vesicular nucleus, and the cytoplasm contains many scattered mitochondria. The Golgi material forms a cap at one pole of the nucleus. Division of the spermatogonia occurs by the ordinary process of mitosis. One of the daughter cells resulting from such a division becomes displaced towards the tubule lumen, and is now known as a primary spermatocyte. The nucleus of this cell type is larger than that of the parent spermatogonium, and the mitochondria become collected around it. A centriole appears in the cell cytoplasm. Division of the primary spermatocyte by a special process (meiosis, see p. 10) involving reduction of the chromosome content of the nucleus to one-half, results in the formation of secondary spermatocytes. Then, mitosis of the secondary spermatocytes gives rise to spermatids which metamorphose into the adult spermatozoa without further cell division. The nucleus of the spermatid is a dense chromatic structure eccentrically situated in the cell, and to one pole of it is closely applied part of the Golgi material, the acrosome. This is ensheathed by a thin layer of cytoplasm, the head cap, and the two are destined to become the perforatorium of the mature spermatozoon. The centriole divides into two which migrate to that part of the cytoplasm opposite to the acrosome. From the distal centriole an axial filament grows out through the surface of the cell. The proximal centriole remains close to the nucleus, but the distal centriole becomes ring-shaped and moves away from it along the axial filament. During this migration of the

distal centriole the mitochondria become aggregated in spiral fashion around that part of the axial filament between the two centrioles. This is the middle piece or body of the spermatozoon. Further elongation of the axial filament results in the formation of a tail distal to the posterior centriole, most of which is clothed with a very thin film of cytoplasm, the extreme tip alone being naked. During this process of maturation much of the spermatid cytoplasm, together with some of the Golgi material and a few mitochondria is cast off into the tubule lumen and degenerates.

The result of these changes is the formation of a mature spermatozoon composed of three parts—head, middle piece or body and a tail. The development of these three parts may be summarized as follows :

Summary of Development of Spermatozoon.—(1) The head is composed of the nucleus of the spermatid capped by an acrosome formed from part of the Golgi material. A very thin head cap derived from cytoplasm covers the acrosome, and the two together form the perforatorium. The head is oval and somewhat flattened in shape.

(2) The middle piece extends from the head to the ring centriole. Most of it is surrounded by the spiral filament formed from the mitochondria. Anterior to this is a short neck in which is located the anterior centriole.

(3) The tail or flagellum is formed by the axial filament with a very thin sheath of cytoplasm around it ; the terminal part of the tail is bare and formed by the filament alone.

The human spermatozoon measures about 60 microns * in length ; of this, the tail forms about five-sixths. Spermatozoa from the seminiferous

* A micron (μ) is $\frac{1}{1000}$th part of a millimetre.

tubules are not fully mature. They are non-motile, and it is not until they have become suspended in the secretions of the accessory genital glands to form the semen that they become functionally active. In this fluid medium they progress in a forward direction by lashing movements of their tails with a speed of from 14 to 23 μ per second. The number of spermatozoa per cubic millimetre of semen is estimated to be 60,000, and an average ejaculation contains about 200,000,000.

Although it is claimed that spermatozoa may remain alive for a week or longer in the female genital tract, the power to fertilize an ovum lasts only a short time —24 to 48 hours. They are very sensitive to changes in the reaction of the medium, an acid one being very deleterious to them.

Abnormalities in the process of spermatogenesis may result in bizarre forms with two or more heads or tails.

The Female Organs of Reproduction.—The paired female genital glands are known as the ovaries. The associated genital ducts consist of the uterine tubes, the uterus and the vagina. Of these, the ovary alone will be considered at this time. These glands produce the female germ cells or ova, which, when fertilized by the spermatozoa, develop into new individuals. Like the testis in the male, the ovary is the site of formation of important internal secretions.

The ovary is attached at its hilum by a short mesovarium to the posterior surface of the broad ligament of the uterus. Covering the gland, and continuous with the peritoneum of the mesovarium, is a layer of cubical cells termed the germinal epithelium since it is the source of ova and their surrounding follicle cells. It was formerly believed that ova were only formed during the embryonic period of life, and that these, lying dormant until after puberty,

gave rise to the mature ova liberated from the ovary during the reproductive period in the adult female. The work of Evans and Swezy (1931) has, however, demonstrated that these early ova degenerate after birth, and that the germinal epithelium is active after puberty in the production of new female germ cells or oogonia. The main mass of the ovary is divisible into a compact cortical layer and a more loosely arranged medulla. The cortex contains follicles in various stages of growth ; the medulla, on the other hand, contains no follicles but consists of connective tissue in which are many blood vessels.

Oogenesis. — The oogonia, which correspond to the spermatogonia, arise by proliferation from the germinal epithelium ; but whether their source is the epithelium itself or cells which have migrated to it during embryonic life from some other part, is not certainly known. The cells resulting from this proliferation are the primary oocytes located in the peripheral part of the ovarian cortex (Fig. 2 A). Each is surrounded by some flattened cells, the follicular epithelium. The next phase is one of growth in which the oocyte increases in size, and the elements of the ovarian or Graafian follicle become elaborated around it (Fig. 2, B and C). The essential details are these ; a structureless membrane, the zona pellucida, is laid down immediately around the oocyte. The follicle cells proliferate, become columnar and form a many-layered follicle wall. This is termed the membrana granulosa. A cavity (antrum) now appears in the membrana granulosa filled with fluid (liquor folliculi). Continued expansion of this cavity occurs as the follicle becomes mature until it reaches a diameter of 5 to 10 mm. and causes a bulging on the free surface of the ovary. In this state the oocyte, surrounded by the zona pellucida and a number of granulosa cells, is attached to the inner

aspect of the follicle wall forming an elevation, the discus proligerus. During the growth of the follicle surrounding cells of the ovarian stroma become

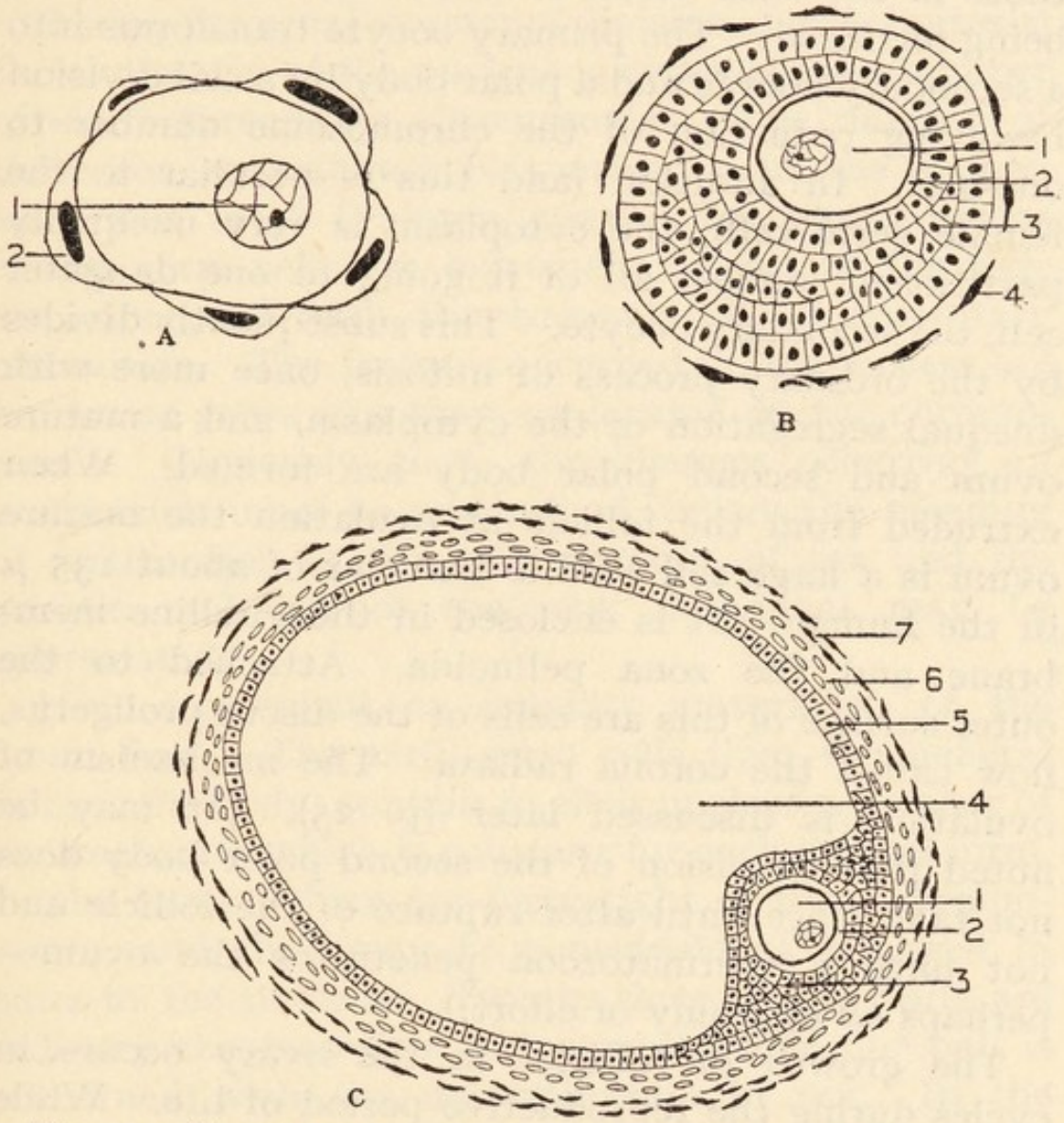

FIG. 2.—DIAGRAMS TO SHOW GROWTH OF THE OVARIAN FOLLICLE.

A.—Primordial follicle. 1, Nucleus of primary oocyte ; 2, follicle cells. B.—1, Primary oocyte ; 2, zona pellucida ; 3, membrana granulosa ; 4, ovarian stromal cells. C.—1, Primary oocyte ; 2, zona pellucida ; 3, discus proligerus ; 4, follicle cavity ; 5, membrana granulosa ; 6, theca interna ; 7, theca externa.

differentiated around the membrana granulosa in two layers ; an inner of epithelioid cells and blood vessels is named the theca interna, while an outer fibrous coat is the theca externa (Fig. 2 C).

During the time of follicle growth the female germ cell has remained in the stage of the primary oocyte. This must undergo certain changes comparable with those in the male before it is mature and capable of being fertilized. The primary oocyte transforms into a secondary oocyte and a polar body by a cell division involving reduction of the chromosome number to one-half. In addition (and this is peculiar to the female germ cell), the cytoplasm is very unequally partitioned, almost all of it going to one daughter cell, the secondary oocyte. This subsequently divides by the ordinary process of mitosis, once more with unequal segregation of the cytoplasm, and a mature ovum and second polar body are formed. When extruded from the follicle at ovulation the mature ovum is a large cell with a diameter of about 135 μ in the human. It is enclosed in the vitelline membrane and the zona pellucida. Attached to the outer surface of this are cells of the discus proligerus, now called the corona radiata. The mechanism of ovulation is discussed later (p. 25). [It may be noted that extrusion of the second polar body does not take place until after rupture of the follicle and not until a spermatozoon penetrates the ovum—perhaps an economy of effort.]

The growth of follicles in the ovary occurs in cycles during the reproductive period of life. While a number of follicles commence growth together, in the human only one normally reaches maturity and escapes from the ovary in each ovarian cycle. The remainder, partly grown, regress in a process called follicular atresia. The cavity of the ruptured follicle becomes invaded by cells to form a corpus luteum (see p. 20) which is an endocrine structure. The control of follicle ripening is discussed later (p. 23).

Maturation of the Germ Cells.—By this term is understood the changes undergone by the nucleus

whereby its chromosome content is reduced to one-half. This is an essential preliminary to fertilization, **i.e.** the union of the spermatozoon with the mature ovum.

During the usual manner of division of cells (mitosis) the chromatin of the nucleus is arranged as a number of short threads or chromosomes. The number of these for any animal is constant: in the human subject it is 48 (Painter, 1923). The chromosomes in the germ cells are extremely important for they are concerned with the transmission of hereditary characters. The factors concerned in this process are known as genes and they are located on the chromosomes. Obviously then, the changes occurring in maturation must be understood, before the meaning of fertilization in the determination of sex and the genetic make-up of the new individual may be appreciated.

It is convenient to consider maturation of the ovum first. The early germ cells (like the general cells of the body) contain in their nucleus a number of chromosomes which is constant for each animal form. In the human there are forty-eight of these chromosomes, and they may be considered as arranged in pairs in the nucleus. Twenty-three of the pairs are ordinary chromosomes (autosomes), while one pair is concerned with the determination of sex. In the early female germ cells each member of this pair is termed an X chromosome. In the usual mode of cell division (mitosis), as seen, for example, in the stage of proliferation of the oogonia (Fig. 3), each chromosome splits lengthwise and one half passes to the nucleus of each daughter cell, which contains therefore 46 + 2X chromosomes. Some time in the development of the germ cells reduction of the nuclear chromosome number to half of this figure must occur. Otherwise in union of the ovum and

spermatozoon at fertilization doubling of the chromosome number would result. Here, in the female, this reductional or meiotic division is that of the primary oocyte. There are two striking events: (*a*) the members of each chromosome pair blend, quickly separate again and an entire chromosome from the pair passes into each daughter cell; the total for each being 23 + X; (*b*) the cytoplasm of the parent cell is split so unequally that almost all passes

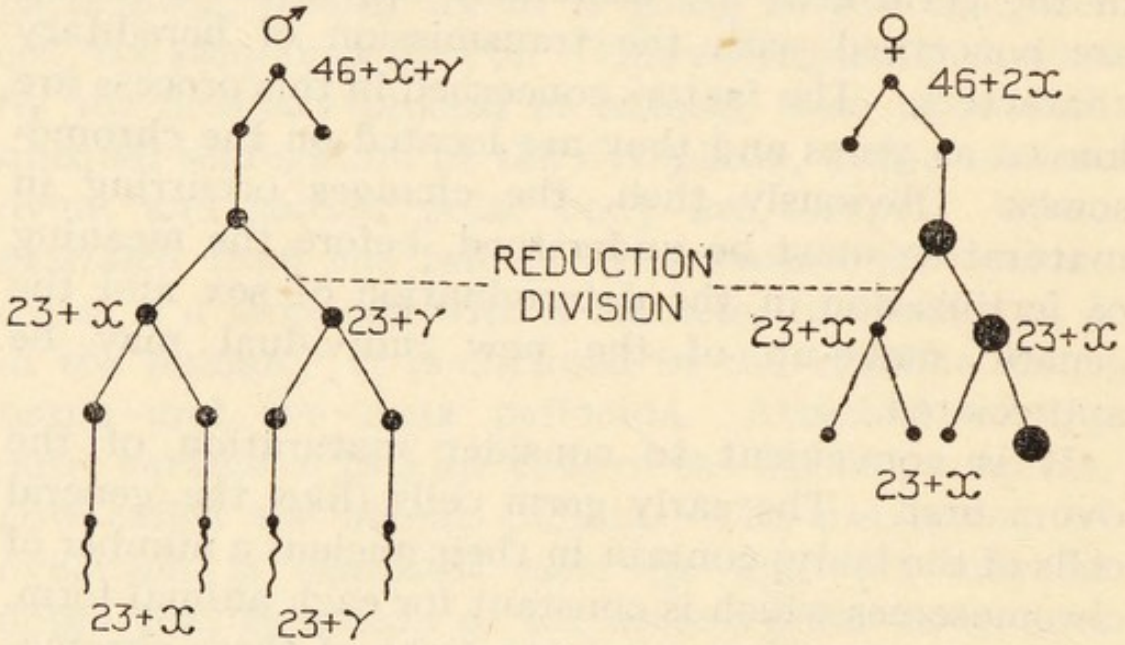

FIG. 3.—DIAGRAM TO ILLUSTRATE OOGENESIS AND SPERMATOGENESIS.

During the reduction division in the male the chromosome number is so changed that half the spermatozoa carry 23 + X chromosomes and the other half 23 + Y chromosomes. The mature ovum has 23 + X chromosomes in its nucleus.

to the secondary oocyte. The other daughter cell, called the first polar body, is very small and consists almost entirely of nuclear material. Although in Fig. 3 the first polar body is shown as capable of further division, it is most improbable that this occurs in man, degeneration soon taking place.

The secondary oocyte divides again by the ordinary process of mitosis. The nucleus of each resultant cell will therefore contain the reduced number

(23 + X) chromosomes; but the partition of the cytoplasm is once more unequal; in fact, a second polar body containing 23 + X chromosomes and little else, is cast out from the secondary oocyte. The latter may now be termed the mature ovum, a large inert cell in which the cytoplasmic volume is excessive in relation to that of the nucleus.

The spermatogonia in the male contain forty-six ordinary chromosomes and two concerned with sex determination. One of these is like the X chromosome of the female, but the other is quite small and is known as the Y chromosome. During maturation the nuclear changes resemble those already described for the female. Reduction of the chromosome number is found during the division of the primary spermatocyte and one secondary spermatocyte thus contains 23 + X chromosomes: the other has 23 + Y chromosomes. Ordinary mitotic division of the two secondary spermatocytes gives four spermatids which transform into spermatozoa. Important differences from the female are: (*a*) four functional spermatozoa are derived from each primary spermatocyte; (*b*) half of these contain twenty-three ordinary chromosomes with one X chromosome, and the other half contain the same number of autosomes with an additional Y chromosome (instead of X); (*c*) during metamorphosis of the spermatid there is elimination of cytoplasm so that the mature spermatozoon contains very little.

Determination of the sex of the embryo occurs at fertilization. From what has been said it is obvious that the chromosome number of the mature ovum is 23 + X while spermatozoa are of two kinds, some containing 23 + X, other 23 + Y chromosomes. When a spermatozoon with an X chromosome fertilizes an ovum the resulting embryo will be female, but the spermatozoon containing a Y chromosome

will, on union with the mature ovum, give rise to a male individual.

Fertilization.—Fertilization is the union of two mature germ cells, an ovum and a spermatozoon, to form a single uninucleated cell, the zygote. While this event has not actually been observed in the human, the known facts of comparative embryology indicate that the processes are fundamentally similar in higher mammals, and they may be described as follows :

In the human, fertilization normally occurs in the lateral third of the uterine tube. It was formerly believed that the spermatozoa deposited in the upper vagina at coitus, actively swim upwards through the uterus and uterine tube to meet the ovum. Hartman and Ball (1933) have shown that sperm transport in the rat is much too quick for this to be the only process involved, for in this animal less than two minutes elapse from the moment of ejaculation until spermatozoa reach the distal ends of the uterine cornua. The transporting mechanism is believed to be the powerful contractions of the uterine musculature which cause rapid disposal of the spermatozoa throughout the fluid-filled uterine cavity. That there is any comparable mechanism for sperm transport in the human is, at present, not proven, but it is believed that spermatozoa reach the outer part of the human uterine tube within a few hours after intercourse.

The first spermatozoon to reach the ovum penetrates the zona pellucida and the head with the middle piece enter into the cytoplasm. Other spermatozoa attempting to enter later become entangled in the zona pellucida owing probably to some change that takes place in the nature of this membrane. After the sperm head has penetrated the ovum it becomes swollen and is termed the male pronucleus. The nucleus of the mature ovum may, correspondingly,

be called the female pronucleus. Union of these two structures occurs to form the segmentation nucleus. This results in two things : (*a*) the reduced chromosome number of the ovum (sometimes called the haploid number) is restored to normal : (*b*) the ovum is now stimulated to enter on a process of division or segmentation.

CHAPTER II

SEGMENTATION AND GERM LAYER FORMATION

Segmentation.—The fertilized ovum, after a short period of rest, enters upon a phase of repeated cell division. This is known as cleavage or segmentation and results in the transformation of the fertilized ovum to a solid mass of cells (morula). The most striking result is that the volume of the cytoplasm diminishes as compared with that of the nucleus and a normal nuclear—cytoplasmic ratio for the cells of the morula is restored.

Information about cleavage stages is lacking in the human subject. The process has been extensively studied for other mammalian forms both in fixed material and with living specimens. The macaque monkey shows cleavage as it presumably is in the human, and the account given here is based on the work of Lewis and Hartman (1933) on this form. The first cleavage has not been observed in the monkey but the two-cell stage was found and studied in tissue culture. The two cells were somewhat unequal ; the larger cell divided first, giving a three-cell stage, and subsequent division of the smaller resulted in a cross-like pattern of four cells. Further divisions of the larger and smaller cells took place, the larger

always first, so that stages with five, six, seven, eight and more cells were observed. At the sixteen-cell stage, the fertilized ovum could be termed a morula. During the process of segmentation the developing ovum passes along the tube to the uterine cavity. It arrives there four days after ovulation in the sixteen-cell stage. We have no absolute data for

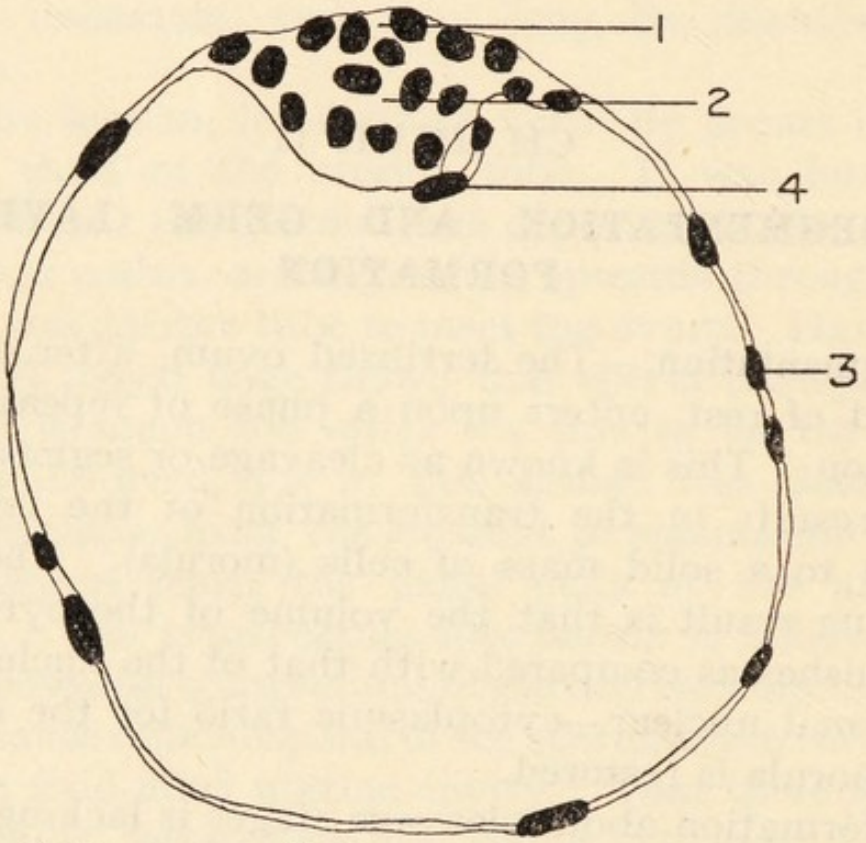

FIG. 4.—DIAGRAM OF A SECTION THROUGH A MACAQUE BLASTOCYST. (Adapted from Streeter.)
1, Trophoblast of the embryonic pole; 2, inner cell mass; 3, trophoblastic wall of the blastocyst; 4, entoderm cells.

the human, but it is reasonable to suppose that transport through the tube requires about the same time (three days) as in the macaque monkey, and also that the human ovum attains the morula stage of development on, or shortly before, arrival in the uterus.

The Blastocyst.—On arrival in the uterine cavity the actively growing morula undergoes important changes in cell orientation. These are mainly due to passage of fluid from the uterine lumen into the

intercellular spaces of the morula. This is converted into a hollow vesicle having an outer layer of flattened cells, the trophoblast, with an inner cell mass attached at one pole of the inner aspect (Fig. 4). About this time, the zona pellucida disappears. The trophoblast is concerned with implantation of the developing ovum in the uterine mucous membrane and the later formation of an organ, the placenta, for nutritive exchanges between the developing individual and the mother. All these will be dealt with in the chapter on Implantation and Placentation (p. 26).

The inner cell mass, with which we are at present concerned, gives rise to the embryo, the amnion and the yolk sac. The early formation of these must necessarily be described together.

The youngest human ovum so far discovered is in the eighth day of development (Hertig and Rock, 1945). It is just commencing to implant in the endometrium and already shows differentiation of the inner cell mass. There is an embryonic disc consisting of a flattened ovoid mass of cells. It is subdivided into a dorsal layer of fairly large ectodermal cells, and small, dark-staining entodermal cells. Between the primitive ectoderm and the inner surface of the trophoblast there is a very small, slit-like space, the future amniotic cavity. The roof of this is closed in by flattened amniogenic cells which are being split off from the true trophoblast of the embryonic pole.

The further development of these parts of the inner cell mass may be understood from study of the diagram of a twelve-day human embryo shown in Fig. 5. This embryo is already implanted in the endometrium but details of its uterine relationships have been omitted from the drawing.

This human blastocyst has an outer trophoblastic wall with irregular projections from the external surface. These are the early villi concerned with

implantation. The embryonic disc is bilaminar with a layer of large columnar ectodermal cells dorsally and a layer of much smaller, cubical entodermal cells ventrally. The amniotic cavity is complete and lies between the embryonic ectoderm and a layer of flattened cells distinct from the overlying trophoblast. Cells continuous with the embryonic entoderm have

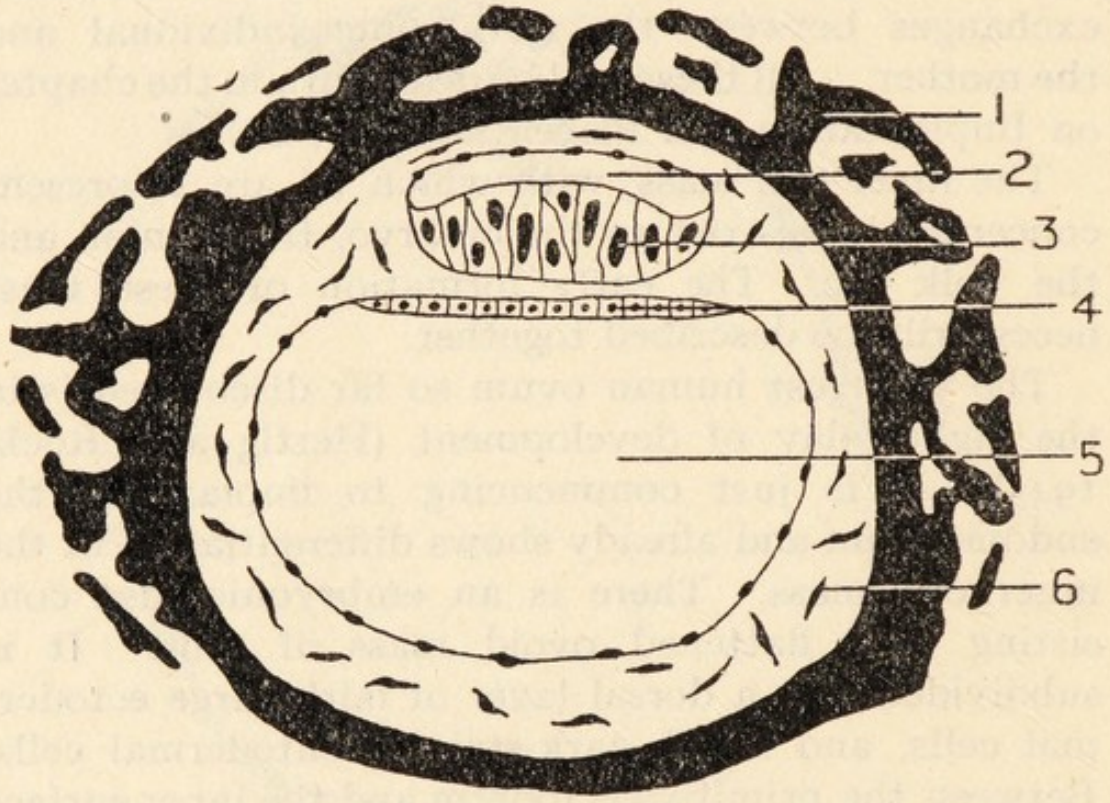

FIG. 5.—DIAGRAM OF A TRANSVERSE SECTION THROUGH A HUMAN BLASTOCYST OF 12 DAYS. (Adapted from Hertig and Rock.)

1, Trophoblast; 2, amniotic cavity; 3, embryonic ectoderm; 4, embryonic entoderm; 5, primary yolk sac; 6, extra-embryonic mesoblast.

extended round the inner aspect of the blastocyst wall to bound a second cavity, the primary yolk sac. Between this and the inner aspect of the trophoblast are a number of loosely arranged cells, the extra-embryonic mesoblast. These have probably arisen by proliferation from the inner aspect of the trophoblast. In slightly later stages of development, cavities appear in the extra-embryonic mesoblast which become

confluent and split these cells into a layer applied to the inner aspect of the trophoblast (which, with the trophoblast forms the chorion), and a second covering the amnion and the primary yolk sac. These two layers are continuous at one place, thus suspending the intrachorial structures from the outer wall of the blastocyst. This portion of the extra-embryonic mesoderm will become the body stalk.

The Embryonic Axis.—Until this time the embryonic disc has been a more or less rounded bilaminar structure. When the embryo is about fifteen days old an antero-posterior axis becomes established with the formation, at the posterior edge of the embryonic disc, of an elongated area where rapid proliferation of ectodermal cells takes place. This is the primitive streak. At its anterior end is a rounded knot of ectodermal cells, Hensen's or the primitive node. In the centre of this is an invagination of the ectoderm, the primitive pit, which corresponds with the blastopore of lower forms. The cells budded off from the primitive streak and from Hensen's node migrate laterally, insinuating themselves between the ectoderm and the entoderm of the disc. This is the mesoderm and its appearance makes the germ disc a trilaminar structure. A cord of cells grows forward in the middle line from Hensen's node between the ectoderm and entoderm. It is called the notochordal, or head process. The tip of this process becomes relatively fixed at the anterior margin of the embryonic disc, and further growth in length of it causes the embryonic disc to become pear-shaped. Such elongation of the disc causes Hensen's node and the primitive streak to retreat towards its posterior, or future caudal margin. The invagination known as the primitive pit extends into the notochordal process as the notochordal canal. The floor of this breaks down allowing temporary communication between the amniotic and

yolk sac cavities (see Fig. 6). Later, the entodermal continuity is restored ventral to the notochordal plate which transforms into a cylindrical bar of cells, the notochord. The anterior tip of this lies just behind the situation of the future hypophysis. The notochord is a vestigial structure in man and begins to disappear at an early date.

Further Differentiation of Embryonic Mesoderm.—The mesodermal cells budded off from Hensen's node and the sides of the primitive streak not only spread

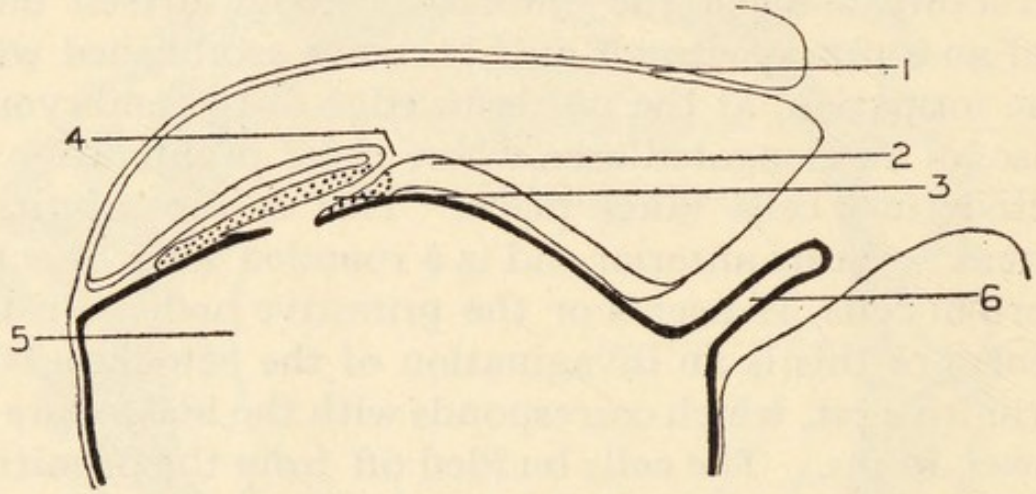

FIG. 6.—DIAGRAM OF A LONGITUDINAL SECTION THROUGH AN 18-DAY HUMAN EMBRYO. (Adapted from Heuser.)

1, Amnion ; 2, primitive streak ; 3, notochordal canal ; 4, blastopore ; 5, yolk sac ; 6, allanto-enteric diverticulum.

laterally but also extend forwards as two wings, one on each side of the notochord. With elongation of the embryonic disc a mid-line ectodermal thickening arises in front of Hensen's node. This thickening rises up as a lip on each side, owing to differential growth, and a median groove, the neural groove, is formed. The further fate of this is dealt with in Chapter VII. What we are concerned with now, is that the mesoderm on each side of the neural groove and notochord becomes thickened as a longitudinal mass, the paraxial mesoderm. This is connected with the mesoderm towards the periphery of the embryonic disc, the lateral plate mesoderm, by the intermediate

cell mass. The lateral plate mesoderm is continuous at the margins of the disc with the extra-embryonic mesoderm (p. 16).

About the twenty-first day of development in the human, the paraxial mesoderm begins a process of sub-division from before backwards into paired cubical masses, the somites. The first ones laid down are in the future occipital region of the embryo and some forty-two pairs are successively formed until the embryo is about 4 mm. in length. The mesodermal tissue of the somites is concerned essentially with the elaboration of parts of the muscular and skeletal systems (see Chapter XIII).

The mesodermal tissues of the intermediate cell mass give rise to the excretory sytem and the sex glands. This phase of development is discussed in Chapter XII. The intermediate cell mass does not exhibit an early segmental arrangement comparable to that of the somites, but hints of its segmental origin may be seen in the formation of the pro- and meso-nephros.

The lateral plate mesoderm continues with the extra-embryonic mesoderm and is split into two layers by the formation of a cavity, the intra-embryonic cœlom. One layer is applied to the inner surface of the embryonic ectoderm and may therefore be termed somatopleure ; the second is in contact with the embryonic entoderm and is designated as splanch-nopleure. The cavities extend forward on each side and eventually fuse with each other in front of the anterior extremity of the embryonic disc in the region of later formation of the primitive heart.

Expansion of the extra-embryonic cœlom from the twelfth day onward for a few days is accompanied by diminution in size of the primary yolk sac (Heuser, Rock and Hertig, 1945). It becomes about equal in size to the amniotic sac at the fifteenth day.

CHAPTER III

CHANGES IN THE FEMALE GENITAL TRACT

BEFORE describing the mechanism of implantation of the embryo and the formation of the fœtal membranes, reference must be made to the cyclic changes which take place in the ovary and uterus during the reproductive period of life in the human female.

Cyclic Changes in the Ovary.—The growth of the ovarian follicle was described earlier in this book (p. 6), and when a mature follicle ruptures at ovulation the resultant cavity is converted into a structure known as the corpus luteum. In the absence of fertilization this degenerates after a life of about two weeks and the cycle recommences with the growth of more follicles. The whole series of events is repeated approximately every twenty-eight days.

At the beginning of the ovarian cycle a number of follicles commence growth. Normally only one of them becomes mature in the human. The others sooner or later degenerate, a phenomenon known as follicular atresia, and are ultimately replaced by fibrous tissue. In the follicle which will eventually rupture at ovulation, growth is very marked just before this event. Certain cells of the follicle (probably the theca interna) produce a hormone known as oestrin, which influences the remainder of the female genital tract (*vide infra*). The whole process of follicular ripening in the ovary is controlled by a hormone produced by the anterior lobe of the hypophysis and called the follicle stimulating hormone (F.S.H.).

The Corpus Luteum.—After ovulation a structure is formed called, from its characteristic yellow colour,

the corpus luteum. The wall of the ruptured follicle consists of stratum granulosum cells. This wall crumples up around some central blood clot and the granulosa cells become greatly enlarged, accumulating granules of yellowish pigment in their cytoplasm. These cells are now termed luteal cells and the whole structure becomes vascularized by ingrowth of capillaries from the theca. The luteal cells produce a hormone called progesterone which has an influence upon the uterine endometrium, and this will be discussed later, while the formation of the corpus luteum itself is controlled by the anterior hypophysis by means of the luteinizing hormone (L.H.).

The fate of the corpus luteum depends on whether fertilization of the ovum occurs or not. In the latter case the structure, a corpus luteum of menstruation, grows for some days until it may be one-third the size of the ovary. Before the next menstruation occurs however, degenerative changes set in and eventually it is represented by a fibrous scar in the ovary, a corpus albicans. If the ovum be fertilized the corpus luteum persists as a corpus luteum of pregnancy until the fourth month of development since its presence is necessary for maintaining pregnancy during this time. Then degenerative changes commence and it slowly regresses.

Cyclic Changes in the Uterus.—During the whole of a woman's sexual life certain changes occur roughly every twenty-eight days in the mucosa of the uterus, in preparation for the possible implantation of a fertilized ovum. There is discharge of blood from the uterus for several days during these changes and the first day of such discharge is reckoned as the first day of the menstrual cycle. Although commonly of twenty-eight days duration, the cycle may be longer or shorter in different individuals.

The endometrial changes may be described in

four phases: (*a*) menstrual; (*b*) post-menstrual; (*c*) interval; (*d*) pre-menstrual; these however pass gradually from one to another and it is not easy to say when one ends and another commences.

The menstrual phase lasts three to five days. Before it commences the endometrium is thick (5 mm. or more) and the superficial part is congested. Leakage of blood from the capillaries into the sub-epithelial tissues results in the molecular disintegration of the superficial parts (stratum compactum and stratum spongiosum) which, with the blood cells, pass to the exterior as the menstrual flow. As a consequence the thickness of the endometrium is greatly reduced (0·5 mm.). The amount of blood and debris lost averages some 50 to 60 cc., but may be considerably more.

In the post-menstrual or early proliferative phase, repair of the denuded surface takes place by re-epithelialization from the terminal parts of the glands remaining in the stratum basale of the endometrium. This process occurs rapidly (about four days or so) and passes insensibly into the next phase, that of the interval.

The interval phase (twelve to thirteen days) corresponds to late proliferation and early secretion and shows progressive increase in the thickness of the mucosa; the uterine glands increase in length and become somewhat coiled and at the end of this period the endometrium may be divided into three strata. Superficially there is a compact layer; next, a zone where the stroma cells are more loosely arranged (the stratum spongiosum), and next to the uterine muscle is a stratum basale, in which the terminal parts of the uterine glands are embedded. This endometrium is 3 to 4 mm. in thickness.

The last phase of the menstrual cycle is the pre-menstrual one. Its duration is from six to eight days.

Here the endometrium increases greatly in thickness and the stroma becomes œdematous. The uterine glands become markedly dilated and convoluted presenting in microscopic sections a characteristic appearance called "saw-tooth". Their secretion contains glycogen and mucin. The veins and capillaries become dilated while the small arteries are described as arranged in spiral fashion in the tissue.

These changes in the endometrium are shown diagrammatically in Fig. 7.

Relation of Uterine Changes to Ovarian Cycle.—Broadly speaking, the first half of the menstrual cycle is associated with the presence of a ripening follicle in the ovary. During the second half a corpus luteum is found. The events taking place in the endometrium are controlled by hormones secreted by these two structures, and so we may distinguish a first or follicular and a second or progestional phase. Follicle growth and corpus luteum formation are in turn controlled by hormones elaborated by the anterior lobe of the hypophysis so the sequence of events may be considered as follows :

The anterior lobe of the hypophysis produces a hormone—follicle stimulating hormone (F.S.H.)—which controls development of the ovarian follicle. This developing follicle produces a second hormone. an œstrogen—which controls the proliferation phase of the endometrium. This corresponds to the post-menstrual and early interval stages. About the fourteenth day of a normal cycle the anterior lobe of the hypophysis commences secretion of another substance called the luteinizing hormone (L.H.). This is principally concerned with the formation and maintainance of the corpus luteum, but the early small amounts of it, secreted by the hypophysis, cause rupture of the follicle and thus the ovum is released from the ovary. There does not seem to

be any evidence for a specific factor causing ovulation. A corpus luteum is formed at the site of the ruptured follicle by the stratum granulosum cells of the follicle wall, and this formation, and the persistence of it, is due to the luteinizing hormone. The cells of the corpus luteum secrete progesterone which is responsible for the secretory phase of the endometrium,

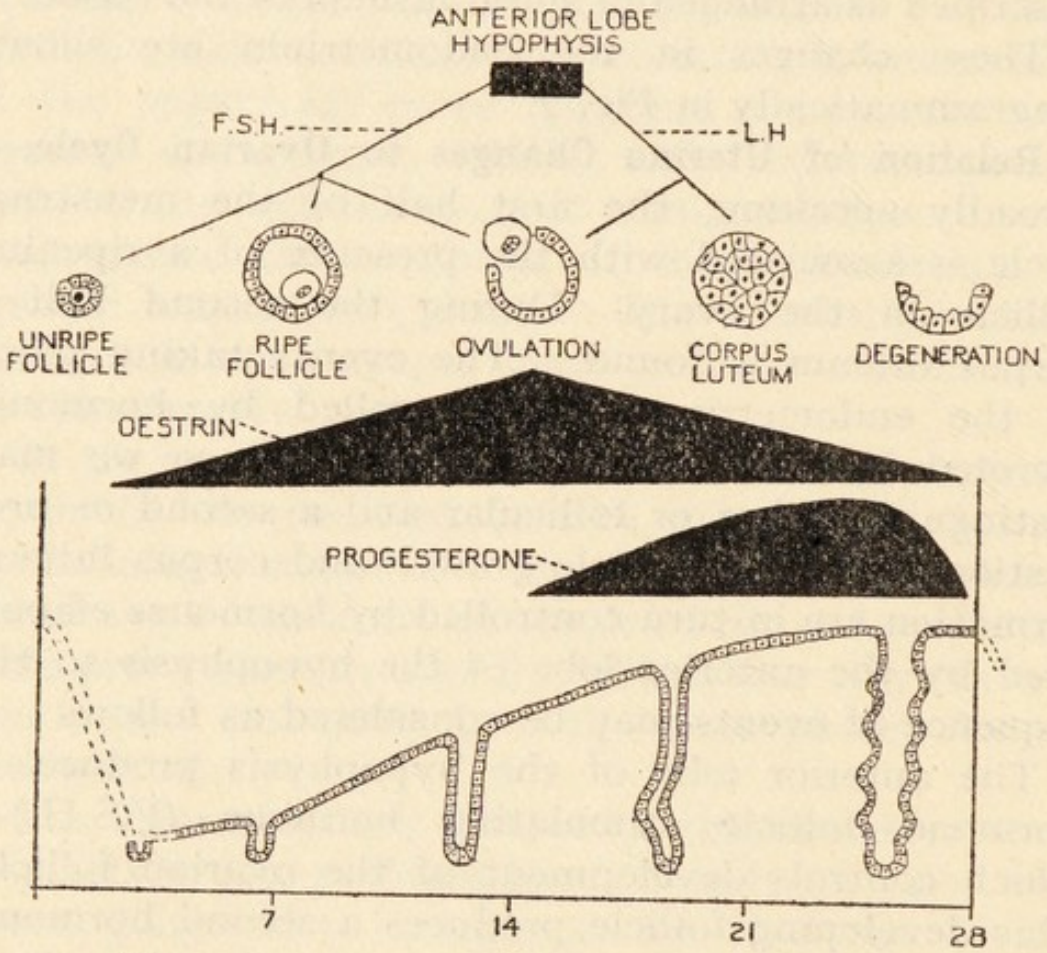

FIG. 7.—DIAGRAM TO SHOW INTER-RELATIONS BETWEEN THE HYPOPHYSIS, OVARY AND ENDOMETRIUM DURING THE MENSTRUAL CYCLE.

that is the late interval and pre-menstrual stages. The changes induced in the endometrium are such as to prepare it for the reception of a fertilized ovum, and if fertilization does not occur the corpus luteum degenerates and the influence of progesterone upon the uterine mucosa is withdrawn. The latter breaks down as the menstrual discharge and the whole cycle begins once more.

Time of Ovulation.—A great deal of work has been carried out in recent years to determine the relation of ovulation to the menstrual cycle. Experiments on the macaque monkey, which resembles the human in its menstrual cycle, point to the mid-interval period as being the most usual time for rupture of the ovarian follicle. Various observations suggest that this is essentially correct for the human female. Probably the most important of these has been the recovery of living unfertilized ova from the uterine tube by Allen and his co-workers (1930), who determined in this way that ovulation took place about the fourteenth day of the cycle. Microscopic examination of specimens of endometrium removed by biopsy demonstrate early secretory changes under progesterone influence and thus it is possible to determine if ovulation has occurred. It is not possible to state exactly when.

A widely held theory (Knaus-Ogino) states that ovulation occurs during a short period of time which bears a constant relation to the succeeding menstruation. According to this view, ovulation occurs fourteen days before the first day of the next menstrual flow. The theory, assuming that the ovum and the spermatozoon have a comparatively short life (see below), claims to afford a means of determining that period in the menstrual cycle when the human female is practically sterile. This period would be, then, the six or seven days preceding menstruation. Reports from different observers vary as to the practical value of the Knaus-Ogino theory.

Viability of Ovum and Spermatozoon.—It was formerly thought that the unfertilized human ovum could remain alive for some two weeks after ovulation. This view is now very seriously questioned, since it is known that the life span of the unfertilized ovum of lower mammals is a short one, ranging from five to

six hours in the rabbit (Hammond, 1934) to less than thirty hours in the ferret (Hammond and Walton, 1934). It seems commonly agreed at this day that the unfertilized human ovum cannot much exceed these times in its viability which may therefore be put at twenty-four hours or somewhat more.

Spermatozoa deposited in the female genital tract remain motile for varying periods of time depending on their environment. Thus, judging by their motility, they survive only a few hours in the vagina owing to the acid reaction of the vaginal secretions. In the cervix uteri survival is longer since they are in an alkaline medium. Motility of a spermatozoon does not, however, constitute ability to fertilize an ovum, and it seems unlikely on the fragmentary evidence to hand that the human spermatozoon retains its fertilizing power for more than forty-eight hours *within the female genital tract.*

CHAPTER IV

IMPLANTATION AND PLACENTATION

The Implantation of the Ovum.—The problem of the mechanism of implantation of the human ovum has presented numerous difficulties in the past, because there were described only a relatively small number of good specimens to illustrate the condition. The investigations of Wislocki and Streeter (1938) gave, for the first time, a connected account of implantation in a primate, and the technical methods devised for their study stimulated other workers, particularly Hertig and Rock to search for earlier stages in human development than had hitherto been known. At the present time our knowledge of the process of implantation in the human has been greatly extended

by the recovery of normal human ova as young as seven and a half days conceptional age. The following account of implantation in the human is based on the work of Hertig and Rock (1944).

The human ovum is fertilized at the outer end of the uterine tube, and while segmentation takes place, the ovum passes to the uterine cavity, its journey occupying probably three days. Its transport is accomplished partly by the downward streaming flow of fluid directed by the ciliary action of the tubal epithelium and partly by peristaltic contractions of the tubal musculature. The ovum arrives in the uterine cavity at the morula stage. It was formerly thought that the human ovum remained free in the uterine cavity for the next six days (Teacher, 1926) being nourished by the secretion of the uterine glands ('uterine milk'). It is now known that the human ovum starts to implant about the seventh day since the youngest human embryo thus far studied (seven and a half days), is already superficially attached to the endometrium. It is then in the blastocyst stage; the zona pellucida has disappeared. The embryonic pole of the trophoblast comes in contact with the epithelium, usually on the anterior or posterior wall of the uterus, and the epithelial cells are broken down by the trophoblastic cell secretion. That part of the trophoblast in contact becomes greatly thickened and shows two kinds of cells: (*a*) peripheral syncytiotrophoblast cells, that is, a layer where cell boundaries are not distinct, which actively erodes and penetrates the endometrium; and (*b*) cytotrophoblast cells forming a layer next to the cavity of the blastocyst. The syncytiotrophoblast cells proliferate rapidly, actually erode and digest the endometrial stroma, and soon they form a thick zone of anastomosing strands with spaces or lacunæ between them. The lacunæ contain broken down endometrial cells

and some maternal blood derived from eroded uterine vessels. While these events take place the developing blastocyst sinks into a cavity in the substance of the endometrium, the implantation cavity. The site of entry into the endometrium becomes obliterated, first by a plug of fibrinous material and later, by re-epithelialization from the surrounding intact uterine cells. This mode of implantation is termed interstitial.

Continued activity of the cells of the syncytiotrophoblast results in further destruction of maternal tissue and opening up of blood vessels so that the lacunar spaces become progressively filled with maternal blood. A few days after implantation commences there is a slow circulation of maternal blood through the lacunæ of the trophoblast. Before this time the developing embryo depends for its nutrition upon the absorption of broken down endometrial stroma cells. Certain of these, termed decidual cells, contain much glycogen and fat and are prominent around the implantation cavity. This type of nutrition is called embryotrophic. When, however, maternal blood flows through the syncytial lacunæ of the implantation cavity a hæmotrophic form of nutrition for the embryo is established.

When the ovum has become implanted in the endometrium the destructive powers of the syncytiotrophoblast gradually diminish and beyond the zone of destruction there is reaction on the part of the maternal tissues to hinder the erosive activities of the growing blastocyst.

In the normal course of events the ovum becomes embedded near the fundus of the uterus, but in certain cases it wanders and implants itself in the lower part of the uterus near the cervix. When later the placenta is formed, it will partly or completely cover the internal os of the uterus, and the important clinical condition of placenta prævia results. Some-

times the ovum may be retarded in its journey towards the uterus and will attempt to embed itself in the tubal mucosa. The embryo develops for a short time but the condition usually terminates by the rupture of the tube, a grave surgical emergency.

The Decidua.—During the process of implantation the developing embryo has come to lie in a little cavity in the endometrium which, altered somewhat in character, is now known as the decidua. Different names are applied to various regions of this: thus the decidua immediately deep to the implanted ovum is the decidua basalis, that covering the developing embryo is the decidua capsularis and the remainder which lines the uterine cavity is the decidua parietalis.

Formation of Chorionic Villi.—The chorion may be defined as the trophoblast along with its somatopleuric lining of extra-embryonic mesoderm. It is through this simple type of chorion that nourishment passes by diffusion in the early stages of implantation, but, with increasing differentiation and the formation of an early embryonic circulation, the chorion undergoes structural modifications leading eventually to the formation of the placenta. The strands of syncytiotrophoblast which form the boundaries of the lacunæ form the primary chorionic villi. These soon show a core of cytotrophoblast and commence to branch. Strands of extra-embryonic mesoderm appear within the cytotrophoblast of the villi and these shortly become continuous with the layer of extra-embryonic mesoderm forming the deeper part of the chorion. It is disputed whether the mesodermal core of the villus arises in situ by delamination from the cytotrophoblast or whether it actively invades the solid villus from the chorionic aspect.

About the end of the third week of development (twenty to twenty-one days) blood vessels differentiate in situ in the mesodermal cores of the villi (Hertig,

1935) and become connected with other vessels which are laid down in the chorionic mesoderm. These in turn become linked up with the primitive intra-embryonic circulation by vessels (allantoic, see p. 35) which run to the embryo in the body stalk. These villi become more complex by branching. Some of

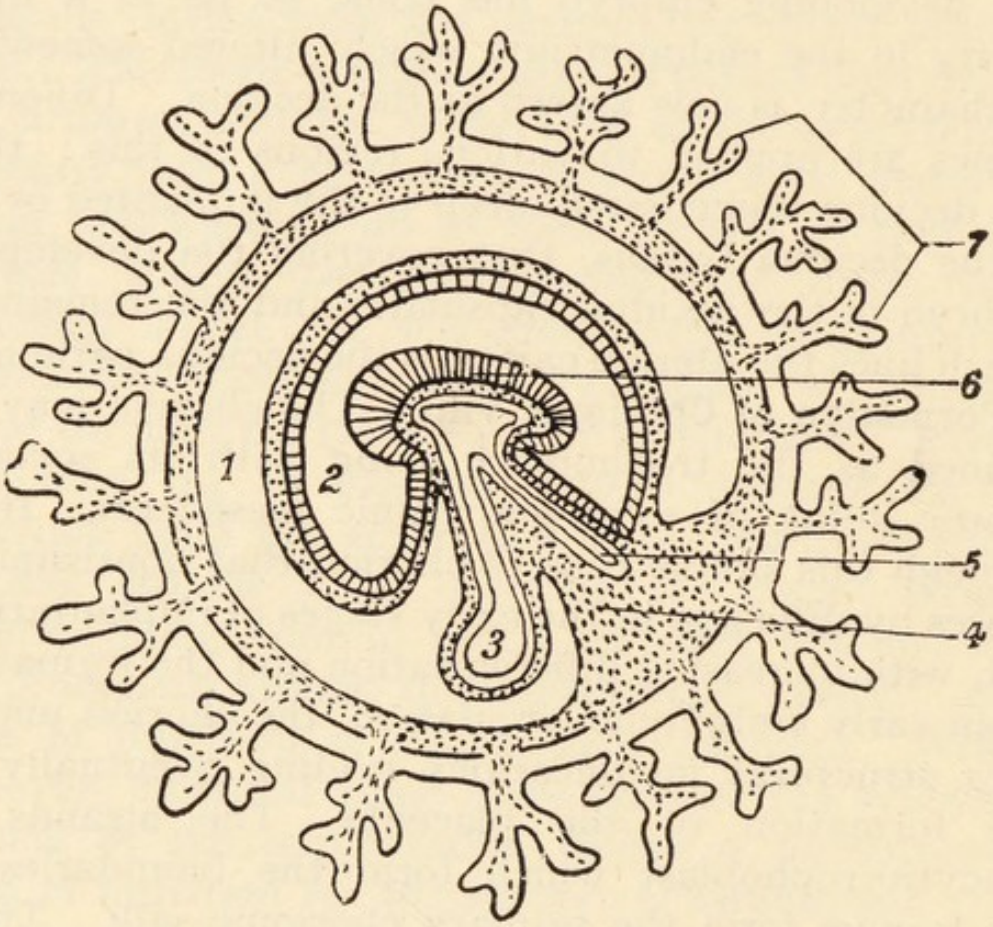

FIG. 8.—LONGITUDINAL SECTION OF EARLY EMBRYO AND MEMBRANES.

1, Extra-embryonic cœlom; 2, amniotic cavity; 3, yolk sac; 4, body stalk; 5, allantoic duct; 6, embryonic disc; 7, chorionic villi.

them pass right through the peripheral layer of syncytiotrophoblast which bounds the now confluent lacunæ, and are attached to the decidua. These are termed anchoring villi, but the majority of the villi hang free in a blood-filled space, the intervillous space, in which maternal blood slowly circulates. There is no communication between this maternal

blood and the embryonic blood cells in the vessels of the villi. The barrier of tissue between the two circulations is the *placental membrane* (see later).

The villi are at first scattered over the surface of the entire chorion, and it is then known as the chorion frondosum. During the fourth month the villi disappear from that part of the chorion related to the decidua capsularis, this portion being termed the chorion læve. The persisting part of the chorion frondosum becomes transformed into the mature discoidal placenta.

The Placenta.—In the human subject the placenta is a disc-like, flattened cake with the chorion attached to its margins. The fœtal surface is loosely covered by the amniotic sac and gives attachment to the umbilical cord. Between the amnion and the fœtal surface of the placenta are found large vessels, the major branches of the umbilical (allantoic) arteries and vein. From the uterine aspect it can be seen that the placenta is subdivided into a number (15 or more) of areas by septa. These areas are called cotyledons and each corresponds to a bunch of chorionic villi. At birth the placenta is about 20 centimetres in diameter, some 3 centimetres in thickness and weighs about 500 grams. The attachment of the umbilical cord is usually eccentric. Sometimes the attachment of the cord is to the outer margin of the placenta forming the so-called battledore placenta; in other cases the cord sub-divides before reaching the placenta giving rise to the placenta furcata. The vessels too, may spread out in the investing membranes instead of at the placental area, and form what is known as the velamentous placenta. Accessory lobules of the placenta separated from the main mass are not uncommon (placenta succenturiata). They probably arise from abnormal persistence of a group of villi of the chorion læve.

Functions of the Placenta.—The placenta functions in a triple capacity; it isolates the fœtal from the maternal organism so that the blood stream of each remains distinct; it permits the exchange of nutritive substances from the maternal to the fœtal circulation, and of waste products from the fœtal to the maternal; hormones probably also pass from the mother to the child; and the placenta itself elaborates hormones (œstrogens) which pass into the maternal bloodstream, and of which large quantities are found in the urine of pregnant women.

The cellular layers which separate the maternal blood in the intervillous spaces of the placenta and the fœtal blood in the chorionic capillaries obviously determine the rate of transmission of substances from the one circulation to the other. These cellular layers are collectively known as the placental membrane. During the latter part of gestation there is a progressive thinning of this placental membrane due to disappearance of the cytotrophoblastic layer of the villi, which are then clothed only by thinned-out syncytium. Without any great increase in size the placenta becomes functionally more efficient. Gellhorn, Flexner and Hellman (1943) have been able to study the transfer of radio-active sodium across the human placenta at various stages and find that the permeability to this substance is increased about seven-fold in the full-term placenta as compared with that of the tenth week of gestation.

The Amnion.—The amniotic cavity is commencing its formation in the eight day human ovum (p. 15). In the twelve-day ovum it is seen to lie between the ectodermal cells of the embryonic disc and a layer of flattened epithelial cells overlying this and continuous with its margin. The outer surface becomes covered with extra-embryonic splanchnopleuric mesoderm. Extension of the extra-embryonic cœlom separates

the amnion from the inner surface of the chorion except at the caudal end of the embryonic disc where a mass, the body stalk, remains (see Fig. 8). When the embryonic head, tail and lateral folds arise, the line of attachment of the amnion is carried ventrally, so that it appears to become constricted and the embryo appears to rise up in the amniotic cavity. The amnion is growing actively and its cavity is increasing in size. Finally, its walls come in contact with the inner aspect of the chorion and the extra-embryonic cœlom is thus obliterated. With this growth the amnion comes to cover the outer aspect of the body stalk and its contained structures (yolk sac, allantois and allantoic vessels) which is now known as the umbilical cord.

The Amniotic Fluid.—The amniotic cavity contains fluid from the time of its first formation. This fluid is derived from the walls of the cavity. In the later stages of pregnancy fœtal urine is added to the amniotic fluid. The body stalk elongates considerably in the formation of the umbilical cord so that the embryo floats in the amniotic fluid suspended by it, and is thus mechanically protected against sudden shocks, blows or pressure. The fluid assists in the maintenance of a constant environmental temperature for the fœtus and allows of its free movements *in utero*. During parturition, the fluid helps to dilate the cervix uteri, acting mechanically within the amniotic sac as a fluid wedge.

At full term about 1·5 litres of amniotic fluid are present, but the volume relative to the volume of the fœtus has diminished somewhat in the latter one-third of pregnancy. Flexner and Gellhorn (1942) using radioactive sodium and heavy water have shown that, in the guinea-pig, at least, there is constant exchange of these substances between the maternal circulation and the amniotic fluid. The exchange of

water is such that a volume equal to that of the amniotic fluid is exchanged every hour.

While the normal volume of the amniotic fluid is about 1·5 litres, an increase (hydramnios) or a decrease (oligamnios) may be found. In the latter event difficulty in parturition may arise.

The Yolk Sac.—The formation of the primary yolk sac and its later diminution in size with the development of the extra-embryonic cœlom has already been mentioned (p. 19). In the later part of the third week of development areas of angiogenesis are found in the splanchnopleuric mesoderm (extra-embryonic) which clothes the yolk sac, and soon a network of vessels covers its surface. These become organized as paired vitelline arteries and veins which link up with the early intra-embryonic circulation. The yolk sac is concerned during early development with transfer of nutritive material from the trophoblast to the embryo, but this function is only transient until the chorionic villi become vascularized. The further fate of the vitelline vessels is considered on page 114.

When the embryonic disc becomes folded into a cylindrical embryo the large yolk sac naturally becomes constricted at the site of the future umbilicus and a portion of it becomes incorporated in the body of the embryo as the entodermal lining of the primitive gut. This part is connected with the remainder of the yolk sac (definitive yolk sac) by an elongated duct buried in the mesoderm of the body stalk (vitelline duct; see Fig. 8). These two structures later degenerate and disappear; the yolk sac may usually be found, however, as a little vesicle situated towards the placental end of the umbilical cord until the fifth or sixth month of pregnancy.

The Allantois.—During the third week of development, a diverticulum grows into the mesoderm of the body stalk from the caudal wall of the yolk sac.

This is known as the allanto-enteric diverticulum or allantois. This grows towards, but does not reach, the chorion, since it is a rudimentary structure in the human. Paired arteries and veins of great importance arise alongside it in the mesoderm of the body stalk. These form a connection between the vessels of the chorion and those of the embryo and are termed the umbilical arteries and veins.

The Umbilical Cord.—The umbilical cord arises by the elongation of the body stalk. Fig. 8 shows how it is formed. It is formed mainly of mesoderm covered externally by the amnion. In section this mesoderm is seen to be loosely arranged in a jelly-like mass (Wharton's jelly) and has embedded in it the umbilical vessels and the vitelline and allantoic ducts. One of the umbilical veins (the right one) and the vitelline duct soon disappear. The allantoic duct persists as a microscopic structure in the proximal part of the cord until full term. At this time the cord is a long twisted rope-like structure about 55 centimetres in length. It shows well-marked spirals running from left to right; these spirals are probably caused by the vessels contained within it, growing more rapidly than the matrix of the cord. The length of the cord varies and may be as little as 10 or 15 centimetres, but sometimes it is excessively long and may measure as much as 105 centimetres.

CHAPTER V

FORMATION OF THE EMBRYO. DETERMINATION OF AGE

At the end of the third week the human embryo consists of three layers of cells, ectoderm, mesoderm and entoderm. The notochord has been laid down, thus establishing an antero-posterior axis and bilateral

symmetry upon the germ disc. Passing reference has been made to a series of foldings which convert the trilaminar germ disc into a cylindrical embryo and certain changes connected with this process must now be further considered.

Formation of Head Fold.—At the anterior end of the notochord the embryonic ectoderm and entoderm are in contact, no mesoderm intervening. This is the future bucco-pharyngeal membrane. The lateral plate mesoderm of each side becomes continuous in front of this area as the protocardiac area in which the heart tubes develop. In the early somite stages of development these two areas become bent ventrally so that the protocardiac area becomes tucked in under the anterior end of the notochord and separated from it by a portion of the intra-embryonic entoderm, the fore-gut. This is bounded anteriorly by the bucco-pharyngeal membrane which forms the floor of a little surface depression of the anterior end of the embryo called the stomatodæum. These changes are shown in Fig. 9.

Another result of the folding at the head end of the embryo is that the mesoderm which in early stages lay anterior to the protocardiac area comes now to occupy a position caudal to the pericardium and ventral to the fore-gut. This mass of mesoderm is known as the septum transversum.

Formation of Tail Fold.—At the posterior end of the embryonic disc behind the primitive streak there is a second area where no mesoderm intervenes between ectoderm and entoderm. This is the cloacal membrane. Commencing in the early somite stages this area becomes folded in, ventral to the caudal portion of the intra-embryonic entoderm. This is the tail fold and the entoderm dorsal to it is the hindgut.

While the head and tail folds are being formed, the

lateral parts of the embryonic disc also fold ventrally and now the general form of the embryo becomes

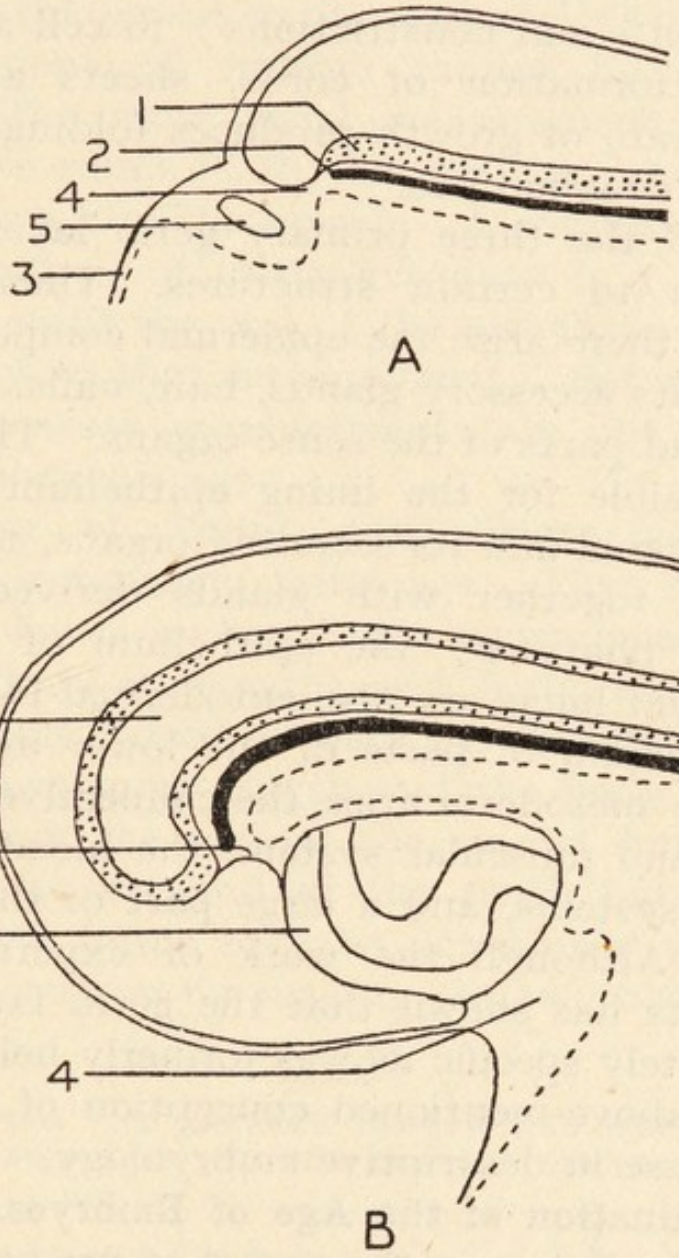

FIG. 9.—DIAGRAM TO SHOW THE FORMATION OF THE HEAD FOLD. (Adapted from Hamilton, Boyd and Mossman.

A.—Late presomite stage. 1, Neural plate; 2, notochord; 3, yolk sac entoderm; 4, bucco-pharyngeal membrane; 5, pericardial cavity. B.—20 somite stage. 1, Neural tube; 2, bucco-pharyngeal membrane; 3, pericardial cavity; 4, septum transversum.

established. The cells of the germ layers begin to take on special characters and to form the primordia of the definitive structures of the adult. In these

changes, which are termed organogenesis, various processes may be observed ; multiplication and migration of cells takes place, and this leads to localized enlargements and constrictions ; to cell aggregations and the formation of cords, sheets and masses. Unequal rate of growth produces foldings, invaginations and evaginations.

Each of the three primary germ layers normally gives rise to certain structures. Thus, from the ectoderm there arise the epidermal component of the skin and its accessory glands, hair, nails, the nervous system and parts of the sense organs. The entoderm is responsible for the lining epithelium of the alimentary canal and its secreting organs, the liver and pancreas, together with glands derived from the primitive pharynx ; the epithelium of the larynx, trachea and lungs are also entodermal in origin as is the epithelium of parts of the lower urinary tract. From the mesoderm arise the connective tissues, the skeletal and muscular system, the blood and lymph vascular systems, and a large part of the urogenital system. Although the work of experimental embryologists has shown that the germ layers are not so absolutely specific as was formerly held, nevertheless the above-mentioned conception of their fate is of great use in descriptive embryology.

Determination of the Age of Embryos.—There are three main phases in the period of pre-natal development, that of the ovum, the embryo and the fœtus. During the first three weeks after fertilization the developing individual is referred to as an ovum. At the beginning of the fourth week the somites commence to appear, and from this time until the end of the eighth week is the embryonic phase. During this time, the main organ systems are established. The fœtal phase extends from the end of the second month until birth and during this time histo-

genetic changes are the most marked feature of development.

Embryos of the same age vary somewhat in their degree of development so that estimations of age from the dimensions of embryo cannot be absolutely accurate. The most usual measurement employed is the crown-rump (C.R.) length, *i.e.*, the distance from the vertex to the breech. A convenient rule is that the embryo of thirty-five days is 5 mm. C.R. length and until the end of the eighth week it adds 1 mm. daily to that measurement. Before the end of the fifth week measurements are not a reliable guide to embryonic age.

Estimation of Fœtal Age.—There are several methods of estimating fœtal age. That most commonly employed is based on measurement of the body length (C.R. length) and body weight. The following table (based on data by Streeter) gives the average crown-rump length and the body weight at intervals from the end of the second lunar month until birth at the end of the tenth lunar month. The age of a fœtus may be determined with a fair degree of accuracy by making the two observations.

TABLE I

TABLE SHOWING THE AVERAGE LENGTH AND WEIGHT OF THE HUMAN FŒTUS AT THE END OF EACH LUNAR MONTH.

Age in Lunar Months.	*C.R. Length in mm.*	*Weight in grams.*
End of 2nd month	23·0	1·25
End of 3rd month	64·0	20·0
End of 4th month	116·0	108·0
End of 5th month	164·0	316·0
End of 6th month	207·0	630·0
End of 7th month	245·0	1050·0
End of 8th month	284·0	1680·0
End of 9th month	324·0	2470·0
End of 10th month	363·0	3400·0

An estimation of fœtal age may also be made by studying the centres of ossification as seen, for example, by X-ray examination. Some data on ossification periods are given on page 175, but this method is of limited application and the results are probably not so accurate as simple estimation of length and weight. If details of the menstrual history of the mother are available, the age of the fœtus may be calculated if it is remembered that ovulation occurs about fourteen days before the *first* day of the first missed menstrual period. There is sometimes, however, a scanty menstrual flow after conception has occurred which may introduce an error in the patient's recollection of her menstrual history.

CHAPTER VI

THE SKIN AND ITS ACCESSORY STRUCTURES

The Skin.—The two parts of the skin develop from different sources, the epidermis from the ectoderm, and the dermis from the mesoderm. At first the epidermis consists of a single layer of cubical cells, but these rapidly proliferate and by the fifth week have arranged themselves in two layers, an outer or epitrichium, and an inner or epidermis proper. The cells of the epitrichium are irregularly dome-shaped with flattened margins and vesicular nuclei. About the sixth month this layer is cast off and its degenerate cells mixed with the secretion of the sebaceous glands form the vernix caseosa, a substance which covers the fœtus until birth and is supposed to protect it from maceration while it floats in the amniotic fluid. The cells of the epidermis proliferate and the more superficial ones become flattened and cornified and give rise to the stratum corneum. The deepest

layer of ectodermal cells forms the stratum germinativum. Superficial to this a layer of granular cells, the stratum granulosum, appears, and superficial to this again, there is a layer of clear cells, the stratum lucidum. These two strata vary greatly in their degree of development in different parts of the body. Differentiation of the mesodermal portion of the skin (the corium) begins in the third month of fœtal life and up-growths of the compact corium into the epidermal layers form the characteristic dermal papillæ.

The Nails.—The nails begin to develop towards the end of the third fœtal month in relation to shallow epidermal folds at the tips of the digits. At the fifth month, the deep surface of the proximal part of each nail fold (the nail bed) gives rise to a plate of compact keratinized cells, the nail plate, which is at first buried in the substance of the stratum corneum. This is pushed forward towards the tip of the digit by continual proliferation of the nail bed which extends distally to the convex border of the lunula. At first, the nail is covered by the outer layers of the stratum corneum but this disappears except at the base of the nail where it forms the eponychium. A similar epidermal thickening is found under the free border of the nail and is known as the hyponychium. During development the nails migrate from the tips of the digits to the dorsum carrying with them the associated palmar or plantar nerves.

The Hair.—About the third month the first sign of hairs may be seen as thickenings of the stratum germinativum of the epidermis which proliferate and form cylindrical ectodermal downgrowths into the corium. The extremities of these become club-shaped and the thickened lower end of each club moulds itself over the summit of a small papilla developed in the mesodermal corium. Proliferation

of the central epidermal cells next the papilla results in a rod-like upgrowth, the cells of which become spindle-shaped and keratinized and passing to the surface of the body form the hair shaft. The outer epidermal cells become cuboidal and form the epithelial wall of the hair follicle with which a sebaceous gland is associated (*vide infra*). The hairs first formed during the fœtal period are called " lanugo " hairs and are cast off at birth. The coarser hair of the adult arises from new follicles.

Sebaceous Glands.—Solid outgrowth of cells from the epidermis grow from the lining cells of the hair follicles during the fifth fœtal month ; they penetrate into the mesoderm of the corium, and their free ends soon become lobed. The central cells undergo fatty degeneration and pass into the hair follicles as sebaceous secretion. The peripheral cells form the lining of the gland, and by multiplication give rise to new generations of central cells, and these in turn degenerate to form the sebum (" holocrine " secretion).

Sudoriferous Glands.—The sudoriferous or sweat glands appear about the fifth month as solid columnar ingrowths from the deep layer of the epidermis into the mesoderm. The great majority are separate from the hair follicles. In the sixth and seventh months the ingrowths become convoluted in their deeper parts and the central cells disappear to give a lumen. This does not open on the surface until the surface epidermal cells of the skin are shed. The outer cells of the epidermal ingrowths become transformed into smooth muscle cells which are therefore ectodermal in origin.

Mammary Glands.—The mammary glands are usually considered to be modified sweat glands. The primordia appear as two thickenings of the ectoderm, one on each side of the trunk during the sixth week of development ; they are known as the

milk streaks. Each streak extends from the axillary region above, to the inguinal region below, but very soon in the human the lower two-thirds disappear. Somewhat later the upper portion of the remainder regresses and a small portion in the pectoral region alone persists. This little thickened plaque of ectoderm sinks below the level of the surrounding ectoderm and about the fifth month some fifteen or twenty outgrowths grow from it into the mesoderm. Each is the primordium of a lobe of the breast and becomes canalized to form a lactiferous duct. The blind terminal parts of these ducts branch and the terminal parts become dilated as acini. The epidermal plaque where the lactiferous ducts open to the surface becomes everted to form the nipple shortly before birth. A certain amount of secretion ("witch's milk") composed of fatty degenerating epithelial cells may sometimes be expressed from the nipple for a few days after birth. The mammary glands normally remain in the infantile condition in the male. In the female, the area of the areola around the nipple becomes elevated at puberty and the breast tissue is much increased by repeated branchings of the lactiferous ducts. Deposition of fat between the epithelial structures causes the breast to assume the rounded contour of the adult.

Anomalies of Development of the Breast.—(1) Supernumary glands (hypermastia) or nipples (hyperthelia) are not uncommon in both sexes. They may occur in any part of the line of the original milk streak. In rare instances a supernumerary breast may be functional.

(2) Gynæcomastia is another developmental anomaly in which a male develops a mammary gland resembling that of the virgin female.

(3) Absence of the mammary gland (amastia) is a rare condition.

CHAPTER VII

THE NERVOUS SYSTEM

The Central Nervous System.—The primordium of the central nervous system appears in pre-somite embryos as a mid-line thickening of the ectoderm in front of Hensen's node. This is the neural plate. The margins of the thickening grow more rapidly than the central portion, and they become raised above the general level of the surrounding ectoderm as the neural folds; the groove between them is the neural groove. With further growth fusion between the neural folds commences, first towards the middle of the embryo and extending from there to the cranial and caudal extremities. Thus is formed the neural tube which presently loses its connection with the ectoderm and occupies a mid-line position just dorsal to the notochord. A chain of ectodermal cells appears in the angle between the neural tube and the general body ectoderm. It is known as the neural crest and provides material for the sensory ganglia of the cranial and spinal nerves. The cells of the neural tube are at first columnar in shape, and proliferation of them makes the wall of the tube several cells thick and the cells are so arranged that the nuclei are aggregated near the central canal while the outer part of the neural tube is made up mainly of cytoplasm. With further development the neural tube shows three zones; from within outwards there are the ependymal, the mantle and the marginal zones. Proliferation of the ependymal cells gives rise to neuroblasts which form the definitive neurons, and spongioblasts from which the neuroglia, or supporting tissue of the central nervous system, arises.

Myelination of the nerve fibres begins in the human fœtus of fourteen weeks gestation, and is not completed until eight months or more after birth (Keene and Hewer, 1931). It proceeds from the nerve cell

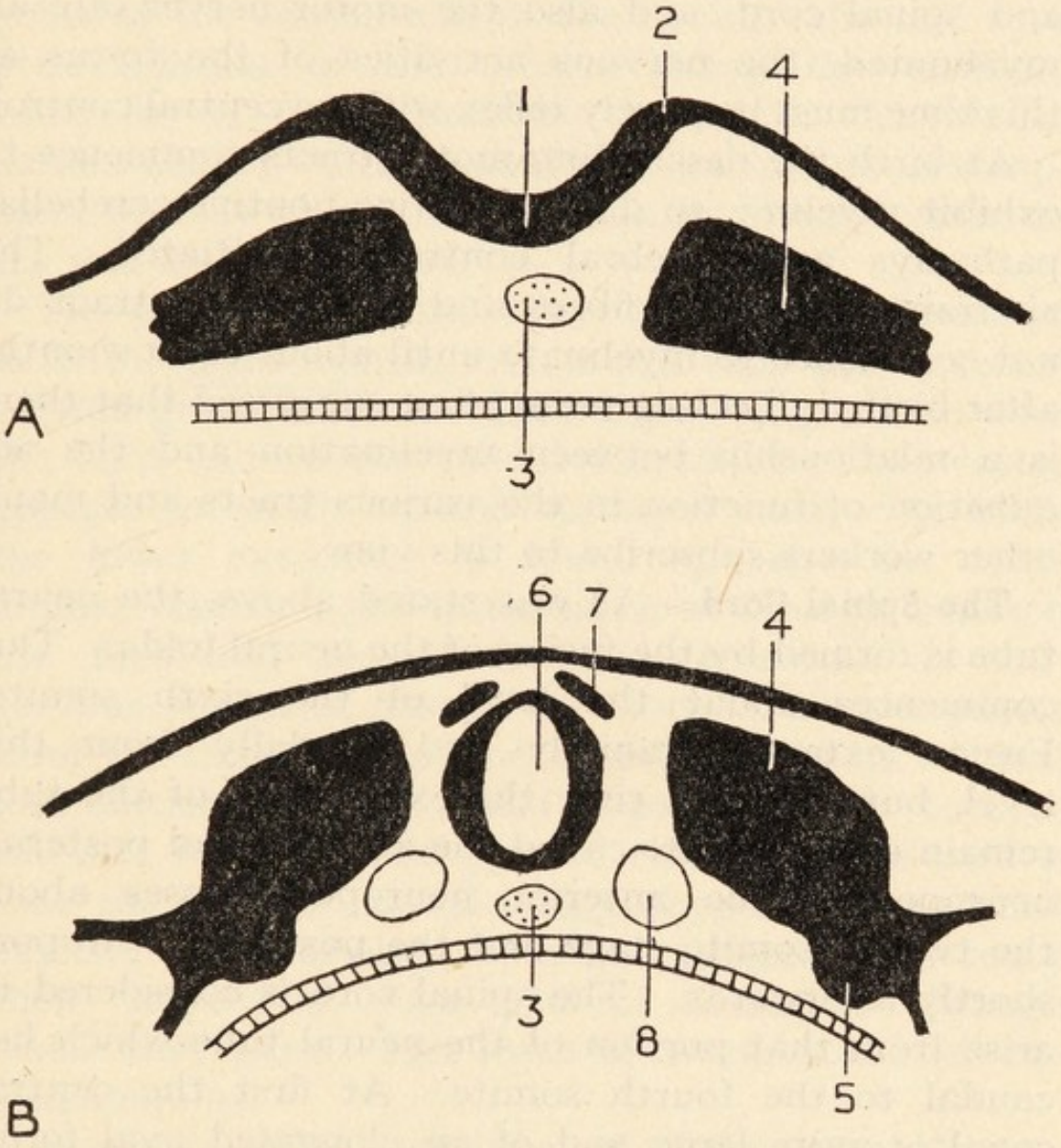

FIG. 10.—TWO STAGES IN THE DEVELOPMENT OF THE NEURAL TUBE.

1, Neural plate; 2, neural fold; 3, notochord; 4, somite; 5, intermediate cell mass; 6, neural tube; 7, neural crest; 8, dorsal aorta.

along the length of the fibre. It is first observed in the sensory pathways and the motor fibres of the cranial and spinal nerves. In the fœtus of twenty-eight weeks all the important sensory tracts are myelinated with the exception of such connections as

Lissauer's bundle and the external arcuate fibres from the nuclei gracilis and cuneatus to the cerebellum. At this stage, the long motor tracts are not myelinated, but as the association paths in both the brain stem and spinal cord, and also the motor nerves, are all myelinated, the nervous activities of the fœtus at this time must be purely reflex with no central control.

At birth the descending motor tracts commence to exhibit myelin ; so do the cortico-pontine-cerebellar pathways and cerebral control is initiated. The aberrant pyramidal fibres and olivo-spinal tract do not commence to myelinate until about eight months after birth. Flechsig (1895) first suggested that there is a relationship between myelination and the acquisition of function in the various tracts and many other workers subscribe to this view.

The Spinal Cord.—As was stated above, the neural tube is formed by the fusion of the neural folds. This commences about the level of the sixth somite. Fusion extends cranially and caudally from this level, but for some time the extremities of the tube remain open and are called the anterior and posterior neuropores. The anterior neuropore closes about the twenty somite stage and the posterior neuropore shortly afterwards. The spinal cord is considered to arise from that portion of the neural tube which lies caudal to the fourth somite. At first the central canal is quite large and of an elongated oval form. Cell proliferation causes the lateral walls to thicken while the roof and floor remain thin. The cavity takes on a rhomboidal shape in transverse section and a well-marked longitudinal groove on each side, the sulcus limitans, marks off a dorsal alar (sensory) lamina, and a ventral basal (motor) lamina in the lateral wall. The two laminæ increase in size and the alar laminæ bulge medially, obliterating the dorsal portion of the central canal. The site of their

apposition persists in the adult as the posterior median septum. The ventral portion of the canal thus forms the central canal of the adult. This reduction in the size of the central canal is not so great at the caudal end of the neural tube and so a little dilation of the central canal, the terminal ventricle, is found here in the adult. The basal lamina bulges ventro-laterally in its further development so that an anterior median furrow is formed in the mid-line of the cord.

The cord extends the whole length of the embryo until the third month. After this time the vertebral column grows much more rapidly in length than does the cord and so the caudal extremity of the latter appears to recede up the vertebral canal. At birth the lower extremity is found opposite the third lumbar vertebra, and in the adult at the disc between the first and second lumbar vertebræ. A non-nervous strand of tissue, the filum terminale, passes from the caudal tip of the spinal cord to its original termination at the dorsal aspect of the coccyx. Another result of this upward retreat of the cord is that the lumbar, sacral and coccygeal nerves must descend for varying distances before they reach their respective intervertebral foramina through which they pass. This leash of nerves is termed the cauda equina.

Summary of the Development of the Spinal Cord.—(1) The spinal cord is developed from a simple tube of ectoderm derived from the mid-dorsal line of the embryo, termed the neural tube.

(2) That portion of the neural tube caudal to the fourth somite forms the spinal cord.

(3) At first single-layered, the tube soon presents three zones, ependymal, mantle and marginal.

(4) Cells of the ependymal layer proliferate and migrate into the mantle layer, where they differentiate

into neuroblasts and spongioblasts. The neuroblasts give rise to nerve cells and their processes while the spongioblasts form the supporting framework, the neuroglia.

(5) The nerve cells arrange themselves in two groups in the cord, a dorsal sensory group, and a ventral motor group. These form respectively the alar and basal laminæ separated by the longitudinal running sulcus limitans.

(6) The central canal is narrowed by the apposition in the mid-line of the alar laminæ to form the posterior median septum. The ventral portion of the original lumen persists as the central canal of the adult.

Anomalies of Development of the Spinal Cord.—These are considered with the anomalies of the brain on p. 59.

The Brain.—The brain is derived from that part of the neural tube in front of the fourth somite. In early stages there are three parts here where rapid growth takes place and so, even before the neural folds have united, three bulgings are found in this region. When the anterior neuropore has closed these bulgings are seen as three dilatations, the fore, mid and hind-brain vesicles. The closed anterior neuropore is represented by the lamina terminalis. The fore-brain region very early shows an evagination on either side. These are the optic bulbs, and their further development is considered in the section dealing with the special senses (p. 63). Much later the antero-lateral aspects of the original vesicle present two swellings which increase rapidly in size, and form the two cerebral hemispheres. These, along with that part of the original vesicle lying between them, constitute the telencephalon. The remainder of the original fore-brain vesicle is termed the diencephalon. The second of the primary brain vesicles remains as the mesencephalon. The hind

brain vesicle becomes divided into two portions, the metencephalon which gives rise to the cerebellum and pons, and the myelencephalon from which develops the medulla oblongata. The cavities of the

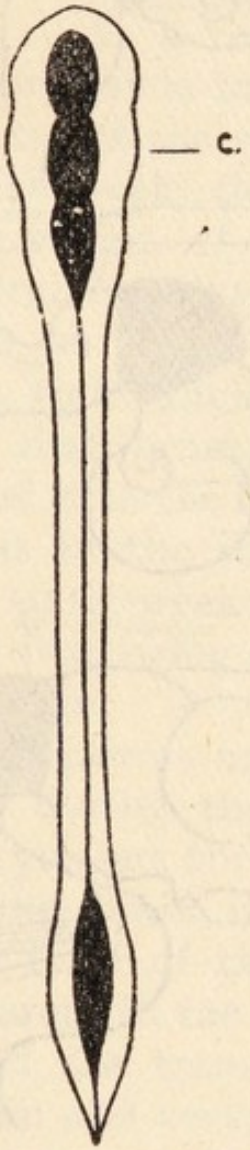

FIG. 11.—DIAGRAM TO SHOW THE FORM OF THE CENTRAL NERVOUS SYSTEM BEFORE FUSION OF THE EXTREMITIES OF THE NEURAL GROOVE.

The three swellings at the cephalic end (*c*) indicate the form of the so-called primary brain vesicles.

three primary brain vesicles are represented in the adult as follows :

The cavity of the third primary brain vesicle becomes the fourth ventricle.

The cavity of the second primary vesicle is transformed into the aqueduct of the mid-brain.

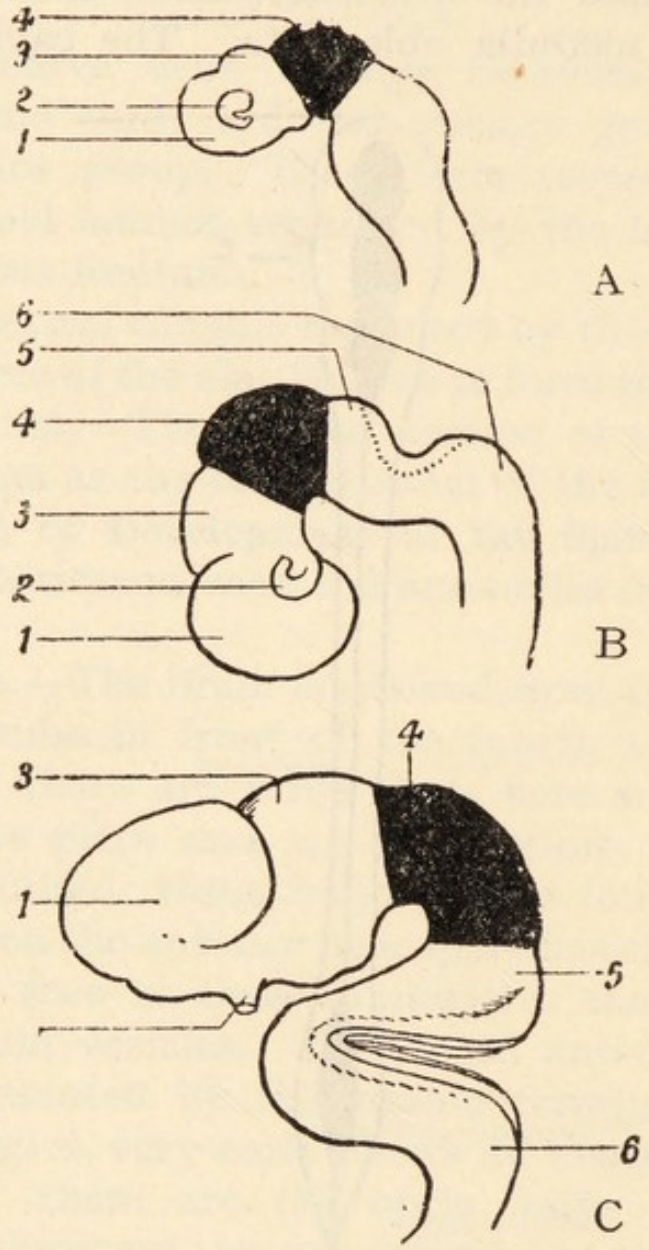

FIG. 12.—THREE FIGURES TO SHOW THE CHANGES PRODUCED IN THE FORM OF THE DEVELOPING BRAIN BY THE BRAIN FLEXURES.

1, Cerebral hemisphere ; 2, optic evagination ; 3, diencephalon ; 4, mesencephalon ; 5, metencephalon ; 6, myelencephalon. A. Mid-brain flexure ; B, cervical flexure ; C, pontine flexure.

The cavity of the first primary vesicle becomes the third ventricle, and is continuous through the interventricular foramina with the lateral ventricles.

During its early growth the future brain region of the neural tube becomes bent upon itself at three places (see Fig. 12). These are the three primary brain flexures. The first appears in the region of the mid-brain during the fourth week and is called the mid-brain flexure. As a result of this flexure, the first primary brain vesicle takes up a position at right angles to the axis of the second brain vesicle. Shortly after this (fifth week) the second or cervical flexure occurs in the region of the future medulla. It is caused by ventral bending of the whole head region of the embryo, so that the axis of the mid-brain forms almost a right angle with the medulla, and the axis of the first brain vesicle takes up a position almost parallel with the latter. The third, or pontine flexure, occurs in the region of the metencephalon during the sixth week and is the reverse direction to the other two, being a ventral bending of the floor of the hind brain.

The first two brain flexures are the expression of changes taking place during the formation of the head end of the embryo, but the third flexure (pontine) is peculiar to the brain itself, and does not influence the external form of the head. The pontine flexure is not apparent in the adult brain because of the development of the transverse fibres of the pons, but the mid-brain and cervical flexures persist, although reduced in acuteness.

The Myelencephalon.—When the pontine flexure occurs it causes the roof plate of both the myelencephalon and metencephalon to become thinned out and expanded laterally. Thus the alar and basal laminæ lie in the ventral part of the myelencephalon. The cells of the basal lamina become segregated in several groups. Most medially are the cells of the hypoglossal nerve. More laterally are cells (branchiomotor) which form the nucleus ambiguus, lateral to

which again lie visceral efferent cells of the dorsal nucleus of the vagus. The alar lamina cells give rise to the gracile and cuneate nuclei, the nucleus of the tractus solitarius (branchial afferent) and part of the dorsal nucleus of the vagus (visceral afferent). A ventro-medial migration of alar lamina cells forms the olivary nuclei.

About the fifth week a transverse groove appears in the roof plate into which mesenchymal cells wander ; this groove deepens, blood vessels are differentiated from the mesenchyme and the choroid plexus of the fourth ventricle is formed. A mid-line evagination of the roof plate (Weed, 1917) becomes perforated as the foramen of Majendie and similar foramina arise in like manner in the lateral recesses of the fourth ventricle.

The Metencephalon.—The most medial cells in the basal lamina of this part of the neural tube form the nucleus of the sixth nerve. The intermediate (branchio-motor) cells make up the motor part of the seventh and fifth nerves while the lateral group of the basal lamina form the salivatory nucleus of the seventh. From the alar lamina come the cochlear and vestibular nuclei, and the sensory nucleus of the fifth nerve. The pontine nuclei are derived by migration of cells from the alar lamina both of the metencephalon and the myelencephalon.

The dorsal portions of the alar laminæ thicken on each side to form the primordium of the cerebellum. This thickened portion is termed the rhombic lip. The thickenings bulge into the fourth ventricle and also project dorso-laterally. Fusion in the mid-line gives rise to a thickening, the vermis, while by expansion dorso-laterally the cerebellar hemispheres are formed. The cerebellar cortex is formed from the cells in the mantle zone of the rhombic lip which proliferate and migrate into the marginal zone. The

dentate and other deep cerebellar nuclear masses arise by proliferations of the mantle layer *in situ*.

The Mesencephalon.—At a stage when the brain flexures have all been formed (sixth week) the mid brain is a prominent feature of the neural tube; but with further growth of the brain this portion increases less than adjacent parts and so becomes relatively less distinctive. The roof and floor plates as well as the lateral zones become greatly thickened and the cavity is thus reduced to a narrow channel, the cerebral aqueduct. The basal lamina cells form the nuclei of the third and fourth nerves, which are somatic motor, the Edinger-Westphal nucleus of the third nerve, however, representing visceral efferent cells. The cells of the alar laminæ migrate into the thickened roof plate to form the superior and inferior colliculi. The red nucleus is also believed to arise from alar lamina cells that migrate ventrally into the basal lamina.

The Diencephalon.—In the beginning of the sixth week, the diencephalon consists of roof and floor plates with thickened lateral walls. The lateral wall on each side shows a longitudinally running groove on the inner surface, the sulcus hypothalamicus. This was formerly believed to be a continuation of the sulcus limitans but it seems more probable that the latter terminates at the cephalic end of the mesencephalon and that the basal lamina of the neural tube is not represented in the diencephalon. A thickening on each lateral wall above the hypothalmic sulcus represents the primordium of the thalamus which grows rapidly and bulges medially into the diencephalic cavity, sometimes fusing across the middle line with its fellow of the opposite side. Above, an epithalmic sulcus limits the thalamus. An evagination in the mid-line of the roof near its junction with the tectum of the mid-brain is the

primordium of the pineal gland, and commissural fibres develop in the roof plate adjacent to this as the posterior and habenular commissures. Anterior to this region (epithalamus), the roof plate becomes thinned out (velum interpositum), and invaginated by vascular mesenchyme into the cavities of the third and lateral ventricles, as the choroid plexuses of these cavities.

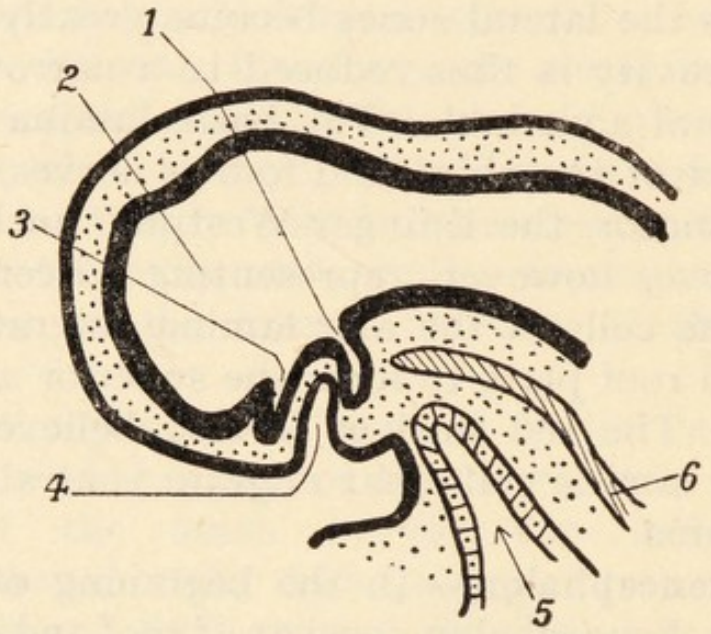

FIG. 13.—DIAGRAM OF THE EARLY DEVELOPMENT OF THE HYPOPHYSIS.

1, Infundibulum ; 2, fore-brain ; 3, optic chiasma ; 4, Rathke's pouch ; 5, foregut ; 6, notochord.

The external surface of the lateral wall of the diencephalon becomes largely hidden from view by the great overgrowth of the telencephalic vesicle, the only parts of it remaining in view in the adult being the geniculate bodies and the pulvinar of the thalamus.

The Hypophysis (Pituitary Gland).—In early somite stages a small ectodermal evagination is found in the roof of the stomatodæum in front of the buccopharyngeal membrane. This evagination, Rathke's pouch, extends towards the floor of the diencephalon.

During the sixth week a down-growth occurs from the floor of the diencephalon and comes into contact with the posterior surface of Rathke's pouch. This downgrowth, the infundibulum, gives rise to the posterior lobe and stalk of the adult hypophysis. Rathke's pouch loses its connection with the ectoderm and its cells proliferate and differentiate. The posterior wall of the original pouch forms the pars intermedia; the anterior wall becomes thickened and extends backwards as two wings on the lateral aspect of the posterior lobe, and the former lumen of the pouch is represented in the adult by a cleft in the gland. Some cells of the pars anterior grow along the stalk as the pars tuberalis. Differentiation of the cells in the anterior lobe commences about the third month when some acidophils may be detected. Basophils appear about a month later but full histological differentiation is not completed until after birth.

The Telencephalon.—The evaginations which form the primordia of the cerebral hemispheres are first seen during the sixth week of development and originally are in wide communication with the cavity of the third ventricle. The cerebral vesicle expands in all directions but least in the downward direction because the lower wall soon becomes thickened as the primordium of the corpus striatum. This expansion soon causes the diencephalon almost completely to be concealed from view, and the cerebral vesicles are separated from each other dorsally by a cleft filled with mesodermal tissue, the future falx cerebri. Here the medial wall of each vesicle is thin and becomes invaginated into the cavity by ingrowth of vascular mesoderm to form the choroid plexus of the lateral ventricle. This invagination extends backwards from the interventricular foramen as the choroidal fissure. The expanding hemispheres at

first grow in a caudal direction, but soon they are checked by the limiting tissue of the brain capsule, and the posterior poles change their direction and grow downwards and forwards as the temporal poles. Each growing temporal pole carries with it the choroid plexus of its own side, together with the fissure through which the latter enters the ventricle, and the choroidal fissure is thus continued around to the under and inner aspect of the temporal pole. The expansion of the hemisphere is further reflected in the formation of the inferior and posterior horns of the lateral ventricle.

The Corpus Striatum.—The corpus striatum first appears as a thickening of the floor of the cerebral vesicle at the end of the sixth week. The thickening bulges into the ventricle, and as that cavity becomes drawn out to attain its adult form so the striatal thickening elongates. Its original posterior part will thus later be found in the roof of the inferior horn. Next, axis cylinder processes running to and from the developing cerebral cortex split up the corpus striatum into two parts; dorso-medially is a mass of cells from which the caudate nucleus is formed, while the ventro-lateral portion gives rise to the lentiform nucleus. The fibres traversing the corpus striatum will thus be the internal capsule. Continued thickening of the ventro-medial wall of the hemisphere causes fusion of it with the lateral aspect of the expanding thalamus in the diencephalon, which thus appears as a medial relation of part of the internal capsule and the caudate nucleus.

The Cerebral Commissures.—The principal cerebral commissures are the anterior commissure, the commissure of the fornix (hippocampal) and the corpus callosum. These are all developed in the lamina terminalis which, it will be remembered, is the closing plate of the anterior neuropore. The anterior com-

missure is the first to develop as a compact bundle of fibres in the ventral part of the lamina terminalis connecting the olfactory tract and hippocampal gyrus of one side with corresponding regions on the other.

Dorsal to the anterior commissure a second fibre bundle appears in the lamina terminalis to unite the two hippocampi. It is closely associated with the fornix which is a fibre system connecting the hippocampus with the hypothalamus, and later growth changes associated with the expansion of the corpus callosum cause it to shift caudalwards.

The corpus callosum appears as a small bundle of fibres at the dorsal end of the lamina terminalis. It connects the non-olfactory parts of the cerebral cortices, and as these increase in size more fibres are added to the corpus callosum and it expands both anteriorly and posteriorly. With this expansion, the upper part of the lamina terminalis is thinned out to form the septum lucidum.

The Cerebral Cortex.—In the early stages of its existence, the wall of the developing cerebral hemisphere presents ependymal, mantle, and marginal zones, but with migration of cells from the mantle layer into the superficial part of the marginal zone the primordium of the definitive cortex appears. This process does not occur simultaneously all over the hemisphere ; the cortex of the hippocampus appears first, then that of the pyriform area and lastly that of the neopallium.

The outer surface of the hemisphere is at first smooth but with increasing development and growth a pattern of convolutions bounded by sulci or fissures becomes established. The lateral sulcus commences about the fourth month of fœtal life in the following way. Part of the lateral surface of the hemisphere lying in relation to the corpus striatum appears to lag behind the rest in its growth. It is termed the

insula and becomes overgrown by opercular coverings from the frontal, parietal and temporal lobes and the lateral sulcus is the cleft between these opercula. About the sixth fœtal month the central, parieto-occipital, calcarine, and collateral sulci make their appearance and secondary and tertiary sulci become visible shortly before birth.

The Meninges.—There is no positive information regarding the origin of the inner meninges, the arachnoid and pia. The transplantation experiments of Harvey and Burr (1926) on the cerebrum of amphibian larvæ suggested these meninges to be of neural crest origin, but this has been denied. It seems fairly certain that the dura mater is developed by condensation in the mesenchyme surrounding the neural tube.

Summary of the Development of the Brain.—(1) The brain develops from that part of the neural tube cephalic to the fourth somite. Three primary swellings or brain vesicles form here.

(2) The original straight neural tube becomes bent by the mid-brain, cervical and pontine flexures.

(3) The first primary brain vesicle gives rise to two optic evaginations at a very early stage of development.

(4) At a later stage two further evaginations occur which form the cerebral hemispheres. Thickenings in the floor of these are the corpora striata.

(5) Most of the first primary brain vesicle forms the diencephalon. A thickening in each lateral wall is the thalamus. The anterior boundary is the lamina terminalis where the cerebral commissures are laid down.

(6) The second primary brain vesicle forms the mid-brain and its cavity becomes the cerebral aqueduct.

(7) The third primary brain vesicle forms the pons,

medulla, and cerebellum, and its cavity is the fourth ventricle.

Anomalies of Development of the Central Nervous System.—(1) Anencephaly is a condition where the neural folds fail to develop in the future brain region and the exposed nervous tissue undergoes degeneration. The cranial skeleton also fails to develop.

(2) Encephalocele is a hernia of brain tissue through a defect in the skull vault.

(3) Rachischisis is a condition where there is a cleft in the vertebral column with varying degree of defect in the underlying spinal cord.

(4) Meningocele is a condition where there is a herniation of the membranes through a cleft in the skull or vertebral column.

(5) Microcephaly is a condition where the brain is abnormally small.

(6) Congenital hydrocephalus, where cerebro-spinal fluid accumulates within the ventricles, may be due to anomalies in development of the pathway for circulation of this fluid such as obliteration of the cerebral aqueduct, or non-appearance of the foramina in the ependymal roof of the fourth ventricle. Failure of the mechanism for absorption of the fluid may be another cause.

The Spinal Nerves.—The anterior and posterior nerve rootlets arise from different sources. The anterior nerve root fibres grow out from basal lamina cells in the developing cord about the fifth week; the tips of these fibres perforate the surface of the cord and grow through the surrounding mesenchyme to unite with a myotome. During the sixth week the posterior nerve rootlets appear as centrally growing processes from neural crest cells which become arranged in groups along the spinal cord. These central processes enter the cord opposite the posterior horn of grey substance. The cells of the posterior

root ganglia are at first bipolar and later become T-shaped. Their distal processes grow out to unite with the anterior nerve root to form the spinal nerve. The neurilemmal sheaths of the spinal nerves are derived from migrating cells of the neural crest.

The spinal nerves are segmentally arranged and when the limb buds grow out from the body, each is invaded by nerve fibres of the body segments opposite which it arose. It is the anterior primary rami which are concerned in this ingrowth, and at the base of the limb bud loops occur between the successive anterior primary rami to form the brachial and lumbo-sacral plexuses.

The Cranial Nerves.—The cranial nerves may be subdivided into three groups on the basis of their developmental origin.

(1) The first group consists of the nerves of the special senses—olfactory, optic and auditory nerves. Since these develop in connection with the special sense organs and in a peculiar manner, they will be considered later (p. 63).

(2) A second group is made up of the trigeminal, facial, glossopharyngeal, vagus and accessory nerves. These nerves contain several components. Special visceral efferent fibres innervate the musculature derived from the branchial arches. In this way, the mandibular division of the trigeminal innervates the muscles of mastication derived from the first (mandibular) arch, and so on (see p. 76). General visceral efferent fibres pass to visceral muscle and glands. Sensory fibres correspondingly transmit general and special visceral afferent impulses, and there are a few somatic afferent fibres in the auricular branch of the vagus.

(3) The oculomotor, trochlear, abducent and hypoglossal nerves form a group of nerves which are essentially somatic efferent in nature. The first three

are distributed to the muscles of the orbit which are deemed, on comparative grounds, to be derived from three pre-otic myotomes. The hypoglossal nerve innervates the tongue musculature which is derived from the occipital somites.

The Autonomic Nervous System.—The primordia of the thoraco-lumbar gangliated sympathetic chains are laid down in the fifth week dorso-lateral to the aorta. The cells forming these chains migrate along the anterior primary rami. They are ectodermal and their site of origin is variously ascribed to the neural crest or the neural tube. Migration of cells from the thoraco-lumbar chains towards the heart, intestine, etc., gives rise to the visceral sympathetic ganglia. There are also extensions of the primitive chains upwards into the neck and downwards to the sacral region. The fibres of distribution from the sympathetic to the viscera and to the skin are arranged essentially in a segmental fashion.

Some of the ectodermal cells which are found in the primitive sympathetic chains become transformed into cells which have a characteristic reaction with chrome salts and hence are called chromaffin cells. These produce the sympatho-mimetic hormone adrenalin and are found related to many parts of the embryonic sympathetic system especially around the abdominal aorta. In post-natal life, practically the only chromaffin tissue that persists forms the medulla of the adrenal gland (see below).

The cells which form the para-sympathetic ganglia apparently arise within the neural tube and migrate peripherally along the nerves with which these ganglia are associated.

The Adrenal Gland.—The adrenal gland consists of two parts, cortex and medulla, which are embryologically quite distinct. The cortex is mesodermal in origin and is first seen at the 9 mm. stage (sixth

week) as a proliferation of the cœlomic mesothelium between the root of the mesentery and the upper end of the mesonephros. This mass of cells sink into the underlying mesenchyme and a few days later has added to its surface a second mesothelial proliferation. This second group of cells will form the permanent cortex of the gland, the first proliferation being the transitory or fœtal cortex which regresses during the first year after birth. Due to its presence the human adrenal is relatively large at birth. Histological differentiation of the permanent cortex into the classical zones, glomerulosa, fasciculata, and reticularis is not completed until some time after birth. Cells derived from the sympathetic system congregate at the medial side of the developing gland during the sixth and seventh weeks and then become surrounded by the cortical cells. They mainly become transformed into chromaffin cells but some give rise to ganglionic cells of the sympathetic system.

Summary of Development of the Peripheral Nervous System.—(1) The motor nerve fibres sprout out from cells of the neural tube and secondarily connect up with the myotomes.

(2) As the myotomes resolve themselves into the various muscles, each remains connected with its primitive segmental nerve.

(3) The posterior root ganglia are formed from cells of the neural crest which develop central processes growing into the neural tube and peripheral processes passing to the end organs.

(4) The cranial nerves (apart from the special sense nerves) develop as : (*a*) branchial arch nerves—the trigeminal, facial, glossopharyngeal, vagus, and accessory ; (*b*) somatic motor nerves—oculomotor, trochlear, abducent, and hypoglossal, which supply muscles derived from the "pre-otic" and occipital somites.

(5) The sympathetic system and the chromaffin bodies are formed from ectodermal migratory cells from either the neural crest or the neural tube.

(6) The adrenal gland has a double origin; the medulla is ectodermal being derived from chromaffin cells and the cortex mesodermal since it arises from the cœlomic mesothelium.

CHAPTER VIII

DEVELOPMENT OF THE ORGANS OF SPECIAL SENSE

The Olfactory Organ.—During the fourth week two ectodermal thickenings appear on the anterior surface of the head just below the developing forebrain. These are the olfactory placodes which soon become lodged in olfactory pits caused by upgrowth of the peripheral tissues. With the formation of the nose this placodal epithelium becomes lodged in its upper part and at the end of the seventh week nerve fibres are growing centrally towards the anterior end of the telencephalon. Connection being established, this part of the telencephalon becomes the olfactory bulb. Secondary neurons running from it backwards to the pyriform area constitute the olfactory tract.

The Eye.—The eye is derived from several primordia —general body ectoderm, neur-ectoderm and mesoderm.

The Optic Cup.—This is derived from the neural ectoderm of the first primary brain vesicle. Before the anterior neuropore has closed it may be recognised as a stalk-like evagination from the side of this part of the neural tube with an expanded blind extremity. This, the optic bulb, approaches the surface ectoderm

and its presence causes the formation of a thickening here which is the first rudiment of the lens. The thickening sinks below the general body surface and becomes pinched off as a little vesicle (see Fig. 14). Along with this separation of the lens vesicle from the surface ectoderm the optic bulb becomes invaginated into a cup in such a manner that the concavity of the cup is continued inwards along the under surface of the optic stalk. This groove is known as the fœtal fissure. The optic cup is now a double-layered structure and both layers of it will take part in the formation of the retina. Blood vessels pass forwards into the optic cup along the fœtal fissure, the margins of which fuse in the seventh week so that the blood vessels now run in the substance of the distal part of the optic stalk. These will eventually be the central artery and vein of the retina. The two layers of the optic cup come together obliterating the original cavity. The outer layer remains thin, pigment accumulates in its cells and it forms the pigmented layer of the retina. The inner layer of the cup becomes thicker and the anterior part of it (pars caeca or the part that does not develop rods and cones) lines the developing ciliary body and iris. The main posterior part becomes the retina proper and the junction between it and the pars caeca is marked by the ora serrata. The retina at first shows ependymal, mantle and marginal zones just like the neural tube. The ependymal zone, located next to the pigmented layer, elaborates rods and cones. Migration of cells and stratification of the retina follows so that by the seventh fœtal month all the layers found in the adult are to be seen. The axons of the ganglion cell layer grow backwards to the brain along the original optic stalk which thus becomes converted into the optic nerve.

The Lens.—The lens vesicle is a hollow sphere when

it becomes separated from the general ectoderm during the sixth week. The cells which form the posterior wall of the vesicle proliferate while those of the anterior wall remain as a single-layered cuboidal epithelium. With proliferation, the cells of the posterior wall elongate, bulge into the cavity, and eventually obliterate it. They become transformed

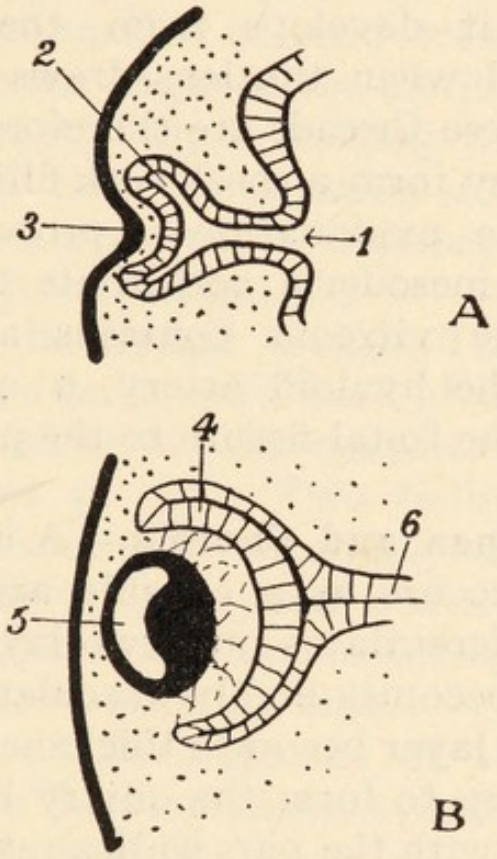

FIG. 14.—THE DEVELOPMENT OF THE OPTIC CUP AND LENS VESICLE.

1, Optic evagination ; 2, optic bulb in process of invagination ; 3, lens plate ; 4, optic cup ; 5, lens vesicle ; 6, optic stalk.

into the lens fibres, the cuboidal epithelium of the anterior wall of the vesicle being converted into the anterior lens epithelium. In further growth of the lens, proliferation is mainly at the equator so that it becomes a laminated structure. The developing lens is at first surrounded by a layer of mesodermal tissue in which blood vessels arise which are continuous with the artery of the fœtal fissure ; this investment is

termed the tunica vasculosa lentis. The vessels of the tunica begin to disappear after the seventh month of fœtal life and have usually completely gone at birth.

The Vitreous Humour.—The vitreous humour was formerly believed to be developed from the mesoderm which had insinuated itself into the optic cup with the development of the lens. T. H. Bryce (1908) claimed that it develops from the protoplasmic threads formed when the lens draws away from the optic cup. These threads are therefore ectodermal in origin, and they form a meshwork filling up the optic cup. The true explanation is probably that both ectoderm and mesoderm contribute to the vitreous. The embryonic vitreous contains a central canal having in it the hyaloid artery, a continuation of the artery of the fœtal fissure to the posterior surface of the lens.

Sclera, Cornea and Choroid.—A condensation of mesenchyme occurs as a capsule around the optic cup, which differentiates into two layers. The layer next the cup becomes highly vascular and forms the choroid. This layer becomes thickened at the margin of the optic cup to form the ciliary body. Anterior to this it fuses with the pars iridica retinæ to form the iris which is therefore partly ectodermal and partly mesodermal, the musculature of the iris probably arising from the ectodermal component. The outer mesenchymal layer differentiates into the sclera and cornea. The latter, becoming transparent, has added to its structure the overlying surface ectoderm. A fluid filled cleft, the anterior chamber, forms between the posterior surface of the cornea and the anterior surface of the iris. An important drainage space, the canal of Schlemm, appears just lateral to the margin of this chamber.

The Eyelids.—The eyelids develop as two folds of

ectoderm with a mesodermal core, above and below the cornea. First seen about the seventh week these folds fuse with each other in the tenth week and remain fused until late fœtal life. The mesenchymal core gives rise to the tarsal plates and muscles, while eyelashes and tarsal glands are derived from the ectoderm.

The Lachrymal Glands.—The lachrymal glands develop as a number of solid ectodermal buds from the upper outer angle of the conjunctival sac during the eighth week. By branching these buds become intermingled and canalization of the solid cords results in a gland with a number of ducts opening into the conjunctival sac.

The Naso-lachrymal Duct.—The naso-lachrymal duct develops as a solid cord of ectodermal cells at the line of fusion of the maxillary and fronto-nasal processes (see p. 77). Two bulbs develop at the conjunctival end, and becoming canalized, form the upper and lower lachrymal ducts. The cord itself acquires a lumen and opens below into the inferior meatus of the developing nose.

Summary of Development of the Eye.—(1) The eye begins to develop as an evagination of the first primary brain vesicle.

(2) This approaches the overlying ectoderm of the head region, causes a lens vesicle to be formed and pinched off from this, and then is invaginated as a cup-shaped structure.

(3) The outer layer of this optic cup forms the pigmented layer of the retina, while the inner layer thickens and differentiates into the nervous layer.

(4) The sclera and cornea differentiate from the surrounding mesenchyme. The choroid, ciliary body, and part of the iris also develop from the mesenchyme, while the iris musculature is derived from the ectoderm of the anterior margin of the optic cup.

(5) The eyelids develop as folds of surface ectoderm above and below the cornea. The ectoderm on the deep surface of these, together with that covering thefibrous coat of the eyeball, is transformed into the conjunctiva.

Anomalies of Development of the Eye.—(1) Anophthalmia, or absence of the eye, is the condition found when the optic bulb fails to develop.

(2) Cyclopia is a condition in which there is a single median eye. It is usually associated with abnormal development of the nose which is situated above the median eye.

(3) Congenital glaucoma is caused by failure in development of the canal of Schlemm.

(4) Congenital coloboma is due to failure of closure of the fœtal fissure. The cleft is infero-medial and may involve iris alone or also affect the ciliary body and choroid.

(5) Atresia of the pupil. If the tunica vasculosa lentis fails to degenerate there is a persistent pupillary membrane causing interference with vision. Defective vision may also be caused by a persistent hyaloid artery.

(6) Congenital cysts may form at the mouths of the lachrymal ducts; the puncta lachrymalia may be absent; the naso-lachrymal duct may be incomplete, and may fail to open into the inferior meatus of the nose.

The Auditory Apparatus.—The auditory apparatus is composed of several parts which differ in their origin. The external and middle ears serve for collection and transmission of sound waves to the internal ear, in the cochlear part of which are the end organs for hearing. The remainder of the internal ear serves for equilibration.

The Internal Ear.—The first indication of the future internal ear is a thickening of the ectoderm on each

side of the neck region early in the fourth week of development (Streeter, 1907). Each thickening (otic placode) sinks below the level of the surrounding ectoderm and forms a pit. The margins of the pit gradually meet and fuse, and a little vesicle of ectoderm is formed, termed the otocyst. This hollow vesicle then loses its connection with the ectoderm, and lies free in the mesenchyme lateral to the hind-brain and just posterior to the acoustico-facial portion of the neural crest. A hollow diverticulum arises from the medial aspect of the vesicle which is the

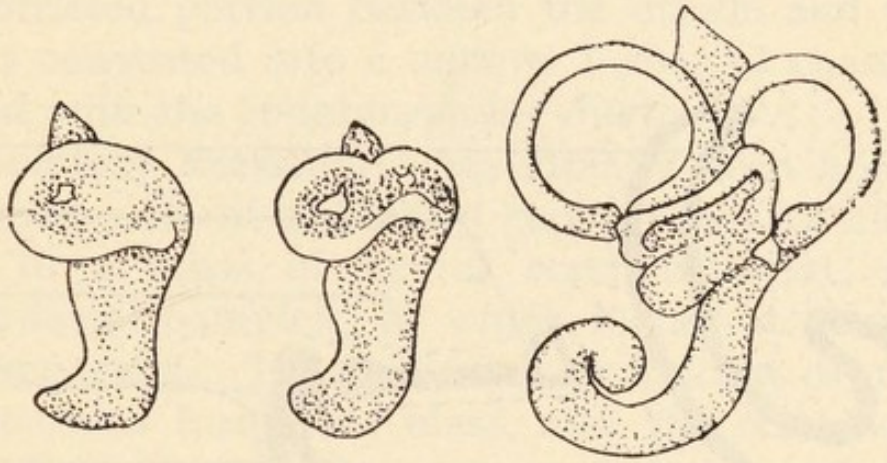

FIG. 15.—THREE STAGES IN THE DEVELOPMENT OF THE INTERNAL EAR. (From models prepared by G. L. Streeter.)
Note the three flat pouchings from which the semi-circular canals are developed.

ductus endo-lymphaticus. Three flat pouchings arise in the upper part of the vesicle and from these the semicircular canals develop. The pouch which represents the superior vertical semicircular canal is the first to appear, the horizontal appears next, and the posterior vertical one is the last. These three pouchings project more and more from the surface of the wall of the otocyst, and becoming increasingly flattened, the central portions of each pouch are inflected until the walls meet and fuse. By breaking down of the fused parts the peripheral margin is left as a curved tube, the definitive semicircular canal.

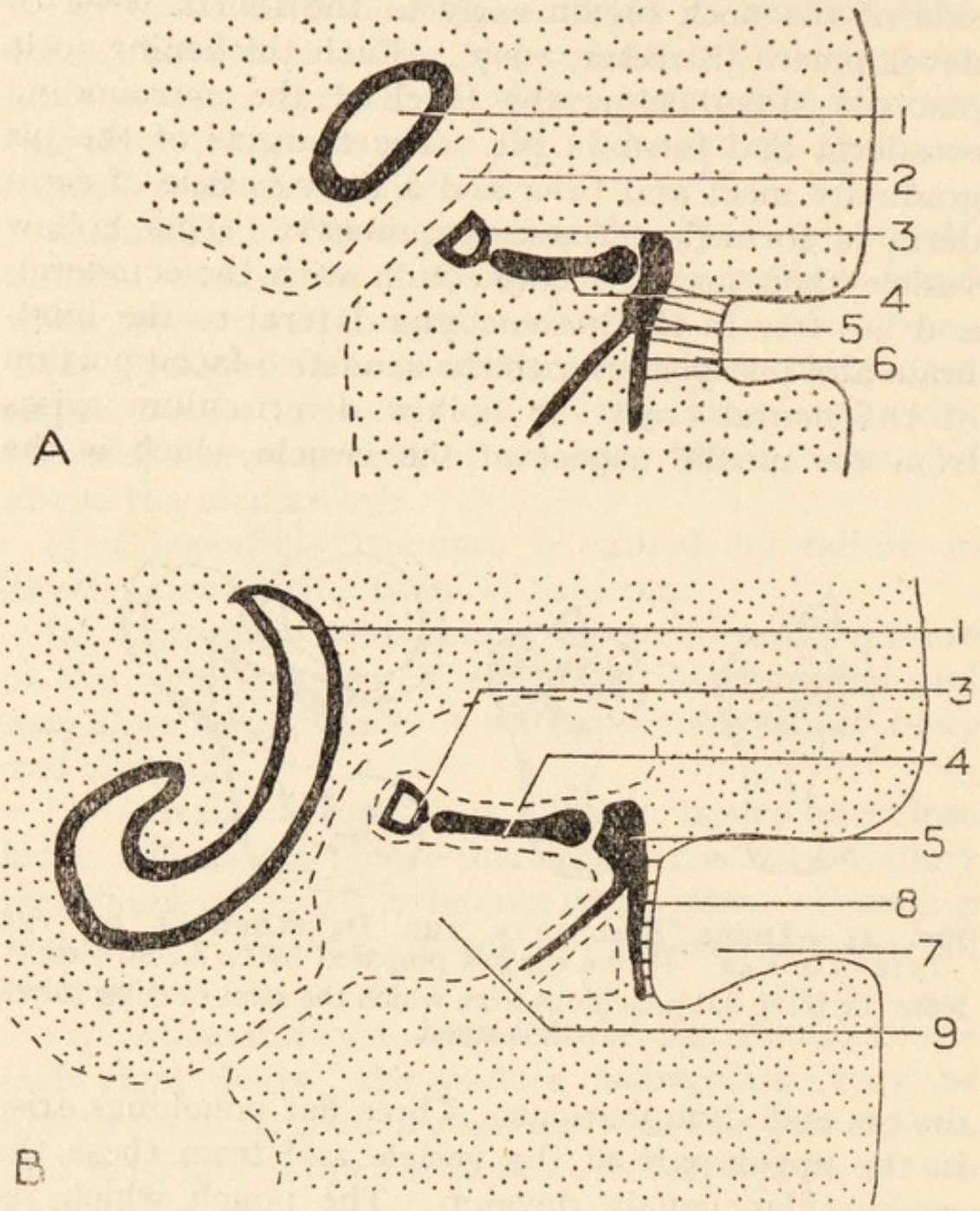

FIG. 16.—THE DEVELOPMENT OF THE TYMPANIC CAVITY.

1, Otocyst; 2, pharyngo-tympanic tube; 3, stapes; 4, incus; 5, malleus; 6, ectodermal ingrowth; 7, external auditory meatus; 8, tympanic membrane; 9, tympanic cavity.

At first the posterior semicircular canal is in the same vertical plane as the superior, but the former swings round outwards and forwards over the horizontal canal, and assumes its adult position at right angles to the other two. Each canal develops a swelling

towards one end, and the epithelium of it thickens to form a sensory end organ, the crista acoustica.

The ventral portion of the otocyst becomes elongated into a flattened canal which presently becomes coiled upon itself for two and a half turns. This is the cochlea. A constriction appears between the coiled cochlea and the rest of the otocyst which is termed the ductus reuniens. The remainder of the otocyst now becomes divided into a utricle having the semicircular canals opening into it, and a saccule connected with the cochlea by the ductus reuniens. The constricted portion between the utricle and the saccule is converted into a narrow V-shaped channel connected with the endolymphatic duct.

The Auditory Nerve.—As has already been noted, the anterior wall of the early otocyst lies in close relation to a mass of neural crest material, the acoustico-facial complex, to which indeed it contributes some cells. The geniculate ganglion of the facial separates from this mass, and the remainder becomes divided into two parts, a dorsal vestibular ganglion and a ventral cochlear ganglion. The cells of these ganglia become bipolar, the central processes pass towards the region of the rhombic lip and so form the auditory nerve. The peripheral processes enter into relationship with certain modified cells of the otocyst wall. At first the cells which form the otocyst are columnar in shape, but later they become flattened except in six small areas related to auditory nerve endings. Here the otocyst epithelial cells develop hair-like processes and become sensory receptive organs. These six areas are arranged as follows :

(*a*) One patch in the ampulla of each semicircular canal forms a crista acoustica.

(*b*) A cushion-like patch in the utricle and a similar one in the saccule form the maculæ of these organs.

(*c*) An elongated strip, which extends the entire length of the cochlea, forms the spiral organ of Corti.

The Bony Labyrinth.—While these changes have been taking place, the mesenchyme surrounding the otocyst has formed a condensation around it; this changes to precartilage and then to cartilage. The cartilage cells in immediate relation to the otocyst then de-differentiate to form the perilymphatic

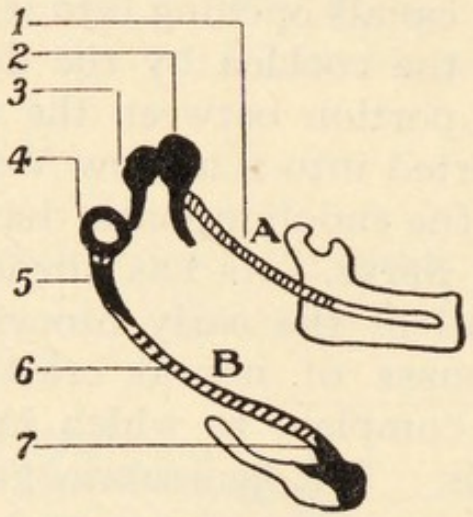

FIG. 17.

A. Meckel's cartilage; 1, spheno-mandibular ligament; 2, malleus; 3, incus. B. Reichert's cartilage; 4, stapes; 5, styloid process; 6, stylo-hyoid ligament; 7, lesser cornu hyoid bone.

spaces. The cartilage cells beyond this area change to bone, and the osseous labyrinth is formed.

The Tympanic Cavity.—From the cartilage of the first branchial arch (Meckel's) is formed the malleus and the incus, each bone ossifying from a separate centre; and from the second cartilage (Reichert's) is formed the stapes. These three bony ossicles, together with the chorda tympanic branch of the facial nerve, become surrounded and enveloped by an entodermal outgrowth derived mainly from the dorsal wing of the first pharyngeal pouch. In the adult they appear to lie within the tympanic cavity, although in reality they are outside it, separated

from it by its lining membrane. Further expansion of this tympanic cavity gives rise to the tympanic antrum, and, after birth, the mastoid air cells.

The Tympanic Membrane.—The external auditory meatus is indicated in part by the first ectodermal groove on the lateral surface of the neck. The middle part of this deepens to form a funnel-shaped pit and the inner end of this proliferates as a solid ectodermal cord of cells which comes into relation with the outer wall of the developing tympanic cavity. This cord later breaks down except for the deepest cells which form the outer layer of the tympanic membrane. This is separated by a small amount of mesoderm from the deep entodermal layer, *i.e.*, the lateral wall of the tympanic cavity.

The Pinna.—The external ear is developed from a number of tubercles grouped around the dorsal end of the first ectodermal groove, that is, the groove giving rise to the external auditory meatus. Both the mandibular and the hyoid arches contribute to the formation of the pinna but the major portion is derived from the second arch. The tragus and the tissue just around it seems to be all that is formed by the first arch. It is commonly held that the rudimentary Darwin's tubercle of the human ear corresponds with the apex of the pointed ear of lower mammalian forms.

Summary of Development of the Auditory Apparatus.—(1) The internal ear is formed from a hollow ectodermal vesicle which originates at the level of the hindbrain.

(2) The vesicle, termed the otocyst, presents three flattened bulgings dorsally (primordia of semicircular canals), a coiled tubular evagination ventrally (cochlea), and an intervening portion subdivided into two parts (utricle and saccule).

(3) Specialized epithelial regions in each of these

become connected with peripheral branches of the auditory nerve cells.

(4) The tympanic cavity and antrum are formed from an evagination of the dorsal part of the first entodermal pharyngeal pouch. The narrow proximal portion of this evagination gives rise to the pharyngo-tympanic tube.

(5) The ear ossicles are developed from the upper ends of Meckel's and Reichert's cartilages.

(6) The external auditory meatus arises as a solid ectodermal downgrowth from the floor of the first external pharyngeal groove towards the tympanic cavity. This cord later becomes canalized.

(7) The deep layer of the tympanic membrane is formed from the outer wall of the tympanic cavity (entoderm), the superficial layer from the deep end of the ectodermal cord, while the middle layer represents the mesoderm which originally separated the two.

Anomalies of Development of the Ear.—(1) The tubercles may not completely fuse, and various forms of malformed auricle, cleft lobule, etc., may result.

(2) Accessory tubercles may develop around a perfectly formed pinna.

(3) Synotus is a rare condition associated with defective formation of the mandible where the pinnae are fused near the mid-ventral line of the neck.

(4) Congenital deafness may be caused by failure of the auditory nerve to connect with the otocyst, or to failure of development of the auditory ossicles.

CHAPTER IX

THE ALIMENTARY CANAL AND RELATED STRUCTURES

THE primitive entodermal gut tube is laid down when the head, tail, and lateral body folds arise (p. 36). The gut is at first limited cranially and caudally by the bucco-pharyngeal and cloacal membranes, and it is subdivided into segments named the fore-, mid- and hindgut. When dealing with the fate of these structures it is convenient to describe the development of certain regions, such as the face and palate, which are associated with the alimentary canal.

The Pharyngeal Region.—During the fifth and sixth weeks of development a number of bar-like ridges separated by grooves become prominent upon the lateral aspect of the neck of the embryo. These are the branchial arches and they correspond to the gill arches of fishes. There are six of these arches in the human embryo, although the fifth one is transitory and its existence is denied by some. The first arch on each side is subdivided into maxillary and mandibular processes which form much of the face. The second is known as the hyoid arch because part of the hyoid bone is developed from it. Each arch contains a skeletal basis of primitive cartilage (branchial arch-cartilage), a blood vessel (aortic arch, p. 109) connecting the heart with the dorsal aorta, a nerve, and mesoderm destined to form muscle tissue. These structures are represented in the adult as shown in the table on p. 76. The nerves of these arches are associated with thickened patches of ectoderm, termed epibranchial placodes, and may possibly receive some

cells from them to their sensory ganglia. These placodes are located at the dorsal end of each arch. Caudal to the region of the arches is a mesodermal downgrowth from the occipital somites which will give

TABLE 2

Arch.	*Skeleton.*	*Blood Vessels.*	*Muscles.*	*Nerve.*
First	Mandible, malleus, incus	Degenerates	Muscles of mastication, mylo-hyoid, ant. belly digastric, tensor tympani, tensor palati	Mandibular division of trigeminal
Second	Lesser cornu and upper part of body of hyoid, styloid process, stapes	Degenerates	Stylo-hyoid, post. belly digastric, stapedius, muscles of expression	Facial
Third	Lower part of body and greater cornu of hyoid	Stem of internal carotid	Pharyngeal	Glossopharyngeal
Fourth	Part of thyroid cartilage	Arch of aorta on left; part of subclavian on right	Pharyngeal and laryngeal	Vagus (superior laryngeal)
Sixth	Part of thyroid and cricoid cartilages	Pulmonary arteries Ductus arteriosus on left side	Pharyngeal and laryngeal	Vagus (recurrent laryngeal)

rise to the muscles of the tongue. Between this and the swelling caused by the developing heart is the epipericardial ridge.

During the sixth week the first and second arches have become large as compared with the caudal ones which lie in an ectodermal-lined depression, the cervical sinus. The hyoid arch grows caudally and fuses with the epipericardial ridge so that the cervical sinus becomes obliterated during the seventh week and the caudal arches are buried in the side of

the neck. Ectodermal remnants of the sinus may persist and may give rise to branchial cysts in later years.

The Face.—During the fifth week (Fig. 18) the stomatodaeum, or primitive mouth, is bounded above by the fronto-nasal process of mesoderm in front of the developing brain; laterally are the maxillary processes, while infero-laterally the boundary is completed by the mandibular processes. The fronto-nasal process bifurcates on each side to surround the

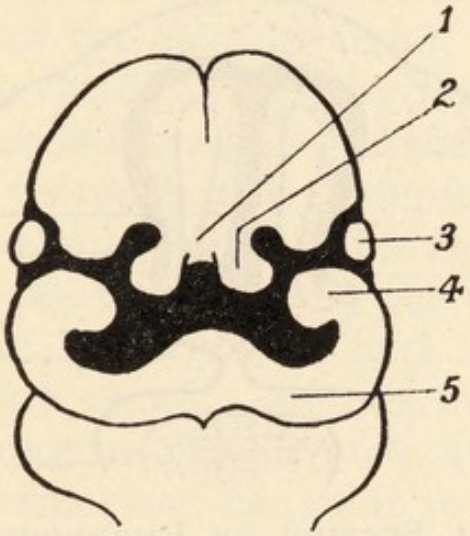

FIG. 18.—THE DEVELOPMENT OF THE FACE.

1, Fronto-nasal process; 2, lateral nasal process; 3, lens; 4, maxillary process; 5, mandibular process.

olfactory placode. The olfactory pit thus becomes bounded by medial and lateral nasal processes. At first, each pit communicates at its ventral margin with the oral fossa by the oro-nasal groove, and with the primitive orbit by the naso-lachrymal groove. By the fusion of the adjacent margins of these processes the orbital, nasal, and oral cavities become demarcated. The naso-lachrymal groove is overgrown by fusion of the maxillary process with the lateral nasal. The former then continues to grow anteriorly below the olfactory pit to fuse with the medial nasal process, and then unites superficial to this with its fellow of

the opposite side (Boyd, 1933). Thus the upper lip and anterior nares are formed. The two mandibular processes unite in the mid-ventral line to form the lower jaw and lip, and then there is a certain amount of union between the adjacent margins of the maxillary and mandibular processes to narrow down the primitively wide mouth to more adult proportions.

The Palate.—When, during the sixth week, the maxillary processes fuse with each other and with the frontal-nasal process to form the upper lip, the

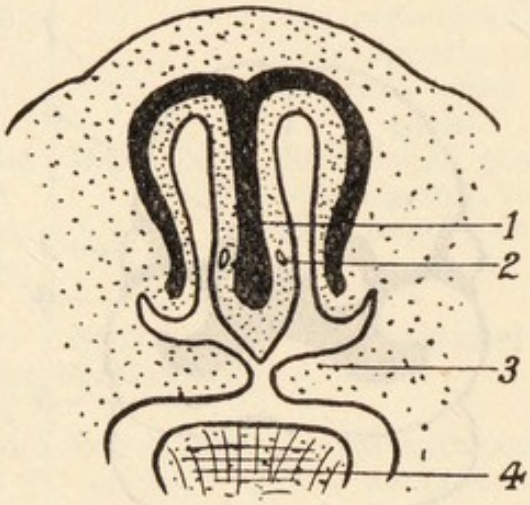

FIG. 19.—CORONAL SECTION OF EMBRYONIC HEAD TO SHOW THE DEVELOPMENT OF THE PALATE.

1, Fronto-nasal process (primitive nasal septum); 2, organ of Jacobson; 3, palatal process of maxilla; 4, tongue.

anterior part of the stomatodaeum is subdivided into upper and lower parts. This partition is the primitive palate. The deep part of the fronto-nasal process forms a rudimentary nasal septum. Then a shelf-like projection of mesoderm grows inwards on each side from the maxillary process and with continued growth the free edges of these palatal processes fuse with each other from before backwards; union also occurs with the nasal septum lying above, which becomes elongated in an antero-posterior direction. The primitive palate gives rise to the premaxillary portion of the adult palate, while the palatal processes

form the remainder of the hard, and all of the soft palate. A small gap between these three components persists as the naso-palatine canal of the adult.

The Tongue.—During the fifth week the primordia of the tongue can be seen on the floor of the pharyngeal region. There is a median swelling, the tuberculum impar, which lies between the ventral ends of the first pharyngeal grooves. Antero-lateral to this are paired swellings derived from the ventral extremities of the mandibular processes. Just behind the tuberculum impar a little diverticulum indicates the site of origin of the thyroid gland. Posterior to this is a median elevation formed by fusion of the ventral ends of the second branchial arches and termed the copula. The paired lateral swellings increase greatly in size and fuse in the middle line to form the anterior two-thirds of the tongue while the tuberculum impar lags greatly in development and forms little or no part of the adult organ. Mesoderm derived from the third arch overgrows the copula (which consists of second arch tissue) and causes it to become buried in the substance of the tongue so that the posterior one-third of the organ is formed by third arch tissue, with a small contribution of fourth arch tissue, at the extreme caudal part. The sensory nerve supply of the tongue supports such a conception of its development. The body, derived from the mandibular swellings is supplied by the proper nerve of that arch (mandibular division of the trigeminal) aided by the pre-trematic branch of the second arch nerve (chorda tympani). The root of the tongue, derived from third and fourth arch mesoderm, is supplied by the glosso-pharyngeal and superior laryngeal branch of the vagus. The foramen caecum on the adult tongue represents the site of the original thyroid downgrowth while the sulcus terminalis very roughly marks the boundary between first and third branchial

arch tissue. The striated muscle of the tongue is derived from the occipital somites.

The Teeth.—It is not easy to mark off the ectodermal part of the mouth from the entodermal but it is generally considered that the vestibule and much of the upper part is derived from the former. Ectoderm also gives rise to the enamel of the teeth.

In the human subject two sets of teeth are developed, a deciduous or milk set of twenty teeth, and a permanent set of thirty-two teeth. These begin to develop at an early date in the human embryo as a continuous curved ectodermal thickening which grows into the mesenchyme of each developing jaw. Each of these dental laminae develops ten buds which represent the enamel epithelium of the deciduous teeth. Opposite each bud a condensation of mesenchyme occurs to form a dental papilla and the enamel epithelium becomes moulded over this in the form of a cap. At a later date, from lingual extensions of each original dental lamina, a further series of sixteen enamel caps are formed which represent the primordia of the thirty-two permanent teeth. The development of these is exactly analogous to that of the milk set.

The enamel organ is a two-layered epithelial cup in the concavity of which lies the mesodermal dental papilla. The inner epithelial layer is converted into ameloblasts which lay down the enamel on the surface next to the dental papilla. When they have completed this function, they disappear. The outer epithelial layer, together with some reticular tissue between it and the enamel, forms a covering for the crown of the tooth, the cuticular membrane of Nasmyth. This membrane disappears soon after eruption in those parts exposed to attrition, but persists on the basal part. The surface cells of the dental papilla become transformed into odontoblasts which lay down dentine deep to the enamel. In the

dentine are filamentous processes of the distal ends of the odontoblasts known as Tomes' dental fibrils. The remaining tissue of the dental papilla becomes vascularized to form the dental pulp.

The mesenchyme around the developing tooth germ becomes condensed to form what is known as the dental follicle, from which is developed the cementum, a bone-like substance, and the fibrous membrane between the tooth and its socket, termed the periodontal membrane.

As the permanent teeth enlarge they press upon the roots of the deciduous teeth and partial resorption of the roots of the latter occurs. By a combination of this pressure and resorption the deciduous teeth are finally forced from their original position and shed.

One cannot give precise dates for the eruption of either the milk or permanent dentitions as a number of factors operate to cause variation in their time of appearance. It may be stated, however, that the first milk teeth to appear are the lower central incisors at the sixth month, and that these are quickly followed by the other incisors. A pause then ensues and the molars and canines then erupt, the process being usually completed by the end of the second year. There is a general tendency for the lower teeth to precede the upper teeth.

The permanent set of teeth begin with the eruption of the first permanent molars, generally during the seventh year, and these are followed by the incisor group during the following year. A pause of about two years then occurs before the premolars, canines, and second molars erupt and the permanent dentition should be complete by the end of the twelfth year except for the third molars. These appear between the eighteenth and twenty-fifth years, or may not erupt at all. The permanent teeth of girls erupt from six to nine months earlier than those of boys (McKeag,

1937). Like the milk teeth, the general tendency is for the lower teeth of the permanent set to precede the upper, and a year may elapse before apposing teeth meet.

The Salivary Glands.—The mode of development of the three salivary glands is very similar, but the parotid differs from the submandibular and the sublingual in being ectodermal in origin, while the latter two arise from the entoderm. The submandibular salivary gland is first seen during the sixth week as a solid rod of cells growing caudally from the entoderm of the floor of the mouth close to the developing tongue. Dichotomous branching takes place and the solid epithelial cords become hollowed out during the third month, alveolar rudiments appearing at the tips. A groove in the floor of the mouth runs forwards from the place where the original outgrowth occurred, and the lips of this groove close over, so forming the submandibular duct which thus extends forward to below the tongue close to the middle line. Here the process ceases and the tube is thus left unclosed at this point. Some heaping up of tissue takes place at this point and the sublingual papilla is formed.

The sublingual gland develops as a series of short outgrowths of entoderm from the floor of the mouth on a ridge close to the tongue near the middle line. These outgrowths, appearing in the eighth week, lie to the outer side of the groove for the submandibular duct; they branch extensively and then by a rearrangement of their cells they become hollow and differentiate to form glandular tissue. The outgrowths retain their original openings.

The parotid gland differs from the other salivary glands in being ectodermal in origin (Fraser, 1931). It begins during the sixth week as an epithelial bud close to the angle of the wide primitive mouth. This

grows backwards towards the ear, branching and becoming hollow in the same manner as the other salivary glands. With narrowing down of the wide oral opening a groove on the inner aspect of the cheek closes over to form the parotid duct.

The Pharyngeal Pouches.—Alternating with the system of branchial arches are depressions on the internal surface of the pharynx known as the pharyngeal grooves. These are elongated dorso-ventrally, and the extremities are dilated as the pharyngeal pouches from which certain glandular structures are developed.

In the case of the first pharyngeal groove the ventral part becomes obliterated with the formation of the tongue. The dorsal part of the groove becomes elongated as the tubo-tympanic recess (p. 72).

The Tonsils.—The palatine tonsils develop from the dorsal angles of the second pharyngeal pouches. The entoderm proliferates as a series of buds and almost obliterates the pouch; this thickening later becomes invaded by mesenchyme. The buds become hollowed out as the tonsillar crypts. About the fifth fœtal month lymphocytes become aggregated in the mesenchyme of the tonsil; these may be derived from this mesenchyme or from the blood stream.

The Thymus.—This is derived from the ventral portion of the third pharyngeal pouch on each side. This, at first large and hollow, separates from the pharynx and becomes solid by proliferation of the entodermal cells forming its wall. Migrating caudally into the future thoracic region it meets and fuses with its fellow of the opposite side to form a lobulated organ. During this migration (which is really caused by the "descent" of the heart) the thymus becomes invaded by mesenchyme, and about the tenth week lymphocytes, sometimes called thymocytes, appear

in it. The original entodermal cells become transformed into reticular elements. The corpuscles of Hassall appear later as specializations of the reticulum. Norris (1938) holds that the ectoderm of the cervical sinus contributes to the formation of the thymus. At birth, the gland is of relatively large size and remains prominent until puberty, after which date it regresses.

The Parathyroids.—The upper parathyroids develop as proliferations from the dorsal angles of the fourth pharyngeal pouches while the lower parathyroids develop in a similar manner from the dorsal angles of the third pouches. Similar forces to those acting on the thymic primordia influence the parathyroids arising from the third pouch causing them to descend to a lower level in the neck than those derived from the fourth pouch. The latter seem to be prevented from migrating downwards by the participation of fourth pouch tissue in the formation of the thyroid (see below).

The Thyroid Gland.—The thyroid gland is first seen during the fourth week as an out-pocketing from the floor of the pharynx immediately behind the tuberculum impar (p. 79) at a point which is represented in the adult tongue by the foramen caecum. This diverticulum forms a hollow stalk, termed the thyro-glossal duct, the lower end of which dilates at the fifth week to form a hollow vesicle ; the hollow stalk atrophies and disappears leaving the dilated lower end lying free in the surrounding mesenchyme. The vesicle develops unequally and takes on a bilobed form, and by a proliferation of the cells of its walls, the lumen disappears. The solid bi-lobed mass becomes subdivided into a number of follicles by ingrowth of mesenchymal septa and colloid appears in these about the twelfth week. About the sixth week, cells derived from the ventral end of each fourth

pouch fuse with each lateral aspect of the thyroid primordium. According to Weller (1933) these lateral thyroid masses are transformed into glandular tissue, but this opinion is not held by all. The thyro-glossal duct passes ventral to the hyoid bone in its course downwards from the foramen caecum to the isthmus of the gland ; while it normally disappears completely a remnant may persist in any part of this track and give rise to a cystic swelling in later years.

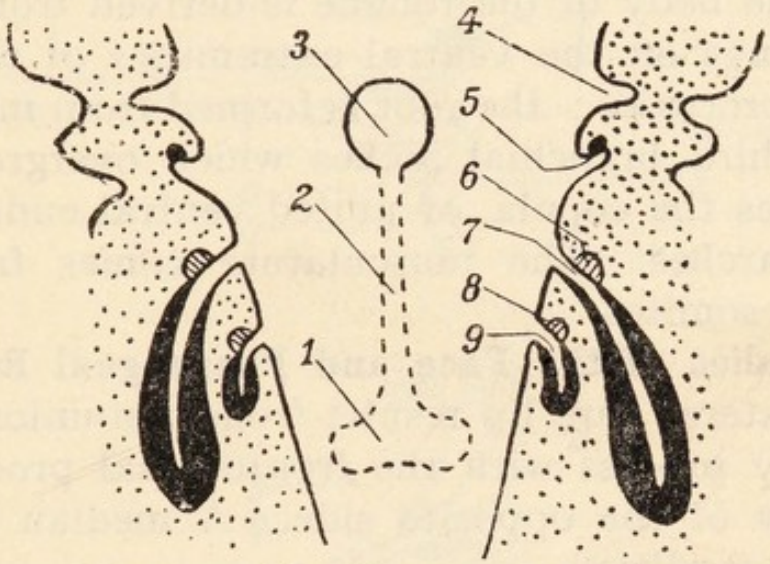

FIG. 20.—THE PHARYNGEAL GROOVES.

1, Thyroid gland; 2, thyro-glossal duct; 3, foramen caecum; 4, pharyngo-tympanic tube; 5, tonsil; 6, lower parathyroid; 7, thymus; 8, upper parathyroid; 9, lateral thyroid.

Summary of the Development of the Pharyngeal Region.—(1) A series of branchial arches is formed on the lateral side of the neck; between the arches are ectodermal grooves externally, and entodermal pharyngeal grooves internally.

(2) From each dorsal angle of the first entodermal groove there develops the pharyngo-tympanic tube and the lining of the middle ear.

(3) From the dorsal angle of the second groove the palatine tonsil is formed.

(4) The ventral end of the third pouch gives rise

to the thymus; the dorsal extremity of this pouch develops into the inferior parathyroid.

(5) The superior parathyroids arise from the dorsal ends of the fourth pharyngeal pouches; cells from the ventral ends of these pouches join with the developing thyroid.

(6) The major portion of the thyroid develops as a median diverticulum from the pharyngeal floor just posterior to the tuberculum impar.

(7) The body of the tongue is derived from fusion of swellings on the ventral extremities of the mandibular processes; the root is formed from mesoderm of the third branchial arches which overgrows and submerges the copula, or united ventral ends, of the second arches. The musculature comes from the occipital somites.

Anomalies of the Face and Pharyngeal Region.—(1) Unilateral hare lip results from non-union of one maxillary process with the fronto-nasal process and its fellow of the opposite side. A median hare lip is a rare condition.

(2) Bilateral hare lip is due to failure of the maxillary processes to unite with each other. The small fronto-nasal process lies free between their extremities.

(3) Oblique facial cleft is caused by non-union of the maxillary process with the lateral nasal process.

(4) Cleft palate may be partial or complete, and in the latter case is often associated with hare lip. It is due to non-fusion of the palatal folds with each other, and with the fronto-nasal process (primitive palate) on one or both sides.

(5) Split tongue may result if union of the anterior elements of the tongue does not occur.

(6) Branchial sinuses and fistulae result from malocclusion of the cervical sinus or persistence of an external branchial groove.

(7) Branchial fistulae result from perforation of an external groove into the pharynx.

(8) Persistence of part of the thyro-glossal duct may cause a mid-line cyst in the neck.

The Primitive Gut.—The primitive gut is at first a simple tube of entoderm extending from head to

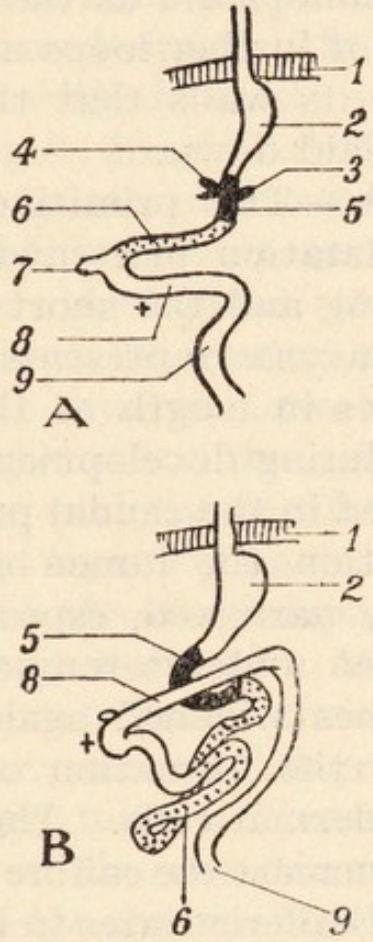

FIG. 21.—TWO DIAGRAMS TO SHOW THE CHANGES BROUGHT ABOUT BY THE ROTATION OF THE GUT.

1, Diaphragm; 2, stomach; 3, dorsal pancreas; 4, liver bud; 5, duodenum; 6, cranial limb of intestine; 7, vitello-intestinal duct; 8, caudal limb of intestine; 9, intra-abdominal colon. The position of the caecum is indicated by a +.

tail of the embryo. It terminates blindly at its extremities until breakdown of the bucco-pharyngeal and cloacal membranes allows communication of its lumen with the exterior. Ventrally it is in communication with the extra-embryonic yolk sac for some time by the vitello-intestinal duct. This

entodermal tube is clothed by that layer of the intra-embryonic mesoderm known as the splanchnopleure (p. 19). The gut tube rapidly increases in length, much faster than the body cavity in which it lies. For this reason, the gut becomes looped and draws away from the walls of the body cavity, elongating part of the splanchnopleure as the mesentery. It is by the formation of further loops and by inequalities of growth within its walls that the pattern of the adult intestine is laid down.

The Œsophagus.—The primitive gut very early shows a slight dilatation just caudal to the septum transversum (p. 36), and the short segment between this and the pharynx represents the œsophagus. This part increases in length as the heart and diaphragm descend during development and the elongation is most marked in the caudal portion of the tube. With this elongation the lumen of the œsophagus becomes markedly narrowed, especially in the lower part, and may even undergo temporary obliteration. The lumen becomes widened again from the sixth week onwards by the formation of vacuolar spaces between the entodermal cells. These open out into the lumen and so increase the calibre of the œsophagus. The muscular coat differentiates from the surrounding mesenchymal cells.

The Stomach.—The dilatation of the primitive tube which represents the stomach is at first spindle-shaped, and is slung from the dorsal body wall by a dorsal mesentery of splanchnopleure and from the under surface of the septum transversum by a ventral mesentery of the same tissue. The dorsal border and the œsophageal end grow more rapidly than the ventral border and the pyloric end, and as a result, the stomach appears to rotate through 90° on its long axis so that the original right side becomes dorsal, and the original left side ventral, in position.

The primitive dorsal border of the stomach then becomes the greater curvature and the lesser curvature represents the primitive ventral border. The rapidly enlarging œsophageal end becomes the fundus. The dorsal mesentery attached to the stomach (more correctly called the dorsal mesogastrium) is influenced by the rotation of the stomach so that a blind retrogastric recess is formed opening to the right. This corresponds in part with the lesser sac of peritoneum in the adult. Rapid growth of the dorsal mesogastrium causes it to sag in a caudal direction and so form the primordium of the great omentum (see Fig. 22). The liver develops as an outgrowth from the primitive gut into the ventral mesentery, which becomes subdivided thus into two parts, the lesser omentum extending between the lesser curvature and the developing liver and the falciform and coronary system of peritoneal ligaments attaching the liver to the under surface of the diaphragm (derived largely from the septum transversum). At first the pyloric portion of the stomach forms almost half the total length, but the later, more rapid growth at the œsophageal end soon produces a stomach of more adult proportions. Pits in the entodermal lining develop about the middle of the second month, and the gastric glands commence to differentiate during the fourth month. At this time, some of the gland cells stain intensely with eosin and are considered to be the future parietal cells, while others remaining pale are designated as zygmogenic cells. Rennin and hydrochloric acid have been demonstrated in the fœtal stomach at the end of the fifth month, while pepsin is present somewhat earlier (Lucas Keene and Hewer).

The Intestine.—The segment of gut caudal to the stomach grows rapidly and soon forms a loop convex ventrally. A vitelline vessel, the future superior mesenteric artery, runs from the dorsal aorta to the

apex of the loop, dividing it into cranial and caudal limbs, and the vitello-intestinal duct is attached to the apex of the loop on its free or ventral aspect. Continued growth of the gut results in increase in length of the intestinal loop until it can no longer be completely accommodated in the abdominal cavity; the developing liver occupies a disproportionately large amount of the available space. A large part of the intestinal loop is therefore herniated into a mesothelial lined cavity, the umbilical sac, continuous with the intra-embryonic cœlom. This protrusion of the gut occurs during the fifth week. The loop in the umbilical sac continues to grow, and the cranial limb of it comes to lie on the right side of the cavity, the caudal limb on the left. This rotation continues until a torsion through 180° has occurred, the torsion being in an anti-clockwise direction when the loop is viewed from the ventral aspect. This torsion may be partly determined by the direction of the pyloric end of the stomach and it is of primary importance in determining the future position of the intestine.

During the sixth week a swelling, the primordium of the caecum, appears on the caudal limb of the intestinal loop, and about the same time the vitello-intestinal duct atrophies and disappears leaving the loop free in the unbilical sac. It is now evident that all the cranial limb and a little of the caudal limb of the loop are destined to form the small intestine, while the remainder of the caudal limb will contribute to the large intestine. The cranial limb of the intestinal loop continues its rapid growth so that a series of coils are formed lying to the right side of, and caudal to, the caecal rudiment. The caudal limb lags in growth and runs in a practically straight line along the left side of these coils.

About the tenth week of development the intestinal loops in the umbilical sac return to the abdominal

cavity. This process is considered by Frazer (1931) to be due to a relative diminution in volume of the liver. The communication between the abdominal cavity and the umbilical sac is a narrow one and so the gut cannot return *en masse*. Instead, first the loops of the cranial limb are withdrawn one by one and the caudal limb follows later since the caecal dilatation offers some resistance to passage through the narrow opening into the abdomen. The entering loops of the cranial limb spread out on the posterior wall of the abdominal cavity pushing the intra-abdominal continuation of the caudal limb over to the left. When the caecum and future large intestine are withdrawn into the abdomen they must lie in front of the other intestinal loops and further " rotation " of them brings the caecum to the right side just below the liver.

The various segments of the gut now become differentiated and fixed in position in the abdominal cavity.

The Duodenum.—The duodenum arises from a short segment of the gut between the stomach and the superior retention band. This latter is a condensation of tissue anchoring the upper extremity of the intestinal loop to the dorsal abdominal wall. The formation of the duodenal loop has been studied by Hunter (1927) who states that at first it forms a loop convex ventrally whose extremities are fixed to the dorsal abdominal wall at the pylorus cranially, and by the superior retention band caudally. With further growth the loop swings to the right and is pressed against the dorsal abdominal wall by the developing large intestine when it is withdrawn from the umbilical sac. The mesentery of the duodenum fuses with the peritoneum on the posterior wall of the abdomen and disappears. The duodenum thus becomes a retroperitoneal structure.

The Caecum, Appendix, and Colon.—The formation of a caecal pouch on the caudal limb of the intestinal loop has been described above. This pouch grows rapidly in length for a time, but the basal part increases in diameter much more than the apical portion. Thus the primordium of the appendix is differentiated from the caecum. When it enters the abdominal cavity the caecum comes to lie immediately caudal to the right lobe of the liver. Progressive diminution in

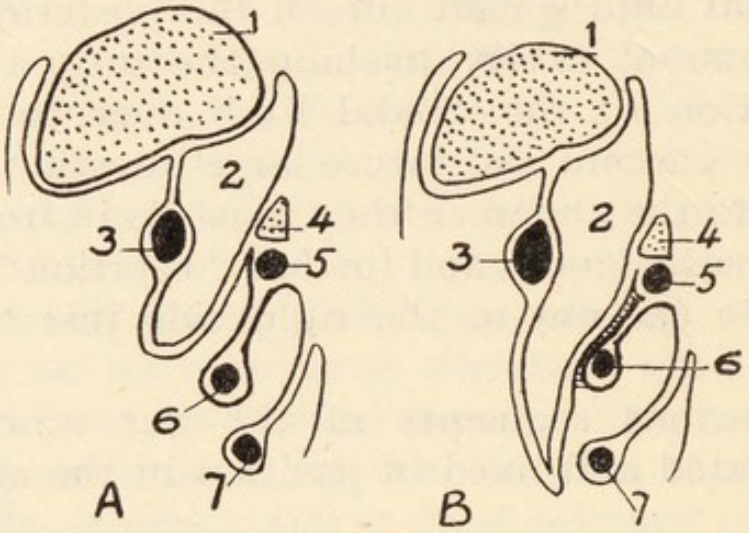

FIG. 22.—DIAGRAMS TO SHOW THE POSITION OF THE PERITONEAL FOLDS: A, IMMEDIATELY AFTER THE GUT HAS BEEN WITHDRAWN FROM THE UMBILICAL SAC; B, AFTER THE FUSION OF THE DORSAL WALL OF THE PRIMITIVE LESSER SAC TO THE VENTRAL WALL OF THE PRIMITIVE TRANSVERSE MESOCOLON.

1, Liver; 2, lesser sac; 3, stomach; 4, pancreas; 5, duodenum; 6, tranverse colon; 7, small intestine.

size of the liver, and growth changes in the large intestine, result in an apparent "descent" of the caecum and formation of an ascending colon. The mesentery of the caecum and ascending colon disappears during this process by fusing with the peritoneum of the posterior abdominal wall. That segment of the gut which forms the descending colon loses its mesentery in a similar fashion. The great omentum arises as a downgrowth of the dorsal mesogastrium (p. 89). This downgrowth lies ventral to

the transverse colon which retains its mesentery and the two structures fuse (see Fig. 22) to give the arrangement found in the adult.

The entoderm forms the mucous lining of the intestine, the muscular coats being derived by transformation of cells of the surrounding splanchnic mesoderm. The circular muscle coat is differentiated rather earlier than the longitudinal which forms during the third and fourth months. The enzymes of the small intestine are stated to be present in the fifth month. At the end of gestation the large intestine is full of meconium, a dark green secretion of the liver and intestinal glands.

Anomalies of Development of the Intestinal Tract.—(1) Duodenal stenosis. This condition may involve the whole length of the duodenum or a section of it. It is usually found as a patch just proximal to the entrance of the bile duct and is due to persistence of an occlusion of the lumen which normally occurs temporarily between the sixth and ninth weeks of development.

(2) Atresia of the intestine. The common sites of atresia are high up in the jejunum, in the terminal ileum, or in the colon. Atresia of the small intestine is often associated with errors of rotation.

(3) Malformations of the rectum are frequently combined with faulty development of the lower urogenital tract (p. 144).

(4) Congenital umbilical hernia may be due to persistence of the umbilical sac, or it may be secondarily acquired.

(5) Meckel's diverticulum found in about two per cent. of adults is due to persistence of the proximal part of the vitello-intestinal duct. It commonly forms a blind diverticulum about 2 inches long on the antimesenteric border of the ileum anywhere from 6 to 60 inches proximal to the ileo-caecal value. In

more pronounced cases of persistence of the vitello-intestinal duct a fibrous cord may unite the diverticulum to the umbilicus. Rarely, there may be a fistulous communication between the gut lumen and the exterior.

(6) Non-rotation of the intestine sometimes occurs and then the jejunum and ileum lie on the right side, and the large intestine on the left side, of the abdominal cavity.

(7) Situs inversus is a condition in which there is mirror-transposition of the viscera. Thus the liver, caecum, and ascending colon are found on the left side, and left-sided organs, the stomach and spleen, are found on the right. This inversion may be confined to the abdominal viscera or may affect the thoracic organs as well. The condition is due to the intestinal loops rotating in the opposite direction to the normal. Carey (1920) believes it to be due to the spiral organization of the developing gut becoming reversed in direction. It is interesting to note that the condition is not infrequent among identical twins.

The Liver.—The primordium of the liver first appears about the twenty-fifth day as a shallow groove on the ventral aspect of the future duodenal segment of the gut. This groove becomes a tubular evagination which invades the mass of mesoderm, termed the septum transversum, which partially subdivides the cœlom into thoracic and abdominal portions (p. 36), and the ventral mesentery which is continuous with it. The hepatic bud enlarges ; part of it remains within the substance of the ventral mesentery and will form the gall bladder and cystic duct ; the major part lying in the septum transversum divides into right and left solid buds which branch repeatedly and become organized as anastomosing trabecular cords of cells. Sinusoidal blood spaces derived from the vitelline and umbilical veins lying

in the septum transversum separate these liver trabeculae. The trabecula becomes hollow to form the bile capillaries whose lining is therefore derived from entoderm. The mesoderm of the septum forms the fibrous tissue of the liver. The original outgrowth from the duodenum forms the common bile duct, and the right and left buds from it become hollow as the right and left hepatic ducts.

The liver cells become arranged in lobules each being related to a radicle of the hepatic vein; and, with the formation of new lobules, there is corresponding branching of the hepatic veins. Likewise do the portal vein and hepatic artery branches (which lie at the periphery of the lobules) subdivide and maintain their proper orientation to the newly formed hepatic veins and lobules. The two systems of veins are connected by the sinusoids, much of the endothelium of which become phagocytic in function as the Kupffer cells of the organ. From the second to the seventh months of fœtal life haematopoiesis is an important function of the liver. Active differentiation of blood cells takes place in foci between the glandular cells and the sinusoidal endothelium and from there the cells pass into the fœtal circulation.

During the second month the liver grows much more rapidly than the remainder of the body and at nine weeks it is relatively enormous and occupies a large part of the abdominal cavity. After this time the growth rate decreases, but even at birth the liver forms a much greater proportion of the body weight than it does in the adult. The decrease in growth rate in the latter part of fœtal life affects the left lobe more than the right. The bile secreted by the fœtal liver from the fifth month onwards gives the characteristic green colouration to the meconium.

As the liver grows it withdraws from the substance of the cranial part of the septum transversum which is

transformed into the diaphragm. The connections between the two persist as the hepatic ligaments and at one part the withdrawal may be considered as incomplete. This is at the bare area of the liver.

The Pancreas.—The pancreas develops as two outgrowths from the duodenal segment of the gut, one from the dorsal aspect a little proximal to the hepatic bud, and one from the ventral and right aspect close to the liver diverticulum. The dorsal bud grows into the dorsal mesentery to the left side of the left vitelline (developing portal) vein. This part forms the body and tail of the adult pancreas. The ventral

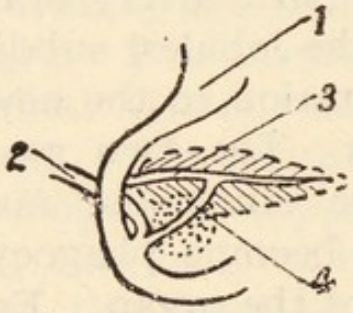

FIG. 23.—THE DEVELOPMENT OF THE PANCREATIC DUCTS
1, Stomach; 2, common bile duct; 3, duct of dorsal pancreas; 4, duct of ventral pancreas.

outgrowth, which will form the head of the adult gland, is swept around dorsally into the mesentery when the duodenal loop is rotated to the right and thus comes to lie on the right side of the dorsal pancreas separated from it by the developing portal vein. These two primordia fuse about the end of the sixth week and so the portal vein comes to lie anterior to the lower part of the head of the pancreas derived from the ventral bud, and dorsal to the neck which is formed by the dorsal bud. The ducts of the two primordia communicate with each other and the proximal part of the dorsal duct partly or completely retrogresses. As a result, the main pancreatic duct of the adult opening into the duodenum in common with

the bile duct is formed by the ventral pancreatic duct plus the distal portion of the dorsal duct. If any of the proximal portion of the dorsal duct persists it opens into the duodenum as the accessory pancreatic duct some distance cranial to the common bile duct. The minor ducts and acini of the pancreas arise by repeated sproutings of groups of cells from the pancreatic buds. Groups of islet cells form as similar sprouts which do not, however, develop a lumen and become separated from the parent tissue about the third month of fœtal life. The secretion of the pancreatic acini may be identified about the fifth fœtal month.

Summary of the Development of the Liver and Pancreas —(1) The liver and pancreas both arise as entodermal evaginations from the gut in the region of the duodenal segment.

(2) The liver bud grows into the septum transversum and forms a mass of anastomosing trabeculae which invade and split up the umbilical and vitelline veins lying in the septum. These split-up veins form the liver sinusoids.

(3) At first solid, the trabeculae become hollow to form the bile capillaries and ducts. The first branch from the original hepatic diverticulum is transformed into the gall bladder and cystic duct.

(4) The pancreatic primordia are two in number, dorsal and ventral. The dorsal bud forms the body and tail, the ventral one represents the head of the adult organ.

(5) The two primordia are brought into contact with each other by the rotation and fixation of the duodenal loop. The respective ducts fuse and the proximal part of the dorsal duct disappears. The main pancreatic duct of the adult is then formed by the distal part of the dorsal duct and the entire ventral duct.

(6) The cell islets of Langerhans arise during the third month of fœtal life as solid masses of cells budded off from the pancreatic acini.

Anomalies of Development of Liver and Pancreas.—(1) The gall bladder may fail to develop, or it may be double.

(2) In situs inversus the liver lies on the left side of the abdomen.

(3) The pancreas may persist as two separate parts. Accessory glands may be present, often some distance from the primary situation of the viscus.

The Respiratory System.—The first indication of the respiratory system is a longitudinal groove, the pulmonary groove, in the floor of the caudal part of the pharynx. The caudal end of this grows as a pouch-like diverticulum whose tip lies free in the mesoderm ventral to the primitive œsophagus. This is the rudiment of the trachea and its tip soon bifurcates to form the primary bronchi. These buds, covered by mesoderm, bulge caudo-laterally into the cœlomic channels on either side of the œsophagus cranial to the septum transversum. These channels are later modified and extended to form the pleural cavities.

The primary bronchi branch, the left one into two and the right one into three ; from these divisions the two lobes of the left lung and the three lobes of the right, are ultimately formed. Repeated dichotomous division of the bronchi takes place, the branches invading and being capped by the surrounding mesoderm in which blood vessels develop. In this way the bronchioles, alveolar ducts, and alveoli are formed and it is to be noted that this process is not completed at birth. The fate of the entodermal cells lining the terminal buds is still a matter of dispute.

The cranial end of the tracheal outgrowth lies at the level of the sixth branchial arch and the surround-

ing mesoderm here differentiates into the cartilages, muscles and ligaments of the larynx. On each side of the opening into the primitive pharynx an arytenoid swelling occurs. These are at first almost parallel to each other but the growth of the epiglottis, derived from the ventral ends of the third and fourth branchial arches, causes them to become folded so that the opening is transformed into a **T**-shaped cleft. The swelling which gives rise to the epiglottis is termed the hypobranchial eminence. The remains of the third arch tissue form the pharyngo-epiglottic fold, and the fourth arch tissue is represented by the ary-epiglottic fold. The true and false vocal cords differentiate from the upper and lower margins of the laryngeal ventricles which form as active epithelial outgrowths of the laryngeal entoderm. The cricoid and arytenoid cartilages are formed from the sixth arches whose ventral extremities form pronounced elevations behind the hypobranchial eminence and the opening of the glottis.

CHAPTER X

THE CIRCULATORY SYSTEM

THE developing blood vessels that are first seen are extra-embryonic in position ; they are the vessels of the yolk sac, chorion, and body stalk. Isolated masses and cords of mesodermal angioblastic tissue, known as blood islands, become hollowed out. The peripheral cells become transformed into endothelium while the central ones are the primitive blood cells. By growth and extension these primitive angioblastic foci become linked up thus giving rise to a plexus of extra-embryonic blood vessels. This process occurs

during the latter part of the third week of development and at the beginning of the fourth week connections are established with the intra-embryonic vessels. It was formerly thought (His, 1900) that the latter were formed from extensions of the extra-embryonic vessels into the embryo, but it is now generally held that the vessels in the body of the embryo originate from local mesodermal foci and secondarily link up with each other.

The Heart.—The heart arises in the cardiogenic area which lies in the splanchnopleuric mesoderm at the anterior end of the embryonic disc. This mesoderm forms the floor of the anterior end of the horse-shoe-shaped cœlom and a pair of endothelial tubes arise in it; these then fuse to form a single heart tube. The formation of the head fold of the embryo (see Fig. 9) brings this heart tube to a position just ventral to the developing fore-gut and slung from the roof (formerly floor) of the anterior part of the cœlom which may now be termed the primitive pericardial cavity. The vitelline veins from the yolk sac pass into the septum transversum where they become connected with the caudal ends of the fusing heart tubes, and the terminal parts of these soon receive the umbilical veins and the common cardinal veins so forming the sinus venosus. Cranially the heart tubes are continued into vessels lying in the first branchial arch and so pass dorsally to the dorsal aortæ lying ventro-lateral to the neural tube.

When the endothelial heart tubes fuse, the splanchnopleuric mesoderm around them is called the myo-epicardial mantle. This is connected for a short time with the dorsal wall of the pericardium by the dorsal mesocardium, but this soon breaks down and the passage thus formed, dorsal to the heart tube, is the rudiment of the transverse sinus of the pericardium.

Differential growth of the heart tube now takes place and four regions, separated by grooves, may be distinguished. From the caudal end forwards they are, in order, the sinus venosus with its right and left horns into which the veins of the corresponding side open, the primitive atrium, the primitive ventricle and lastly the bulbus cordis. The bulbus cordis leads

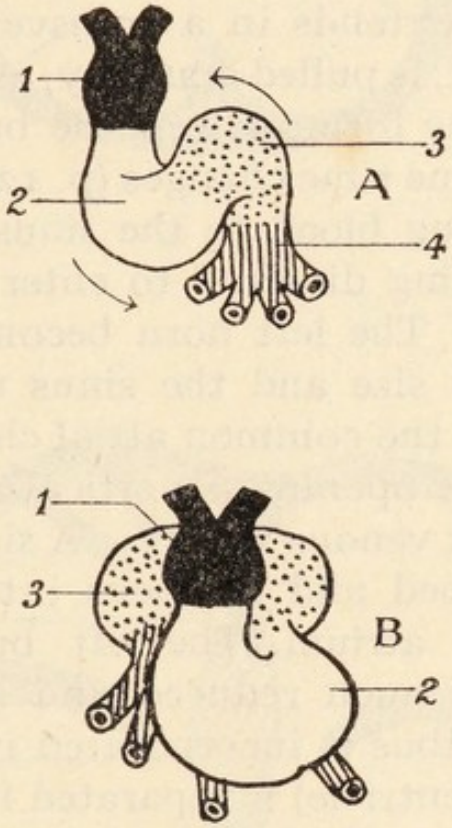

FIG. 24.—THE DEVELOPMENT OF THE BULBO-VENTRICULAR LOOP.

1, Bulbus cordis; 2, ventricle; 3, atrium; 4, sinus venosus. The arrows indicate the direction of rotation of the loop.

into a dilatation (not part of the heart tube) called the aortic sac, from which the branchial arch arteries pass dorsally around the pharynx to the dorsal aorta (p. 109).

Growth of the heart tube causes it to form a loop, convex ventrally, in the pericardial cavity, and as this growth continues the bulbo-ventricular portion of the tube, which is the most mobile portion, swings caudally and to the left, ventral to the primitive

atrium (see Fig. 24). During this process the sinus venosus is to some extent pulled cranially out of the substance of the septum transversum. The primitive atrium now grows rapidly. As it is limited dorsally by the developing pharynx and ventrally by the bulbus cordis, it balloons out on either side of the bulbus into right and left atria. These, of course, communicate freely with each other. The sinus venosus, which extends in a transverse direction in the tubular heart, is pulled cranially, as was mentioned above, during the formation of the bulbo-ventricular loop. At the same time changes (p. 124) in the venous channels returning blood to the sinus venosus result in most of it being diverted to enter the right horn which enlarges. The left horn becomes correspondingly reduced in size and the sinus now opens into the right part of the common atrial chamber upon its dorsal wall. The opening is vertical and guarded by the right and left venous valves. A single pulmonary vein has developed and it opens into the left part of the common atrium. The left bulbo-ventricular groove becomes much reduced and so some of the cavity of the bulbus is incorporated in the ventricle. This chamber (ventricle) is separated from the atrium by a constriction, the atrio-ventricular canal, in which ventral and dorsal swellings, the endocardial cushions, still further narrow the lumen.

Formation of the Interatrial Septa.—The right and left venous valves guard the opening of the sinus venosus into the right part of the common atrium at the fifth week. Their cranial extremities are fused to form the septum spurium. Their caudal ends likewise fuse into a less pronounced ridge running caudally towards the A.-V. canal. During the sixth week, a fold of the endocardium grows caudally in the sagittal plane from the roof of the atrial chamber towards the A.-V. canal. This fold is called the

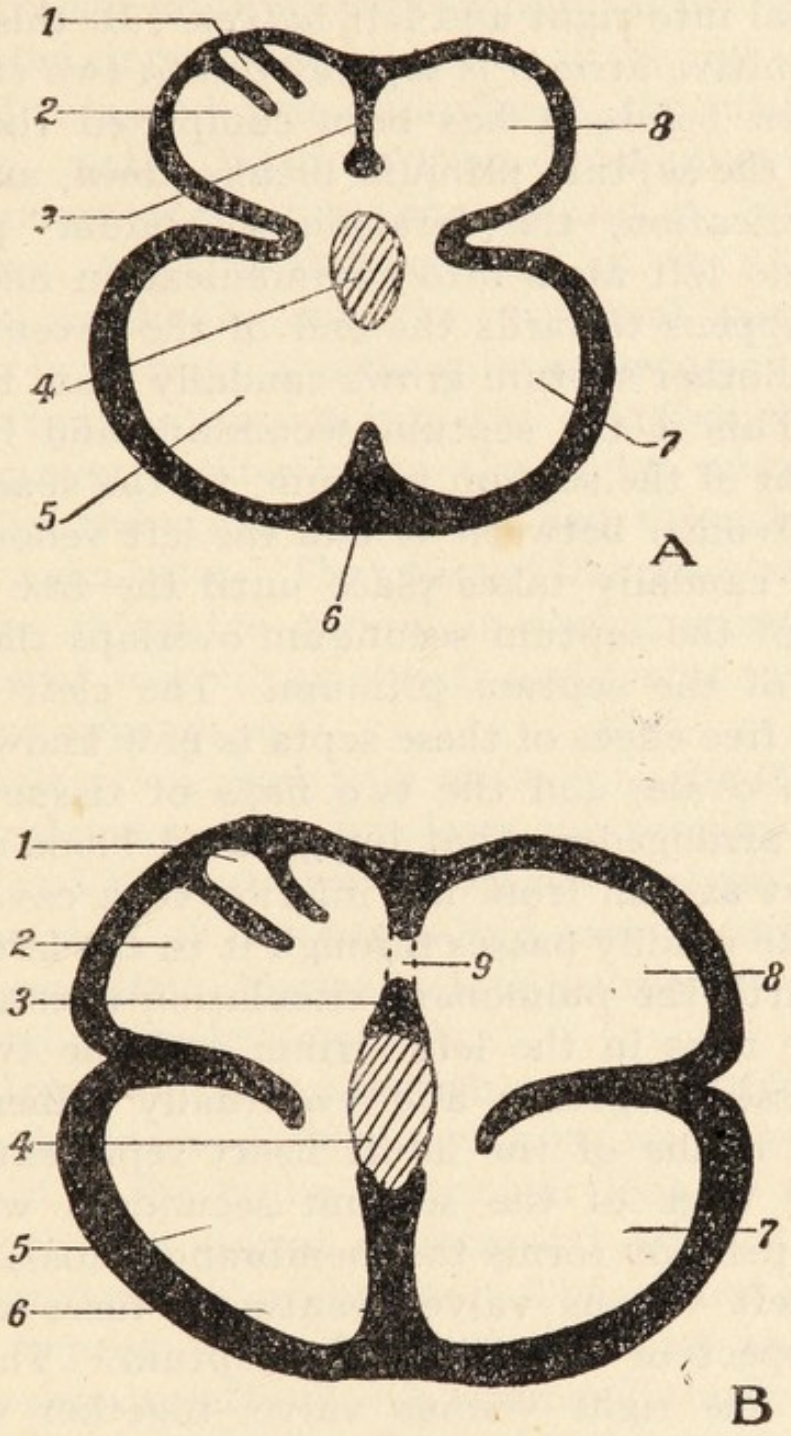

FIG. 25.—THE FORMATION OF THE FOUR CHAMBERS OF THE HEART.

1, Sinus venosus with its valves; 2, right atrium; 3, septum primum; 4, endocardial cushion; 5, right ventricle; 6, interventricular septum; 7, left ventricle; 8, left atrium; 9, foramen secundum.

septum primum and its caudal free border eventually meets and fuses with the two endocardial cushions of the canal which have united with each other to divide

the canal into right and left halves. In this manner the primitive atrium is separated into two chambers, but even before it has been completed the cranial part of the septum primum breaks down, and a new communication, the foramen secundum, puts the right and left atria into communication once more. This happens towards the end of the seventh week. Next, another septum grows caudally from the atrial wall. This is the septum secundum and it lies to the right of the septum primum, in the space (interseptovalvular) between it and the left venous valve. Growth caudally takes place until the free concave border of the septum secundum overlaps the cranial border of the septum primum. The cleft between the two free edges of these septa is now known as the foramen ovale, and the two flaps of tissue are obviously arranged so that oxygenated blood reaching the right atrium from the inferior vena cava during fœtal life readily passes through it to the left atrium. After birth the pulmonary circulation is established, pressure rises in the left atrium and the two septa are pressed together and eventually adhere. The annulus ovalis of the adult heart represents, then, the free edge of the septum secundum while the septum primum forms the membranous fossa ovalis.

The left venous valve eventually fuses with the right aspect of the interatrial septum. The upper part of the right venous valve, together with the septum spurium, is converted into the crista terminalis while the lower part of it is represented in the adult heart by the valves of the inferior vena cava and of the coronary sinus.

Further Development of the Atria.—Reference was made earlier to changes which resulted in the transfer of much of the venous return to the right horn of the sinus venosus, and as a consequence, how the left horn of the sinus became diminished in size. It

persists in the adult as the coronary sinus. The right horn of the sinus has opening into it the right common cardinal vein and a new formation, the inferior vena cava (p. 122). With further development of the right atrium the sinus venosus and its right horn are taken up and incorporated in it. The right common cardinal vein (the proximal part of the superior vena cava) and the inferior vena cava acquire thus separate openings into the chamber, but these are, however, posterior to the right venous valve remnants, the crista terminalis, and the valve of the inferior vena cava. That part of the chamber derived from the primitive atrium is characterized by the presence of musculi pectinati and forms mainly the auricular appendage.

A single pulmonary vein opens into the left atrium in early development, but later the proximal portion of this and its first two tributaries become taken up into the wall of the expanding atrium and help to form its cavity. Normally four pulmonary openings are found in the left atrium.

The Interventricular Septum.—The interventricular septum begins as a ridge which grows upwards from the floor of the bulbo-ventricular loop to meet and fuse with the dorsal endocardial cushions of the A.-V. canal near its right side. The ventral extremity of the septum extends to the ventral endocardial cushion near its left end. A foramen (interventricular) persists for some time between the two ventricles cranial to the free border of the interventricular septum and this is eventually closed in the eighth week by the fusion of the proliferations from the right and left bulbar ridges (see below) and the fused endocardial cushions of the A.-V. canal with the free border of the interventricular septum. The pars membranaceae septi marks this place in the adult heart.

Formation of the Aortic and Pulmonary Trunks.—During the fifth week longitudinal endocardial thickenings appear in the bulbus cordis. Proximally these are situated on the right and left walls of the bulbus and when traced distally towards the aortic sac they pursue a spiral anti-clockwise course and then fade out. These two ridges fuse during the eighth week so giving rise to a spiral aortico-pulmonary septum dividing this portion of the heart tube into aorta and pulmonary trunks. Closure of the interventricular foramen puts each of these vessels into communication with the appropriate ventricle.

The Valves of the Heart.—The atrio-ventricular valves arise from sub-endocardial proliferations of tissue at the A.-V. canals. These become excavated or hollowed out on the ventricular aspect in such a manner that strands of muscle tissue, which are later transformed into chordæ tendineæ and papillary muscles, connect them with the ventricular wall. There are three proliferations developed in the right A.-V. canal, and two in the left, and these form the cusps of the tricuspid and mitral valves.

The semilunar valves of the aorta and pulmonary artery are found in the distal part of the bulbus cordis. Two accessory thickenings form here between the main bulbar swellings. When the main swellings fuse and the aortico-pulmonary septum is formed, each resultant channel contains three swellings which become excavated on their distal aspect to form the semilunar valve cusps.

The Atrio-ventricular Bundle.—The myo-epicardial mantle gives origin to the heart muscle which is at first continuous throughout the heart. A ring of fibrous tissue is developed at the A.-V. canal and so the continuity of the primitive cardiac muscle is interrupted except at one place just dorsal to the

dorsal endocardial cushion. This persisting band of tissue forms the atrio-ventricular bundle of His.

Summary of the Development of the Heart.—(1) The heart is formed by the fusion of two endothelial tubes which arise in the splanchnic mesoderm of the cardiogenic area at the anterior end of the embryonic disc. Folding of the head end of the embryo brings this heart tube ventral to the fore-gut in the roof of the pericardial cœlom.

(2) The primitive veins (vitelline, umbilical, and common cardinal) open into a caudally placed sinus venosus segment of the heart tube; the branchial arch arteries lead away from the cephalic end to the dorsal aorta.

(3) The tube is fixed at its cephalic and caudal ends, and between these points it bulges ventrally to form an S-shaped loop.

(4) The ventricular portion of the tube at first grows more rapidly than the atrial, and as a result it falls caudally ventral to that segment.

(5) The atrial portion grows laterally and ventrally forming a dilatation on each side of the bulbus cordis, the right and left atrium.

(6) The primitive atrium is partitioned into right and left chambers by the septum primum and the septum secundum. The A.-V. canal is subdivided into two by the fusion of dorsal and ventral endocardial cushions. The septum primum fuses with the cranial aspect of these.

(7) The proximal part of the bulbus cordis is absorbed into the primitive ventricle. The remainder becomes split into aorta and pulmonary artery by the union of spirally running bulbar ridges.

(8) The ventricle is subdivided into two by a primitive interventricular septum aided by growth of tissue from the caudal aspect of the endocardial cushions and the proximal ends of the bulbar ridges.

(9) The sinus venosus and its right horn become incorporated in the right atrium, while the left horn forms the coronary sinus.

(10) During fœtal life the right and left atria communicate by way of the foramen ovale, which lies between the free edges of septum primum and septum secundum.

Anomalies of Development of the Heart.—(1) "Double heart" is a rare condition due to incomplete fusion of the paired primordia of the heart.

(2) Ectopia cordis is another rare condition where the heart protrudes through a cleft in the ventral thoracic wall. It is probably due to failure of the lateral body folds to meet and fuse in this region.

(3) Dextrocardia may occur alone or as part of general situs inversus. The arteries and veins are found on the opposite side to the normal, and the heart apex is directed to the right. The aortic and pulmonary trunks may be transposed if the aortico-pulmonary septum rotates in the reverse direction to the normal.

(4) Persistent foramen ovale is due to defective development of the interatrial septum.

(5) Persistent interventricular foramen is due to failure of development of the upper part of the interventricular septum. If the interventricular septum is not developed at all, a cor triloculare results.

(6) Stenosis or atresia of the aorta or pulmonary artery result from excessive development of the aortico-pulmonary septum. They are often associated with other defects such as patent interventricular foramen.

The Vascular System.—The primitive vascular system has already been described (p. 99) as arising in the extra-embryonic mesoderm from blood islands which coalesce and form a plexus of vessels from

which main channels develop, and these become continuous with the caudal end of the primitive tubular heart. Within the embryo a fine plexus develops in the embryonic mesoderm and this plexus becomes continuous with the cephalic end of the heart. The main blood vessels of the embryonic body differentiate from this plexus in response to various factors. At first these vessels are simple tubes of endothelium ; differentiation into definitive arteries and veins occurs later but the vessels may be named according to their relationships. The first vessels to appear in mammals are the aortic arches (branchial arch arteries) which arise from a bulbous aortic sac lying ventral to the pharyngeal floor cranial to, and connected with, the bulbus cordis. These arches, of which six pairs appear in succession, run dorsally around the lateral aspect of the pharynx and are connected with the dorsal aortæ. These pass obliquely caudo-medially to fuse at an early date, forming a single dorsal aorta. The dorsal aortæ give off various branches in their course caudalwards, prominent among which are vitelline arteries to the yolk sac and a large umbilical branch on each side to the body stalk and thence to the chorion. A series of modifications of the aortic arches gives rise to the definitive vessels of the head end of the embryo and these will now be described.

The Branchial Arch Arteries.—Six pairs of branchial arch arteries are normally developed in the human embryo, and of these, the fifth pair is rudimentary. As for the others, they are never all present at the same time. The first two pairs regress at an early stage leaving only unimportant mandibular and stapedial vessels to represent them. The distal portion of each third arch artery together with the dorsal aorta extending cranially becomes the internal carotid artery. The cephalic extremity of each

grows alongside the developing brain where an ophthalmic branch is given off to the optic vesicle, and anterior and middle cerebral branches to the brain. It terminates as the posterior communicating artery turning caudally to link up with the developing basilar. The external carotid arteries arise as new vessels which bud out part of the way along the third arch vessel. The proximal part of the third arch artery between this bud and the aortic sac becomes the common carotid artery.

By this time the current of blood in the third arch is directed towards the head end of the embryo, and the blood of the fourth arch caudally, so the segments of the dorsal aortæ between the third and fourth arches disappear. The fourth pair of arch vessels have a different fate on the two sides. That of the right side forms the proximal part of the right subclavian artery. The distal part of the adult subclavian represents the seventh right cervical intersegmental artery (p. 113) which has migrated along the dorsal aorta to the place where the fourth arch artery connects with it. The right dorsal aorta between the subclavian and the common dorsal aorta disappears. The aortic sac becomes drawn out into right and left limbs, the right one elongating to form the innominate artery. The left one, together with the aortic sac and the left fourth arch artery, forms the arch of the adult aorta.

From the sixth arches a pair of capillary plexuses arise which extend into the developing lung buds. On the right side, distal to the capillary outgrowth, the arch degenerates and disappears so that the proximal part, and the outgrowth, form the right pulmonary artery and its branches. On the left side, that part of the arch distal to the capillary outgrowth persists as the ductus arteriosus. The inner part of the arch forms the proximal part of the

left pulmonary artery, which remains therefore in communication with the left dorsal aorta through the ductus. When the pulmonary circulation becomes established after birth the ductus arteriosus

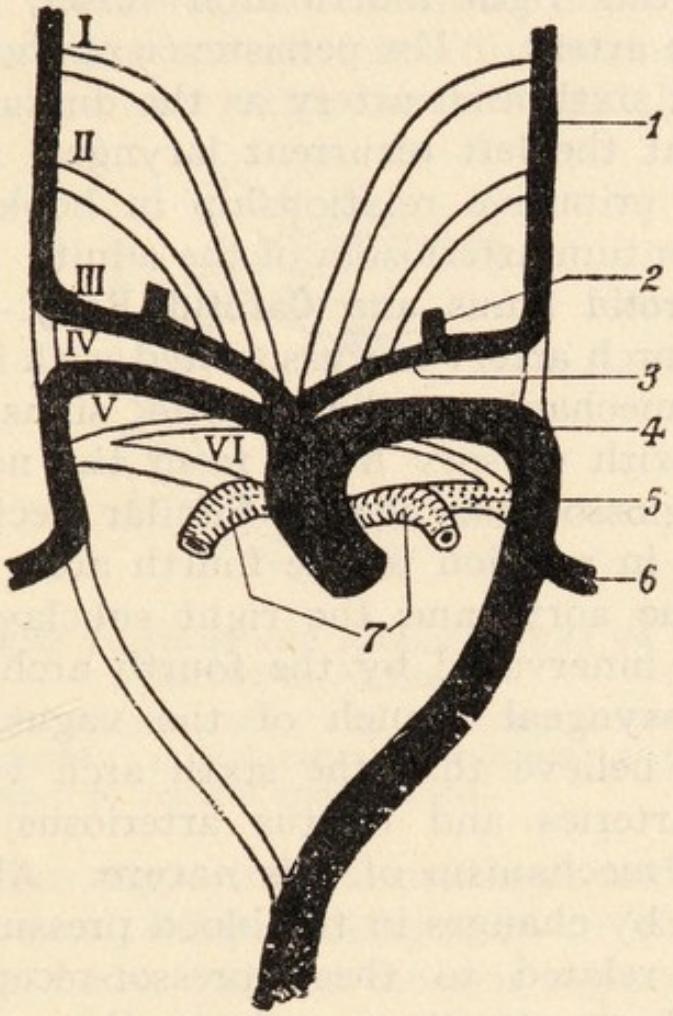

FIG. 26.—SCHEME TO SHOW THE VESSELS DERIVED FROM THE BRANCHIAL ARCH ARTERIES. (Adapted from Congdon.)

1, Internal carotid artery; 2, external carotid artery; 3, common carotid artery; 4, arch of the aorta; 5, ductus arteriosus; 6, left subclavian artery; 7, pulmonary artery. The definitive arteries are printed in solid black, the transitory portions in outline.

contracts down and is obliterated. It is represented in the adult by the fibrous ligamentum arteriosum.

It may now readily be understood why the right and left recurrent laryngeal nerves differ in their course and relations. Initially these nerves arise from their respective vagal trunks immediately caudal to the

sixth branchial arch vessel. The degeneration of the lateral part of this vessel on the right side, and the elongation of the structures of the neck cause this nerve eventually to loop around the caudal aspect of the persisting right fourth arch vessel, that is, the subclavian artery. The persistence of the distal part of the left sixth arch artery as the ductus arteriosus means that the left recurrent laryngeal nerve must retain its primitive relationship in hooking around the ligamentum arteriosum of the adult.

The Carotid Sinus and Carotid Body.—The third branchial arch artery has associated with it a pressor-receptor mechanism, the carotid sinus, which is supplied with sensory fibres from the nerve of the arch, the glosso-pharyngeal. Similar mechanisms are developed in relation to the fourth arch vessels, the arch of the aorta and the right subclavian artery. These are innervated by the fourth arch nerve, the superior laryngeal branch of the vagus. There is reason to believe that the sixth arch vessels (pulmonary arteries and ductus arteriosus) may also develop a mechanism of this nature. All these are influenced by changes in the blood pressure.

Closely related to these pressor-receptors there develop chemo-receptors such as the carotid body and the aortic arch bodies. The carotid body develops primarily as a condensation of mesoderm around the third branchial arch artery (Boyd, 1937). This condensation is later invaded by neuroblasts which are transformed into chemo-receptor cells, and the structure is supplied by the glosso-pharyngeal.

Branches of the Dorsal Aorta.—From the entire length of the definitive dorsal aorta, branches arise which may be arranged in three groups : (*a*) intersegmental dorso-lateral branches to the body wall and neural tube ; (*b*) lateral branches to the derivatives

of the intermediate cell mass of the mesoderm (p. 19); (*c*) ventral branches to the gut and its associated structures.

The Intersegmental Arteries.—These vessels are branches of the dorsal aorta which lie between the somites. Running laterally each divides into a dorsal and a lateral ramus. The dorsal rami give rise to

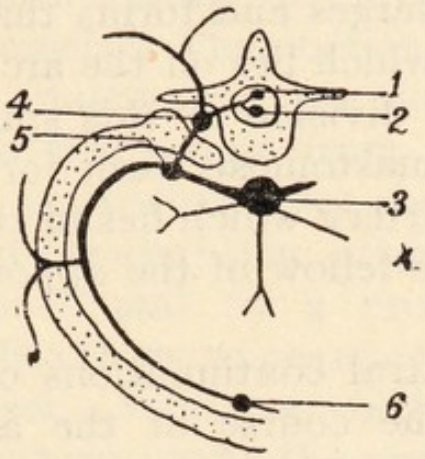

FIG. 27.—SCHEME TO SHOW THE ARRANGEMENT OF THE INTERSEGMENTAL ARTERIES.

1, Post-neural anastomosis; 2, pre-neural anastomosis; 3, dorsal aorta; 4, post-costal anastomosis; 5, pre-costal anastomosis; 6, ventral anastomosis.

spinal branches supplying the meninges and the cord. The lateral rami behave differently in the various regions of the body. In the thoracic region they give rise to the intercostal arteries; in the lumbar region the upper four represent the four lumbar arteries, but the fifth of the series becomes much enlarged and develops into the common iliac artery. Longitudinal anastomoses between the successive intersegmental arteries are formed in pre-costal, post-costal, pre-neural, and post-neural situations. The position of these is indicated in Fig. 27, and they are of importance in forming certain vessels in the neck, such as the vertebral artery. This vessel has a composite origin as follows:

(*a*) The dorsal branch of the seventh cervical intersegmental artery forms that part of it from the

origin to the foramen in the tranverse process of the sixth cervical vertebra.

(*b*) Enlargement of the post-costal anastomoses from the sixth to the first cervical segments, with regression of the stems of the upper six cervical vessels, gives rise to the second part of the vertebral.

(*c*) The spinal branch of the first cervical intersegmental artery enlarges and forms that portion of the vertebral artery which lies on the arch of the atlas.

(*d*) The neural division of this spinal branch with the pre-neural anastomosis then forms that portion of the vertebral artery which lies in the cranial cavity and fuses with its fellow of the opposite side to form the basilar.

The main ventral continuations of the segmental arteries follow the course of the anterior primary divisions of the corresponding nerves, and form ventral anastomotic chains on each side of the middle line in the trunk region. From these chains there are derived the internal mammary and the superior and inferior epigastric arteries.

The Lateral Branches of the Aorta.—These vessels supply the derivatives of the intermediate cell mass and at first these structures extend along a great length of the body. The vast majority of the vessels disappear, but some persist as the renal, spermatic or ovarian, suprarenal, and inferior phrenic arteries.

The Ventral Branches of the Aorta.—The primitive ventral branches of the dorsal aorta are paired and pass to the yolk sac and the mesoderm of the body stalk surrounding the allantois. With fusion of the dorsal aortæ the yolk sac (vitelline) vessels become median in position and are eventually reduced to three in number. These represent the cœliac axis, the superior mesenteric, and the inferior mesenteric arteries of adult anatomy. They are the original branches of the seventh cervical, third thoracic, and

fifth thoracic segments respectively, which have migrated from their primitive to their definitive adult positions by a progressive subaortic anastomosis with successive new caudal stems. By similar migration the umbilical arteries move caudally from their original position, and when in the lower lumbar region they establish connections with the fifth lumbar intersegmental vessels. The portion of the umbilical proximal to this anastomosis now disappears and the vessel appears to take origin from the fifth lumbar artery which is converted into the common iliac. The external and internal iliac arteries then bud off from the umbilical, and by a process of unequal growth the umbilical later appears as if a branch from the internal vessel. When, at birth, the placental circulation is interrupted, the umbilical arteries become fibrosed and remain as the obliterated umbilical arteries. The proximal portion however remains pervious as the stem of the superior vesical artery.

Arteries of the Upper Limb.—The seventh cervical intersegmental artery grows outwards into the limb bud and terminates in a capillary plexus. Later on, digital branches form from this plexus. The primitive axial vessel is divided into two portions, a proximal, or brachial artery, and a distal, or interosseous artery. A median branch growing distally from the brachial segment connects up with the palmar vessels, and the interosseous now loses its communication with them. Ulnar and radial arteries also grow out from the brachial and connect distally with an arch formed at the proximal parts of the digital branches. With this the distal part of the median vessel regresses. The origin of the radial is at first high up in the arm. Later, a connection forms between the brachial and this superficial radial in the elbow region, and the proximal part of the latter vessel disappears. The

original interosseous artery is represented by the anterior interosseous of the adult.

Arteries of the Lower Extremity.—The original axial artery of the lower limb is an outgrowth from the fifth lumbar inter-segmental artery. It runs along with the sciatic nerve and hence is termed the sciatic artery. Passing distally it ends in a plexus from which digital branches arise (Fig. 28*a*). A retiform plexus appears in the ventral part of the thigh and becomes connected with the sciatic vessel by a branch which represents the adult femoral artery (stage *b* in Fig. 28). The middle portion of the sciatic now disappears. The distal portion, lying deep to the tibialis posterior muscle, forms a connection with the new popliteal artery, which has grown distally from the femoral and lies posterior to the popliteus muscle, and so the peroneal artery is formed. A prolongation of the ventral plexus has grown distally to form the anterior tibial artery which secondarily links up with the popliteal vessel at the lower border of the popliteus, the proximal portion of the downgrowth disappearing. A superficial descending artery growing from the popliteal now forms the posterior tibial vessel. In the adult the proximal portion of the original sciatic artery is represented by the arteria comes nervi ischiadici.

Summary of the Development of the Arteries.—(1) Six pairs of aortic or branchial arch vessels are normally developed in the human embryo; the fifth pair are rudimentary and soon disappear.

(2) The first two pairs of arches degenerate and disappear.

(3) Each third arch and the dorsal aorta leading cranially forms the common and internal carotid arteries of that side.

(4) The dorsal aorta between the third and fourth arches disappears on each side.

(5) The right fourth arch persists as the proximal portion of the right subclavian artery.

(6) The fourth arch of the left side forms the arch of the adult aorta.

(7) The proximal portion of the sixth right arch forms the right pulmonary artery. The distal part disappears.

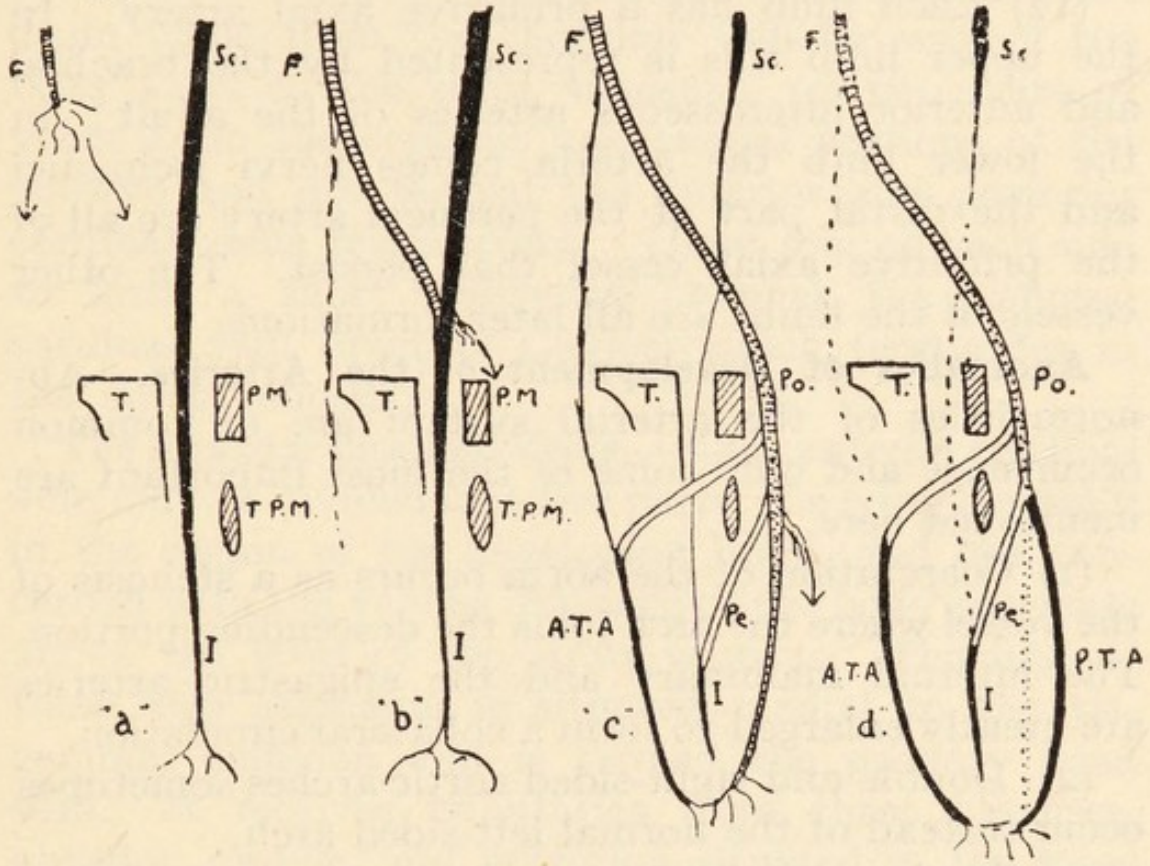

FIG. 28.—DIAGRAMS TO ILLUSTRATE THE DEVELOPMENT OF THE ARTERIES OF THE LOWER EXTREMITY. (Modified from Senior.)

F., Femoral artery; Sc., sciatic artery; T., tibia; P.M., popliteus muscle; T.P.M., tibialis posterior muscle; I., interosseous artery; Po., popliteal artery; A.T.A., anterior tibial artery; P.T.A., posterior tibial artery.

(8) The proximal portion of the sixth left arch forms the left pulmonary artery, and the distal portion, as the ductus arteriosus connects it with the left dorsal aorta.

(9) The right dorsal aorta disappears between the level of the seventh right intersegmental artery and the place of fusion with the left one.

(10) The dorso-lateral intersegmental arteries supply the structures of the body wall and spinal cord ; the lateral branches of the aorta supply the kidneys and gonads ; the ventral branches become the arteries to the gut and the umbilical arteries to the placenta.

(11) The middle sacral artery represents the caudal portion of the fused primitive dorsal aortæ.

(12) Each limb has a primitive axial artery. In the upper limb this is represented by the brachial and anterior interosseous arteries of the adult ; in the lower limb the arteria comes nervi ischiadici and the distal part of the peroneal artery are all of the primitive axial vessel that persist. The other vessels of the limbs are all later formations.

Anomalies of Development of the Arteries.—Abnormalities of the arterial system are of common occurrence and only some of the most important are mentioned here.

(1) Coarctation of the aorta occurs as a stenosis of the vessel where the arch joins the descending portion. The internal mammary and the epigastric arteries are greatly enlarged to form a collateral circulation.

(2) Double and right-sided aortic arches sometimes occur instead of the normal left-sided arch.

(3) Persistence of a lumen in the ductus arteriosus occurs in some instances. After birth blood will pass from the aorta along the ductus to the pulmonary artery giving an " arterio-venous shunt ". In uncomplicated cases there is no cyanosis.

(4) It is not uncommon to find that the right subclavian artery takes origin from the descending thoracic aorta and passes upwards and to the right behind the œsophagus. Here the fourth right arch has degenerated and that part of the right dorsal aorta caudal to the seventh cervical intersegmental artery has persisted.

The Venous System.—The venous system arises

from capillary plexuses in the mesoderm just as does the arterial system and from these certain channels differentiate which, in early embryos, form the following primitive veins : (*a*) right and left vitelline veins pass from the yolk sac wall into the septum transversum and there join the corresponding horn of the sinus venosus ; (*b*) right and left umbilical veins drain blood from the chorionic villi by way of the body stalk to the sinus venosus ; (*c*) two pairs of veins drain the cephalic and caudal portions of the embryo and are termed the anterior and posterior cardinal veins respectively. These join on each side to form a short transverse channel, the common cardinal vein (duct of Cuvier) which terminates in the sinus venosus.

The Anterior Cardinal Veins.—Each anterior cardinal vein may be divided into two parts, one lying cranially in the region of the developing brain, and one concerned with the venous drainage of the body segments above the level of the sinus venosus. The first of these two segments is situated medial to the trigeminal ganglion and is termed the primary head vein. It receives tributaries from three plexuses, anterior, middle, and posterior, situated in the loose mesoderm around the three developing brain vesicles. From these plexuses are formed the venous sinuses of the dura mater and the cerebral veins (Streeter, 1918). The three plexuses establish connections with each other, the posterior with the middle, and the middle with the anterior. This is shown in Fig. 30, A. Those parts of the primary head vein in front of, and behind the trigeminal ganglion disappear. The persisting portion medial to the ganglion forms the cavernous sinus, and this has already established a connection with the anastomosis between the middle and posterior plexuses. This connection is transformed into the superior petrosal sinus of the adult (Fig. 30, B).

The superior sagittal sinus is formed from the dorsal parts of the two anterior plexuses, while the straight and inferior sagittal sinuses are differentiated from parts of all the plexuses which extend downwards in the mid-line between the two cerebral hemispheres. The superior sagittal and straight sinuses open into the trunk connecting the middle and posterior plexuses, which trunk ultimately becomes the transverse sinus. The inferior petrosal sinus is formed by a reconstitution of the posterior part of the primary head vein, and this, together with the termination of the developing transverse sinus, is continuous with the second

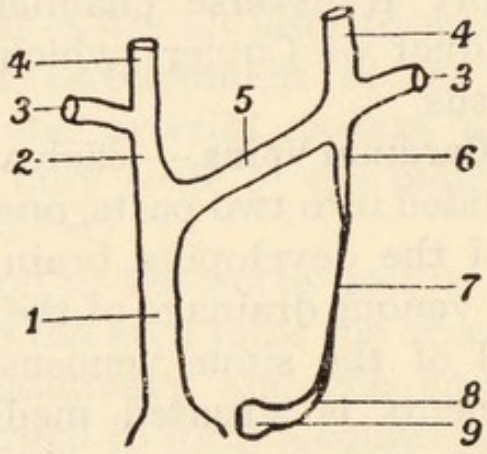

FIG. 29.—THE FATE OF THE ANTERIOR CARDINAL VEINS.
1, Superior vena cava; 2, right innominate vein; 3, subclavian vein; 4, internal jugular vein; 5, left innominate vein; 6, left superior intercostal vein; 7, ligament of Marshall; 8, oblique vein of Marshall; 9, coronary sinus.

part of the anterior cardinal vein. This latter portion of the anterior cardinal undergoes a series of changes which result in the formation of the internal jugular and innominate veins. The anterior cardinal veins are at first short, but they elongate as the neck develops and the heart descends in the thorax. During this elongation the segmental veins which drain into the cephalic end of the posterior cardinal become transferred to them. During the eighth week an obliquely placed cross anastomosis is formed, which passes between the left anterior cardinal close

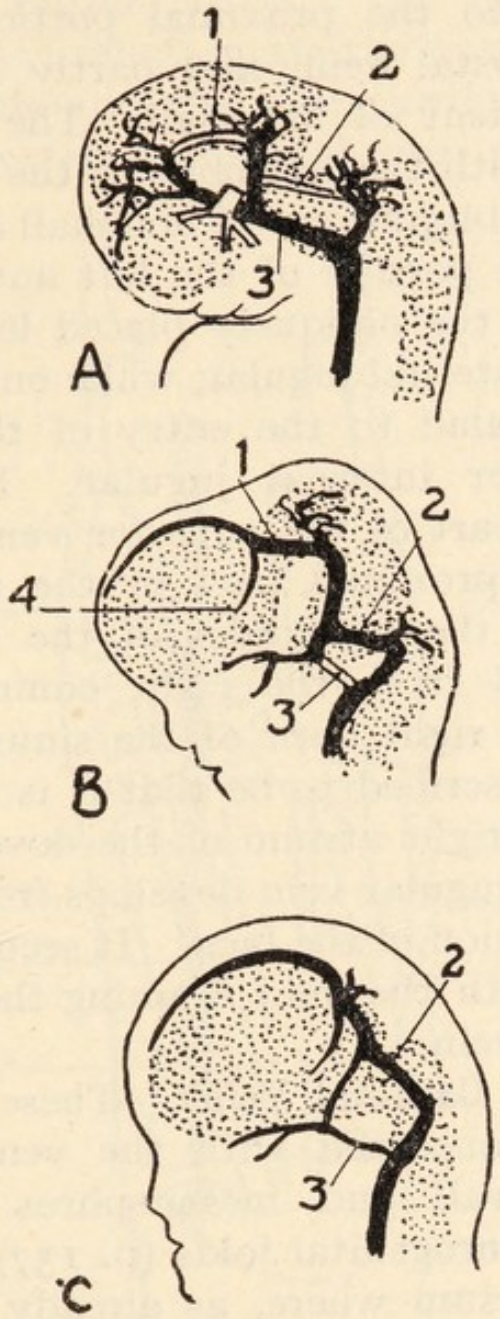

FIG. 30.—DIAGRAMS TO SHOW THE DEVELOPMENT OF THE INTRACRANIAL VENOUS SINUSES FROM ANTERIOR, MIDDLE AND POSTERIOR PLEXUSES. (Modified from Streeter.)

1, Secondary communication between anterior and middle plexuses; 2, secondary communication between middle and posterior plexuses; 3, portion of the primary head vein which disappears, and is later reconstituted as the inferior petrosal sinus.

to the termination in it of the left subclavian vein, and the right anterior cardinal. This is the left innominate vein of the adult. The left anterior cardinal lying caudal to this anastomosis is partly

transformed into the proximal portion of the left superior intercostal vein, and partly into a fibrous cord, the ligament of Marshall. The left common cardinal vein with the left horn of the sinus venosus persists as the oblique vein of Marshall and the coronary sinus. The portion of the left anterior cardinal vein cranial to the obliquely placed left innominate forms the left internal jugular, while on the right side that part cephalad to the entry of the subclavian forms the other internal jugular. The right innominate and part of the superior vena cava represent the most proximal part of the right anterior cardinal, while the remainder of the superior vena cava is derived from the right common cardinal. The fate of the right horn of the sinus venosus has already been described to be that it is absorbed into the wall of the right atrium of the developing heart.

The external jugular vein develops from a capillary plexus in the region of the face. It secondarily forms a connection with the vein draining the upper limb, the subclavian vein.

The Posterior Cardinal Veins.—These paired veins are primarily concerned with the venous drainage of the body wall and mesonephros. Each runs cranially in the urogenital folds (p. 137) to reach the septum transversum where, as already described, it unites with the anterior cardinal vein. The posterior cardinal veins are transitory structures and are soon supplemented and eventually replaced in large part by other longitudinal venous plexuses. The most important are the subcardinal, supracardinal and azygos line veins. The subsequent changes in these veins have been described differently by various writers and there is still confusion with regard to their fate.

The Inferior Vena Cava.—The development of the inferior vena cava in man has been described by

McClure and Butler (1925). The embryonic veins concerned in its formation are the posterior cardinals. the subcardinals and the supracardinals. The position of the posterior cardinal vein dorso-lateral to

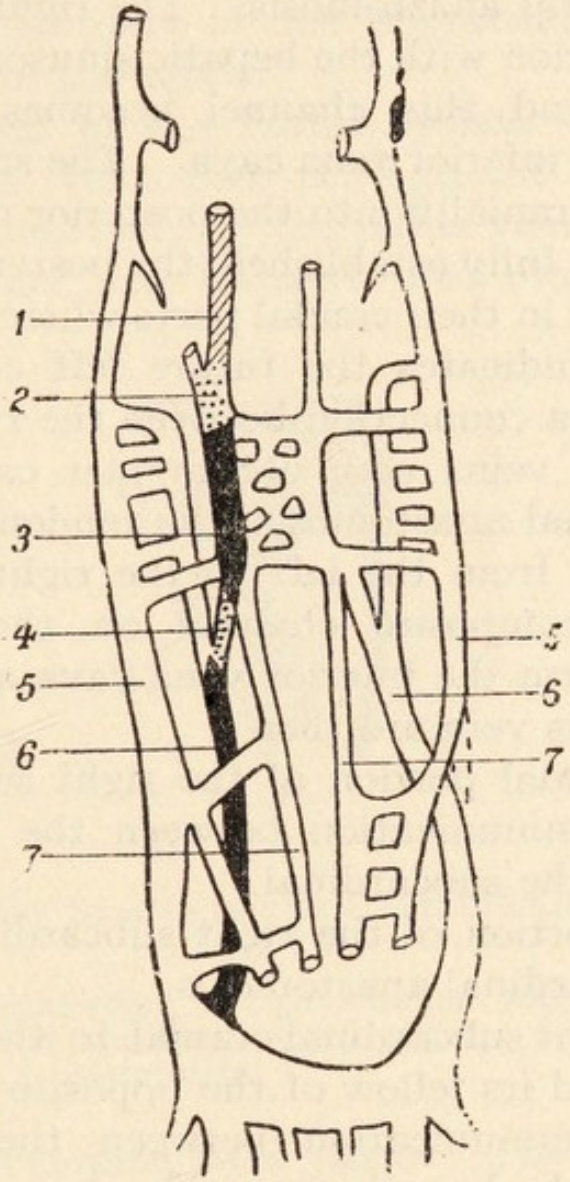

FIG. 31.—SCHEME TO SHOW THE DEVELOPMENT OF THE INFERIOR VENA CAVA. (Adapted from Huntingdon and McClure.)

1, Hepatic segment; 2, pre-renal segment of subcardinal vein; 3, renal segment of subcardinal vein; 4, connection between sub- and supracardinal veins; 5, posterior cardinal vein; 6, supracardinal vein; 7, subcardinal vein.

the mesonephros has already been described. The subcardinal vein is to be found along the medial aspect of the mesonephros and it is connected cranially and caudally with the corresponding posterior cardinal.

The supracardinal develops just lateral to the sympathetic trunk. The subcardinal veins anastomose freely with the corresponding posterior cardinals, and, during the sixth week are joined to each other by an intersubcardinal anastomosis. The right subcardinal effects a junction with the hepatic sinusoids about the same time, and this channel becomes the hepatic portion of the inferior vena cava. The supracardinals are draining cranially into the posterior cardinals and when they are fully established, the posterior cardinals regress except in their caudal parts where a transverse anastomosis indicates the future left common iliac vein. When a connection between the right sub- and supracardinal veins now occurs just caudal to the intersubcardinal anastomosis, the tendency is for the blood to pass from the left to the right side of the body. The composite channel on the right side enlarges to form the inferior vena cava and the components of this vein are then :

(1) The caudal portion of the right supracardinal.

(2) The communication between the right supracardinal and the subcardinal.

(3) That portion of the right subcardinal opposite the intersubcardinal anastomosis.

(4) The right subcardinal cranial to the connection between it and its fellow of the opposite side.

(5) The communication between the right subcardinal and the hepatic sinusoids.

(6) The terminal part of the right vitelline vein which connects the hepatic sinusoids with the sinus venosus.

The left renal vein is formed from the intersubcardinal anastomosis. Since the subcardinals drain the genital glands their caudal parts form the testicular or ovarian veins. The azygos and hemiazygos veins are variously described. According to McClure and Butler (1925) they arise from the cranial portions of

the supracardinals, but Reagan, in a series of papers, contends that they take origin from a pair of longitudinal venous channels (the azygos line veins) which lie medial to the sympathetic trunks. In this view, the cranial portions of the supracardinals are not represented in the adult.

Development of the Portal System.—The vitelline and umbilical veins pass through the septum transversum on their way to the sinus venosus, and consequently they are brought into close association

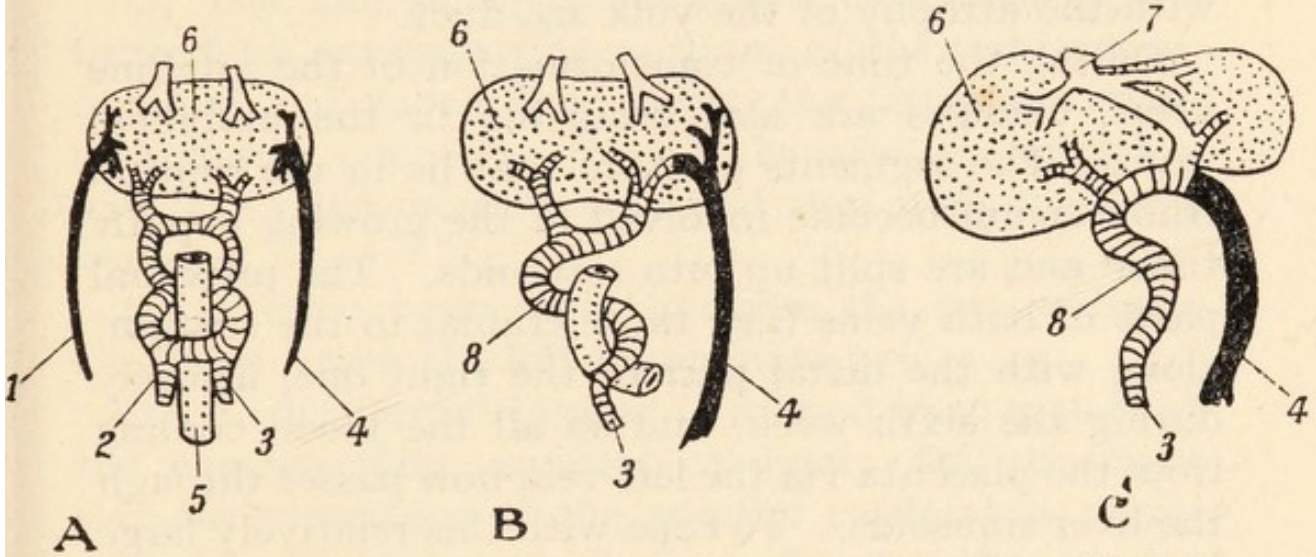

FIG. 32.—THREE STAGES IN THE DEVELOPMENT OF THE PORTAL VEIN.

1, Right umbilical vein; 2, right vitelline vein; 3, left vitelline vein; 4, left umbilical vein; 5, gut; 6, liver; 7, ductus venosus; 8, portal vein.

with the developing liver tissue. The vitelline veins become broken up in this part of their course into sinusoids lying between the developing columns of liver cells, and there remain caudal portions of the original veins between the liver and yolk sac, and cranial portions between the liver and the sinus venosus. Two transverse communications, cephalic and caudal, passing ventral to the primitive gut, develop between the caudal portions of the two veins. A third communication arises dorsal to the gut and midway between the other two. The right vitelline

vein degenerates between the caudal and middle anastomoses, and the left one between the middle and cranial anastomoses. This results in the formation of an S-shaped spiral vitelline venous channel around this segment of the gut, the primitive duodenum. This is the portal vein. From the dorsal aspect of the middle communication a new vein is growing out and it passes in the mesentery to the gut wall. It is the superior mesenteric vein. The distal portions of the vitelline veins disappear along with the atrophy of the yolk sac duct.

During the time of transformation of the vitelline veins, changes are also occurring in the umbilical veins. The segments of them that lie in the septum transversum become involved in the growing hepatic tissue and are split up into sinusoids. The proximal parts of both veins (*i.e.*, those cranial to the septum) along with the distal part of the right one, atrophy during the sixth week, and so all the blood coming from the placenta via the left vein now passes through the liver sinusoids. To cope with this relatively large volume of blood a short circuiting channel forms between the left umbilical vein where it enters the liver and the right vitelline vein. This new structure (Fig. 32, C) is the ductus venosus and it appears as the direct continuation of the left umbilical, most of the blood in which now passes direct to the inferior vena cava without entering the hepatic sinusoids.

After birth, when the placental circulation ceases, the left umbilical vein becomes impervious forming the ligamentum teres of the falciform ligament. The usefulness of the ductus venosus being ended, it, like the umbilical vein, becomes fibrosed and persists in the adult as the ligamentum venosum of the liver.

Summary of Development of Venous System.—(1) The main intra-embryonic veins are the anterior and

posterior cardinals, the subcardinals, the supra-cardinals and the azygos line veins. These are all paired structures.

(2) The posterior cardinal veins disappear except for their extreme caudal parts which are connected by a transverse channel, the primordium of the left common iliac vein.

(3) The subcardinal veins enter into the formation of the genital gland veins of the adult. The right one also contributes to the inferior vena cava.

(4) The inferior vena cava is a composite vessel formed by anastomosing portions of the right supra-cardinal and subcardinal veins, the latter becoming secondarily connected by an hepatic prolongation with the right vitelline vein and thus with the sinus venosus.

(5) A cross connection between the two anterior cardinals forms the left innominate vein.

(6) Each internal jugular is formed from a part of the corresponding anterior cardinal. On the right side the remainder of the anterior cardinal is represented by the right innominate and part of the superior vena cava. On the left side this segment forms part of the left superior intercostal vein and a fibrous cord, the ligament of Marshall.

(7) The vitelline veins form three transverse communications, one behind and two in front of the duodenal segment of the gut. An **S**-shaped portal vein arises by the disappearance of the left vitelline between the upper and middle communications, and the right vitelline between the middle and lower communications.

(8) The umbilical veins in the septum transversum become broken up by the liver tissue into sinusoids. Distal to this the right one atrophies, and a short circuit, the ductus venosus, between the left one and the inferior caval segment of the right vitelline

allows the placental blood easy access to the right atrium of the heart.

Anomalies of Development of the Veins.—As in the case of the arterial system abnormal veins are of relatively common occurrence.

(1) Two superior venæ cavæ may be present; they are due to the persistence of both right and left anterior cardinal veins.

(2) Two inferior venæ cavæ may be found; they are due to persistence of the sub-supracardinal systems on the left as well as on the right side.

(3) The great veins may be transposed giving rise to left superior and inferior venæ cavæ.

The Fœtal Circulation.—Oxygenated blood from the placenta is returned to the fœtus by way of the left umbilical vein. Most of it passes directly into the inferior vena cava through the ductus venosus, a little entering the liver sinusoids. In the inferior vena cava the placental blood is diluted somewhat by impure blood coming from the caudal region of the fœtus. It then passes into the right atrium where the remains of the right sinus valve direct it towards the foramen ovale. The sharp concave margin of the upper border of the foramen splits the blood stream into two parts. Most of it passes into the left atrium through the foramen ovale, thence into the left ventricle and out into the systemic circulation. This blood is chiefly distributed to the arteries of the head, neck, and upper limbs which have therefore priority as regards the oxygen content of their blood supply. The lesser amount of blood from the inferior caval stream is mixed in the right atrium with venous blood entering by way of the superior vena cava. The mixed blood passes into the right ventricle, and emerging from this chamber, is mostly carried through the ductus arteriosus to the descending thoracic aorta. Here it has added to it the oxy-

genated blood not required for the supply of the head and neck and is distributed in small part to the organs of the fœtus, the rest passing along the umbilical arteries to the placenta where it is once more purified and recommences the circulation.

Changes in the Circulation at Birth.—The changes that occur in the circulation after birth are of two kinds; there are the functional changes which occur in a matter of minutes, and the structural changes which are spread over a period of months. Very shortly after birth the umbilical arteries in the cord contract down and cease pulsating. Somewhat later the umbilical vein and the ductus venosus also contract so that if the cord be not tied some of the placental blood is drained back in the interval into the infant's body. The ductus arteriosus is very muscular and very soon after birth it contracts like a sphincter causing the right ventricular blood to pass now into the pulmonary circulation. The expansion of these pulmonary vessels with the commencement of respiration results in an increased flow of blood to the left atrium. At the same time there is diminished venous return to the right atrium because the placental circulation is interrupted. These changes mean that the pressure in the left atrium is now relatively greater than in the right and the septum primum is pressed against the septum secundum thus functionally obliterating the foramen ovale.

Thrombosis and fibrosis of the occluded channels results in their anatomical closure, but this is a slow process requiring several months for its completion. Fusion of the apposed tissues at the foramen ovale is also a slow process, and even in adults may not be quite complete. In such cases, however, there is no functional disability.

The Lymphatic Vessels and Glands. The lymphatic vessels arise in close relationship with the venous

system in five regions of the embryo. There are lymph sacs in the region of the internal jugular veins on either side, similar lymph sacs associated with the sciatic veins, and an unpaired retroperitoneal sac. There has been considerable discussion with regard to the origin of these primordia. One view states that the lymphatic vessels develop as endothelial sprouts from already formed venous channels. A second view claims that they arise primarily by the running together of spaces in the mesenchyme to form lymphatic vessels which secondarily become connected with the venous system. The cells bounding such spaces become transformed into endothelium. The work of Huntingdon (1914) and of McClure (1915) is strong evidence in favour of the second view. The lymph sacs appear during the sixth and seventh weeks and numerous anastomosing vessels grow outwards from them tending in their course to be perivenous. The jugular sacs obtain connections with the internal jugular veins which persist as the terminal part of the thoracic duct and the right lymphatic duct. Lymphoblasts become aggregated in various places around these capillary meshworks from the eighth week onward and produce lymphocytes. These embryonic lymph nodes are later encapsuled by condensation of the surrounding mesenchymal cells.

The Blood Cells.—The red and white cells of the body are all derived from a common ancestral cell, the haemocytoblast of mesodermal origin (Maximow, 1927). The first blood cells arise in blood islands in the mesoderm covering the yolk sac (p. 99) as spherical cells with a relatively large nucleus and finely granular basophilic cytoplasm. Following one line of differentiation from this cell the erythrocyte arises. The stages in its formation are, first the megaloblast, which is a cell with a large vesicular

nucleus and slightly acidophilic cytoplasm, and then the normoblast, which has a small compact nucleus and a considerable content of haemoglobin. From this cell, by loss of the nucleus, the erythrocyte is formed. According to some observers, the nucleus of the normoblast is extruded into the blood plasma ; others claim that it is absorbed.

Haemocytoblasts are also the stem cells for the granular leucocytes. They give rise to myelocytes, which are acidophil, basophil, or neutrophil according to the nature of the specific granules in their cytoplasm, and from which are formed the various types of granular leucocytes. The lymphocytes likewise result from changes in cells known as lymphoblasts which are in turn derived from haemocytoblasts or from undifferentiated mesenchymal cells.

While the earliest formation of blood cells takes place in the wall of the yolk sac, the liver soon becomes an important centre for their formation. Shortly afterwards the spleen also joins in the process. Both the liver and spleen continue to function in erythropoiesis until birth, although from the third fœtal month onward the bone marrow becomes increasingly important in this connection. After birth the bone marrow remains as the sole blood forming tissue.

The Spleen.—During the sixth week the primordium of the spleen may be recognised as a thickening on the left side of the dorsal mesogastrium. This splenic condensation subdivides this part of the dorsal mesentery into two, and the more dorsal of these becomes partly applied to, and fused with, the peritoneum in front of the developing left kidney. The attachment of the spleen to the dorsal abdominal wall is thus moved to the left and the attaching part of the mesentery may now be called the lienorenal ligament. The remainder of the mesentery between

the splenic condensation and the greater curvature of the stomach is the gastro-splenic ligament.

Commencing about the ninth week the cells of the mesodermal condensation become arranged in anastomosing columns with sinusoidal spaces between them. These spaces secondarily become connected with branches of the splenic artery and vein. The cells of the trabeculae resemble lymphoblasts, and for some time red cells, lymphocytes and leucocytes are produced in the spleen. During the later months of fœtal life the production of granulocytes ceases, and red cells are not formed after birth.

CHAPTER XI

THE CŒLOMIC CAVITIES

THE primitive cœlomic cavity is formed by the confluence of spaces which arise in the lateral plate mesoderm on each side of the embryonic disc (p. 19). Anteriorly, the two cavities thus formed communicate with each other across the mid-line in the region of the cardiogenic plate so that the early cœlom is horseshoe-shaped. It becomes subdivided into pericardial, pleural, and peritoneal cavities by the formation of a transversely placed mass of mesoderm known as the septum transversum, and also by certain changes associated with growth of the heart and lungs.

The Pericardial Cavity.—When the developing heart becomes folded under the foregut, the anterior part of the cœlom, from whose roof it is now suspended by the dorsal mesocardium, occupies a position at right angles to the remainder of the body cavity and is limited caudally by the septum transversum. This caudal boundary is not complete, for on each side there is a dorso-lateral communication, the

pleuro-peritoneal canal. The free dorsal edges of the septum bounding this in front contain the common cardinal veins. The lung buds now appear and bulge caudo-laterally into the upper part of each pleuro-peritoneal canal, which may now be regarded as the primitive pleural cavity. The heart undergoes

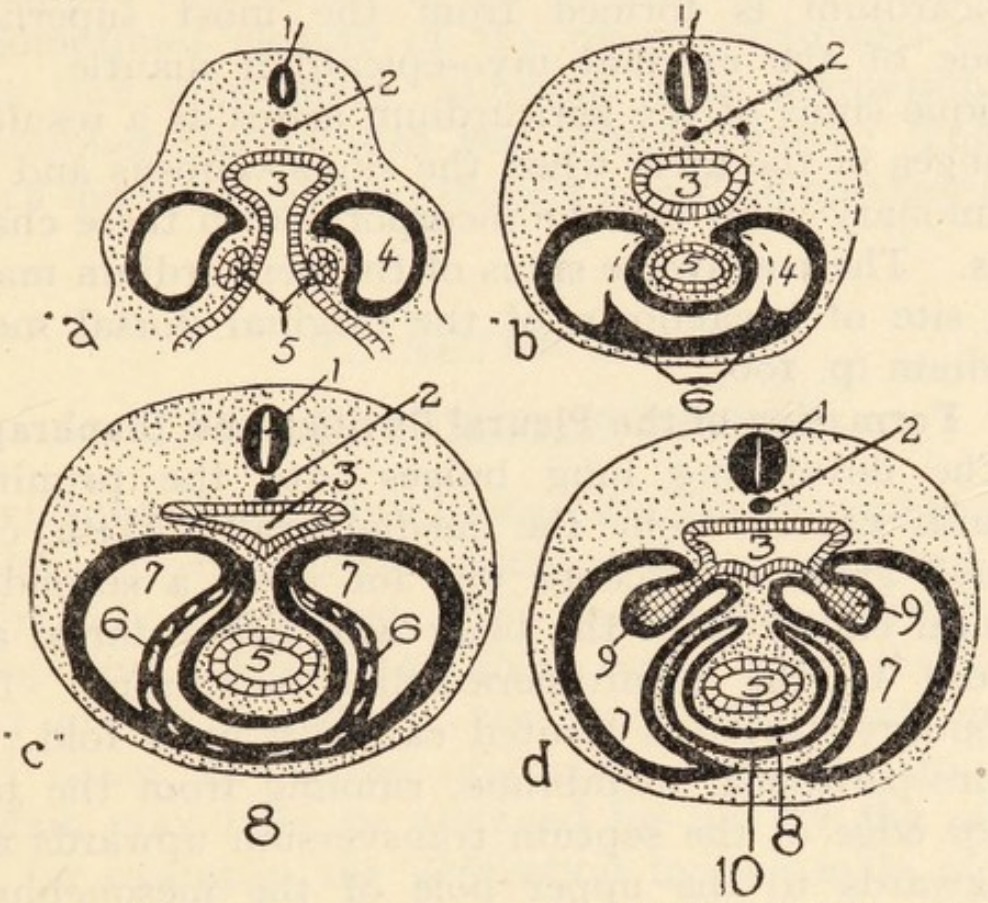

FIG. 33.—FIGURES TO SHOW THE DEVELOPMENT OF THE PERICARDIAL CAVITY.

1, Spinal cord ; 2, notochord ; 3, pharynx ; 4, pleuro-pericardial recess ; 5, heart tube ; 6, pleuro-pericardial folds ; 7, pleuro-peritoneal recess ; 8, pericardial cavity ; 9, lung bud ; 10, fibrous pericardium.

a descent relative to the surrounding structures and so the common cardinal veins are forced to run in an increasingly oblique direction caudomedially to reach the sinus venosus. Each vein raises up a ridge whose free border is directed inwards. These are the pleuro-pericardial folds, and their free edges eventually fuse with the mesoderm ventral to the œsophagus, so closing off the pericardial cavity from

the rest of the cœlom. These pleuro-pericardial walls now become differentiated into pleural membranes externally and parietal serous pericardial membranes internally. The mesodermal tissue on the outer surface of the latter forms the fibrous pericardium. The visceral layer of the serous pericardium is formed from the most superficial tissue of the original myo-epicardial mantle. The oblique sinus of the pericardium arises as a result of changes in the atria when the sinus venosus and the pulmonary veins become incorporated in these chambers. The transverse sinus of the pericardium marks the site of breakdown of the original dorsal mesocardium (p. 100).

Formation of the Pleural Cavities and Diaphragm.—The developing lung bulges into the primitive pleural cavity from the medial wall. With continued growth it scoops out for itself a secondary pleural cavity from the body wall tissue dorsal and caudal to the pleuro-pericardial membrane. This secondary cavity is limited caudally by a fold, the pleuro-peritoneal membrane, running from the posterior edge of the septum transversum upwards and backwards to the upper pole of the mesonephros. With further growth of the lung the dorsal end of the pleuro-peritoneal membrane is displaced caudally, and the lung also insinuates itself from behind on to the lateral aspect of the common cardinal vein and the phrenic nerve in the pleuro-pericardial membrane. Eventually in the eighth week the free medial edge of the pleuro-peritoneal membrane fuses with the mesoderm on the lower part of the œsophagus and the pleural is closed off from the peritoneal cavity.

The diaphragm is made up of the following components :

(1) The cephalic layer of the septum transversum.
(2) The paired pleuro-peritoneal membranes.

These become invaded by muscle cells from the third, fourth and fifth cervical segments during caudal migration.

(3) The œsophageal mesentery.

(4) Tissue derived from the body wall by the continued excavation of the pleural cavity into it.

Sometimes closure of the pleuro-peritoneal canal does not take place, allowing thus herniation of abdominal viscera into the pleural cavity. This is much more frequent on the left side than on the right.

CHAPTER XII

THE UROGENITAL SYSTEM

ALTHOUGH in the adult human the urinary and genital systems perform quite different functions. they are intimately associated with each other during development. They take their origin from the same part of the mesoderm, the intermediate cell mass, and some structures originally belonging to one system may later be annexed for use by the other, as, for example, the utilization by the male of the duct of the temporary kidney (the mesonephros) as an efferent duct for the male germ cells. Nevertheless, for purposes of descriptive embryology it is convenient to discuss the two systems separately.

The Urinary System.—Before the permanent kidney or metanephros becomes differentiated in the human embryo, two other excretory organs arise and disappear. The first is called the pronephros and it is a transitory structure. The second, the mesonephros, is a temporary one functioning during the second month of development. These three organs arise in cranio-caudal sequence in the embryonic body from the nephrogenic cord of the intermediate mesoderm.

The Pronephros.—The pronephros is found during the fourth and early fifth weeks of development as a short series of segmentally arranged cell cords in the intermediate cell mass of the future cervical region. In each segment the lateral part of the cord turns caudally, comes in contact with the cord of the succeeding segment and fuses with it. In this way a longitudinal pronephric duct is formed, and the lateral end of the last tubule continues to grow caudally until it reaches the lateral wall of the cloaca into

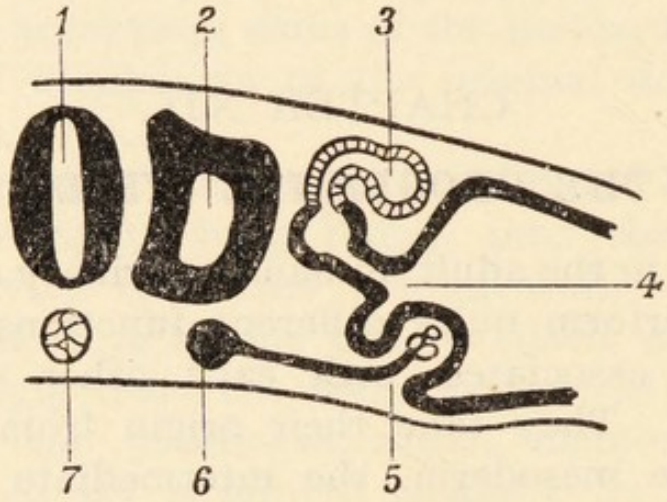

FIG. 34.—THE PRONEPHROS.

1, Spinal cord; 2, myotome; 3, pronephric duct; 4, nephrostome; 5, glomerulus; 6, aorta; 7, notochord.

which it opens. The proximal part of each cord is connected with the cœlomic wall and, the cord becoming hollowed out, this represents a nephrostome. Adjacent to it the cœlomic wall becomes invaginated as a knob of cells representing an external glomerulus. Before the caudal part of the pronephros has yet arisen, the cranial part is already undergoing degeneration.

The Mesonephros.—As the cephalic tubules of the pronephros degenerate, the mesonephros commences to form in the upper thoracic segments as spherical masses of cells in series with the tubules of the pronephros. The cell masses become hollow as mesone-

phric vesicles, and a cord of cells grows towards the pronephric duct from the lateral side of each. The cord becomes S-shaped, develops a lumen and its free extremity fuses with the pronephric duct, which may now be called the mesonephric duct. The medial wall of each mesonephric vesicle becomes invaginated by a branch from the dorsal aorta to form a glomerulus, its thinned out wall becoming Bowman's capsule. The tubule shows a proximal secretory portion lined by tall columnar epithelial cells, and a distal collecting portion where the epithelium is cubical. Each body segment contains several mesonephric tubules and the organ extends as far caudally as the third lumbar segment. When fully developed, it bulges as the urogenital fold on each side into the cœlom from the dorsal body wall, being attached thereto by a broad mesentery. The tubules of the mesonephros differ from those of the pronephros as follows :

(1) They are not segmentally arranged.

(2) They do not develop a duct of their own but make use of the existing pronephric duct.

(3) They possess internal glomeruli.

Degeneration at the cranial end of the mesonephros commences during the fifth week and proceeds caudally. The process is well advanced by the ninth week, but some of the caudal tubules persist in modified form in connection with the genital organs (see later). The work of Gersh (1937) has shown that the mesonephros is functional in lower mammalian forms such as the opossum pouch young, and rabbit, cat, and pig embryos. In these the mesonephros can excrete such substances as ferrocyanide and phenol red. As functional differentiation of the metanephros occurs so the ability of the mesonephros to excrete such substances diminishes.

The Metanephros.—The metanephros takes origin from two primordia; the excretory part of it is derived from the caudal undifferentiated tissue of the nephrogenic cord, while the collecting tubules are formed from the ureteric bud of the mesonephric duct. The latter is the first to appear. In the fifth week there is an outgrowth from the dorsal wall of the mesonephric duct close to its entrance into the cloaca. This is called the ureteric bud, and it grows actively, at first dorsally, and then dorsally and cranially. This brings its tip into contact with the caudal undifferentiated mesoderm of the nephrogenic cord. This tissue forms a cap over the free, somewhat dilated extremity of the ureteric bud, and it is termed the metanephritic blastema. As the ureteric primordium elongates the blastemal cap is carried cranially upon it from the original position opposite the first and second sacral segments.

The tip of the ureteric bud becomes bi-lobed and the blastema divided also into two parts. Each of these gives off three to six tubular diverticula, the blastema at the same time dividing into a corresponding number of caps. Secondary and tertiary tubules are then formed by branching, and the process continues until some thirteen generations are present. The mesodermal caps divide so as to keep pace with the appearance of each new generation of tubules, so that each always has its own blastema. The first two tubules by their subsequent growth form the major calyces; the secondary tubules connected with these form the minor calyces. The tubules of the third and fourth generations are absorbed into the walls of the minor calyces so that the tubules of the fifth generation ultimately open into them as the papillary ducts of the renal pyramids. The tubules of the remaining generations form the collecting tubules of the adult kidney.

The blastema at the tip of each collecting tubule is at first a solid mass of cells, but it soon becomes vesicular and then elongated in an **S**-shape with one extremity in contact with the tip of the collecting tubule. Communication between the lumina of the two tubules now occurs. The lower (distal) limb of

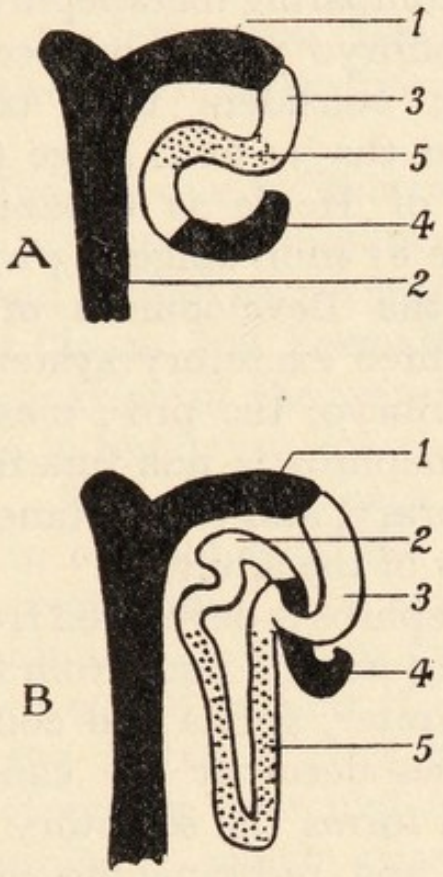

FIG. 35.—TWO STAGES IN THE DEVELOPMENT OF THE SECRETING TUBULES OF THE KIDNEY.

A. 1, Collecting tubule; 2, main collecting tubule; 3, distal convoluted tubule; 4, glomerulus; 5, loop of Henle. B. 1, Collecting tubule; 2, proximal convoluted tubule; 3, distal convoluted tubule; 4, glomerulus; 5, loop of Henle.

the **S**-shaped tubule becomes invaginated by blood vessels to form a renal glomerulus, the neighbouring wall of the loop becoming thinned out as Bowman's capsule. The portion of the tubule next this region elongates and forms the proximal convoluted tubule; the portion next the collecting tubule forms the distal convoluted tubule, while the limb of the **S**

between these two elongates greatly to become the loop of Henle. Not all of the embryonic renal tubules persist into adult life for Kampmeier (1926) has shown that a number in the depths of the kidney, that is, early formed ones, have only a temporary existence.

Gersh (1937), comparing metanephric differentiation in the human embryo with evidence obtained from other mammals, considers that tubular function commences about the 32 mm. stage (9 weeks of age) while the loop of Henle is capable of water re-absorption at the 81 mm. stage (13 weeks).

Summary of the Development of the Kidney.—(1) A series of three excretory systems is developed in the human embryo, the pro-, meso- and metanephros. The pronephros is non-functional, the mesonephros is temporary, and the metanephros forms the functional kidney of the adult.

(2) The metanephros is developed from two sources : (*a*) an outgrowth (ureteric bud) from the mesonephric duct forms the ureter, pelvis and collecting tubules ; (*b*) a mass of mesoderm at the caudal end of the nephrogenic cord forms the secretory system.

(3) Branching and re-branching of the extremity of the ureteric bud gives rise to about thirteen generations of tubules. These become connected with S-shaped tubules derived from caps of mesoderm over the extremity of each.

(4) The lower limb of each S-shaped tubule becomes invaginated by blood vessels to form a Bowman's capsule and glomerulus.

(5) The transverse portion of the S-shaped tubule elongates towards the medulla to form the loop of Henle, while the remaining parts are transformed into the proximal and distal convoluted tubules.

Anomalies of Development of Kidneys and Ureters.—(1) Congenital cystic kidney may be the result of

failure of union of the secretory and collecting tubule systems, or it may be due to persistence of renal tubules which normally degenerate.

(2) Horseshoe kidney is produced by fusion of the two metanephric blastemae. The fusion is usually at the lower ends.

(3) Double ureter is caused by the growth of two ureteric buds. A cleft renal pelvis and partially cleft ureter are a sequel of early division of the ureteric bud.

(4) Pelvic kidney is due to failure of ascent of the organ from its primary developmental position opposite the first and second sacral segments.

Subdivision of Cloaca and Formation of Bladder.—The caudal termination of the primitive gut is somewhat dilated as a blind sac in which the allantois also terminates. This is the cloaca, and the ventral surface of it is in contact with the surface ectoderm as the cloacal membrane. The growth of the tail causes this membrane at first to face ventrally and then to become reversed so that it looks towards the attachment of the umbilical cord to the body wall. The primitive streak is now just caudal to it, and proliferates mesoderm which passes on each side around the margins of the membrane to contribute to the formation of the infra-umbilical part of the anterior abdominal wall and external genitalia (Wyburn, 1937).

During the fifth week the pronephric (later mesonephric) ducts reach the lateral wall of the cloaca and open into it. A coronally arranged septum now arises in the angle between the allantois and the hindgut and grows caudally towards the cloacal membrane. This is the urorectal septum and it splits the cloaca into two parts, a dorsal rectum and a ventral urogenital sinus which has the mesonephric ducts opening into it. The urorectal septum reaches

and fuses with the entoderm of the cloacal membrane during the seventh week at the primitive perineum. Subsequent breakdown of the two subdivisions of the cloacal membrane puts the rectum and urogenital

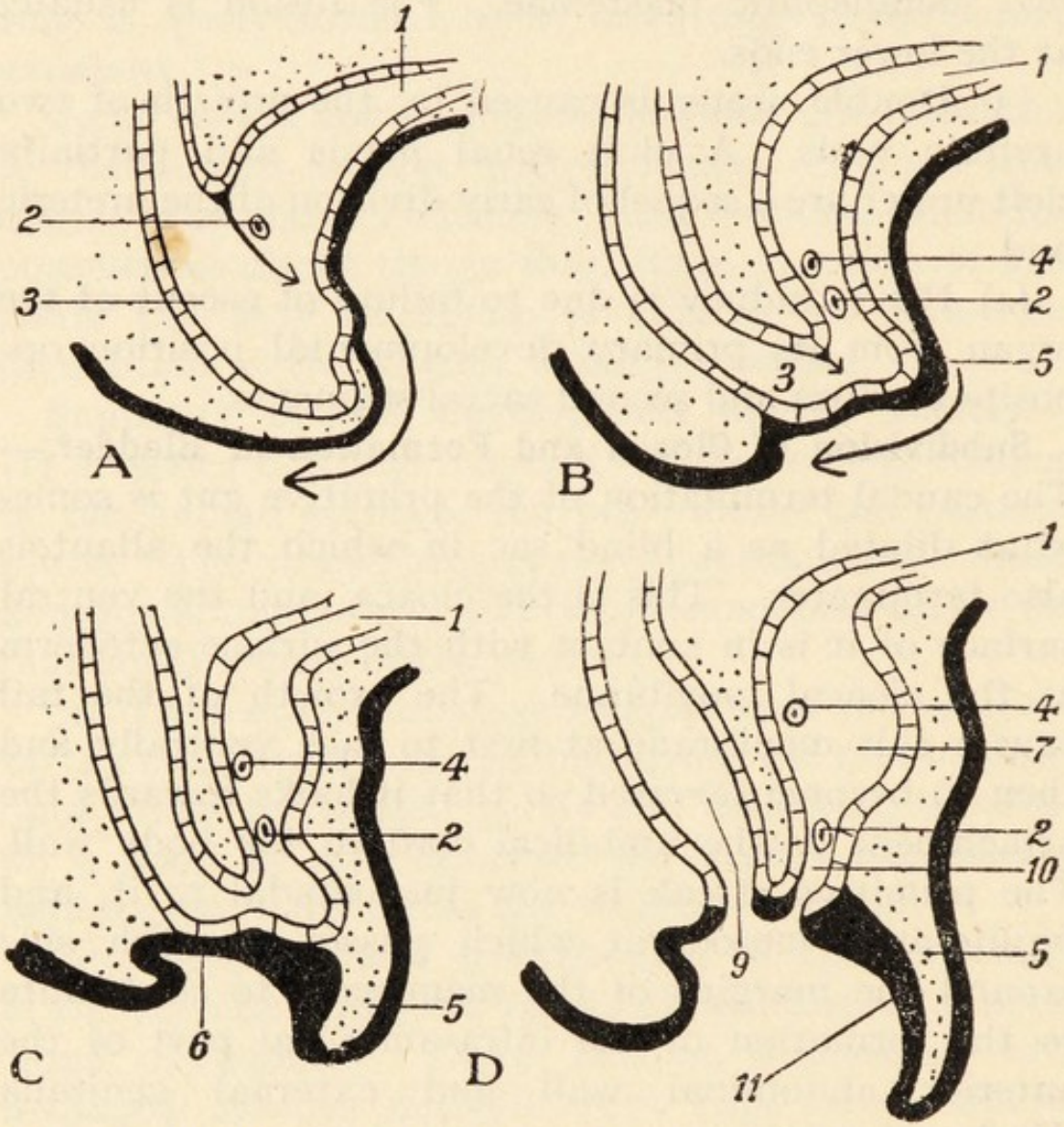

FIG. 36.—FOUR DIAGRAMS TO SHOW THE CHANGES IN THE CLOACA. (Adapted from Corning.)

1, Allantois; 2, opening of mesonephric duct; 3, cloaca; 4, ureteral opening; 5, genital tubercle; 6, cloacal membrane; 7, bladder; 9, rectum; 10, urethra.

sinus in communication with the exterior. The site of entrance of the mesonephric ducts divides the urogenital sinus into an upper vesico-urethral primordium and a lower urogenital sinus proper. The cranial part of the vesico-urethral primordium dilates

to form the bladder. During this process, a series of growth changes occur in the region of the lower ends of the mesonephric ducts. The terminal parts of them are absorbed into the bladder so that the ureters and the mesonephric ducts acquire separate openings, and then the ureteric orifices are carried cranio-laterally by the growth of the bladder. The openings of the mesonephric ducts remain in the primitive urethral part of the primordium. Since the mesonephric ducts are of mesodermal origin absorption of them into the bladder wall contributes a mesodermal component to the otherwise entodermal structure. This mesodermal area is the trigone of adult anatomy. The allantois regresses as development proceeds and ultimately becomes a fibrous cord, the urachus, connecting the apex of the bladder with the umbilicus.

The primitive urethral part of the vesico-urethral primordium grows slowly and so remains relatively narrow. It forms most of the length of the urethra in the female. In the male it forms that part of the urethra extending from the bladder to the openings of the common ejaculatory ducts.

The Prostate Gland.—This is first seen in the male embryo of three months as five solid cords of entodermal cells which grow from the distal part of the primitive urethra and proximal part of the urogenital sinus into the surrounding mesoderm. These become hollow, tortuous, and branched to form the prostatic gland tubules. The surrounding mesoderm contributes smooth muscle and connective tissue fibres to the capsule. Corresponding entodermal cords in the female become the paraurethral glands of Skene.

Summary of the Development of the Bladder.—(1) In the early stages there is a common cloaca in which terminate the hindgut, the allantois and the mesonephric ducts.

(2) A septum (urorectal) grows caudally from the angle between the gut and the allantois to fuse with the cloacal membrane at the primitive perineum. This separates the cloaca into the rectum and the urogenital sinus.

(3) The part of the early urogenital sinus above the openings of the mesonephric ducts becomes the bladder in both sexes ; in addition, it forms most of the female urethra, and that part of the male urethra from the bladder to the openings of the common ejaculatory ducts.

(4) The lower ends of the mesonephric ducts are absorbed into the vesico-urethral primordium in such a manner that the ureteric openings appear to migrate cranially to open into the bladder, while the mesonephric ducts open into the urethra. The bladder thus acquires a mesodermal component, the trigone.

Anomalies of Development of the Bladder.—(1) Persistent cloaca is due to failure, in varying degrees, of fusion of the urorectal septum with the cloacal membrane.

(2) Ectopia vesicae is due to failure of mesoderm from the primitive streak to migrate around the cloacal membrane and form the infra-umbilical anterior abdominal wall. Breakdown of the upper part of the cloacal membrane then exposes the posterior wall of the bladder on the surface of the body.

(3) Cysts may occur in persisting remnants of the urachus. Rarely, a lumen may remain in the whole structure and urine may escape at the umbilicus at a urachal fistula.

(4) Abnormal opening of the ureter into the urethra, seminal vesicle, vagina or elsewhere, may be found.

The Genital Glands and Ducts.—When the mesonephros has attained its full degree of development it projects into the cœlom and is attached to the dorsal

body wall by a broad mesentery. On its lateral aspect the mesonephric duct runs towards the urogenital sinus in what may be called the tubar subdivision of the urogenital fold. This designation is apt, since a second duct appears later in the tubar fold of each side, the paramesonephric duct (see later). The genital gland arises from a thickening of the cœlomic epithelium on the medial side of the urogenital fold in about the middle two-fourths of its extent. Its growth causes it to bulge ventromedially from the mesonephros and to be attached to the latter by a mesentery, the genital mesentery. Cords of cells proliferate from the thickened cœlomic epithelium into the subjacent mesenchyme. This first occurs in the fifth week, but it is not until nearly two weeks later that the genital gland becomes histologically recognisable as a testis or an ovary.

In the male, bundles of fibrous tissue appear in the genital gland primordium, and these split up the genital cells into testis cords. Another dense layer of fibrous tissue forms just under the cœlomic epithelium covering the gland. This is the tunica albuginea and when it has formed no further addition to the testis cords can be made by the germinal epithelium. The testis cords extend towards the mesorchium to form the rete testis which later becomes connected with the mesonephric duct by some persisting mesonephric tubules. These solid testis and rete cords become canalized later in fœtal life. In the female, the cords of genital cells become arranged in masses which are the primordial follicles. A rete ovarii forms in the mesovarium but a definite tunica albuginea is lacking.

Primordial germ cells have been described in various mammals as arising from the gut entoderm and migrating by way of the dorsal mesentery to the genital gland. Hamlett (1935) has reported such

cells in the human embryo, but it has always been a matter of dispute whether they have any definite relation to the ultimate germ cells of the adult. Recent experimental work by Everett (1943) on the mouse, suggests that the adult germ cells are derived from these primordial entodermal elements. If the genital ridge was transplanted to the kidney of a host animal before primordial germ cells were present a testis or ovary was not differentiated although the associated sex ducts were formed. If transplants were made after primordial germ cells were present in the genital ridge, ovarian or testicular tissue was formed.

During the seventh and eighth weeks of development, the paramesonephric or Müllerian ducts are laid down on each side of the embryonic body. This duct is first seen as an invagination of the cœlomic epithelium covering the cranial and lateral part of the mesonephros. The solid tip of the invagination burrows into the underlying mesoderm and grows caudally just lateral to the mesonephric duct until it reaches the lower pole of the mesonephros. Here it crosses ventral to the mesonephric duct to lie on its inner side in a transverse partition of mesoderm in the pelvis, the genital cord. This genital cord is situated just dorsal to the bladder. The duct traverses the genital cord in a caudal direction until its tip fuses with the dorsal epithelial wall of the urogenital sinus. Here the two ducts produce an elevation of the dorsal wall of the sinus, the Müllerian tubercle. The two ducts now fuse with each other in a caudo-cranial direction in the genital cord forming a median utero-vaginal canal. The further changes in the paramesonephric ducts are dependent on the sex of the developing embryo.

The Male Embryo.—The mesonephric duct becomes transformed into the duct of the epididymis and the

vas deferens. It is connected with the rete testis by a number of persistent tubules derived from the caudal part of the mesonephros, which thus become the vasa efferentia. The blind upper end of the mesonephric duct persists as the appendix of the epididymis, while a few blindly ending caudal mesonephric tubules form the paradidymis. Near the termination of the mesonephric duct in the uro-

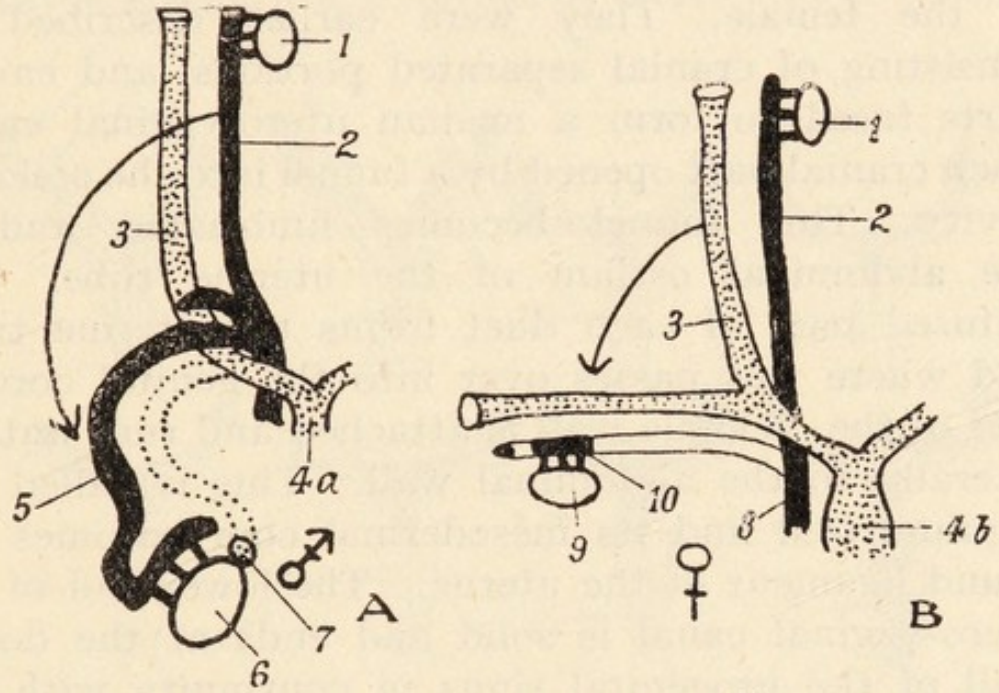

FIG. 37.—FATE OF THE MESONEPHRIC AND PARAMESONEPHRIC DUCTS IN THE TWO SEXES.

A. Male; B., female. 1, Genital gland; 2, mesonephric duct; 3, paramesonephric duct; 4*a*, uterus masculinus; 4*b*, uterus; 5, vas deferens; 6, testis; 7, appendix testis; 8, duct of Gartner; 9, ovary; 10, epoöphoron.

genital sinus a small dilatation marks the site of the ampulla, and an outpocketing from this gives rise to the seminal vesicle. The paramesonephric ducts disappear almost completely in the male. The extreme cranial end forms the appendix of the testis. The caudal part of it *may* contribute to the so-called uterus masculinus, but the evidence on this point is not precise.

The Female Embryo.—Some of the persisting mesonephric tubules along with a part of the mesonephric

duct form the epoöphoron which lies in the broad ligament near the hilum of the ovary. Other caudal mesonephric tubules form the paroöphoron in the medial part of the mesosalpinx. This normally degenerates soon after birth. The caudal portion of the mesonephric duct normally degenerates but may persist in varying degree as the duct of Gartner. The paramesonephric ducts form the genital tract of the female. They were earlier described as consisting of cranial separated portions, and caudal parts fused to form a median utero-vaginal canal. Each cranial part opened by a funnel into the cœlomic cavity. This funnel becomes fimbriated and is the abdominal ostium of the uterine tube. The unfused part of each duct forms the uterine tube, and where this passes over into the genital cord, a fold of the cœlomic wall is attached and runs antero-laterally to the abdominal wall. This is called the inguinal fold and its mesodermal core becomes the round ligament of the uterus. The lower end of the utero-vaginal canal is solid and ends at the dorsal wall of the urogenital sinus in continuity with the epithelium of the latter. The tubular portion of the canal forms the body and cervix of the uterus, which retain their simple columnar epithelial lining. With further growth the paramesonephric ducts appear to recede from the sinus, but in doing so, they retain their connection with it by the formation of a cord of epithelial cells, the vaginal plate. The source of the cells making up this plate has been the subject of much controversy: some workers (*e.g.*, Hunter, 1930) consider them to be mesodermal having their origin from the paramesonephric ducts; others think that the vagina is of compound origin, with a lower component derived from the entoderm of the urogenital sinus (Koff, 1933), or from the mesonephric ducts (Mijsberg, 1924). Certain abnormalities sup-

port the theory of compound origin (McKelvey and Baxter, 1935). Whatever may be the origin of the vaginal plate, its cells proliferate irregularly beginning at the end next to the sinus (Fig. 38, 5). Degeneration of the central cells of the vaginal cord then takes place and the lumen of the organ is formed. The upper limits of this lumen are extended upwards around the external os of the uterus to form

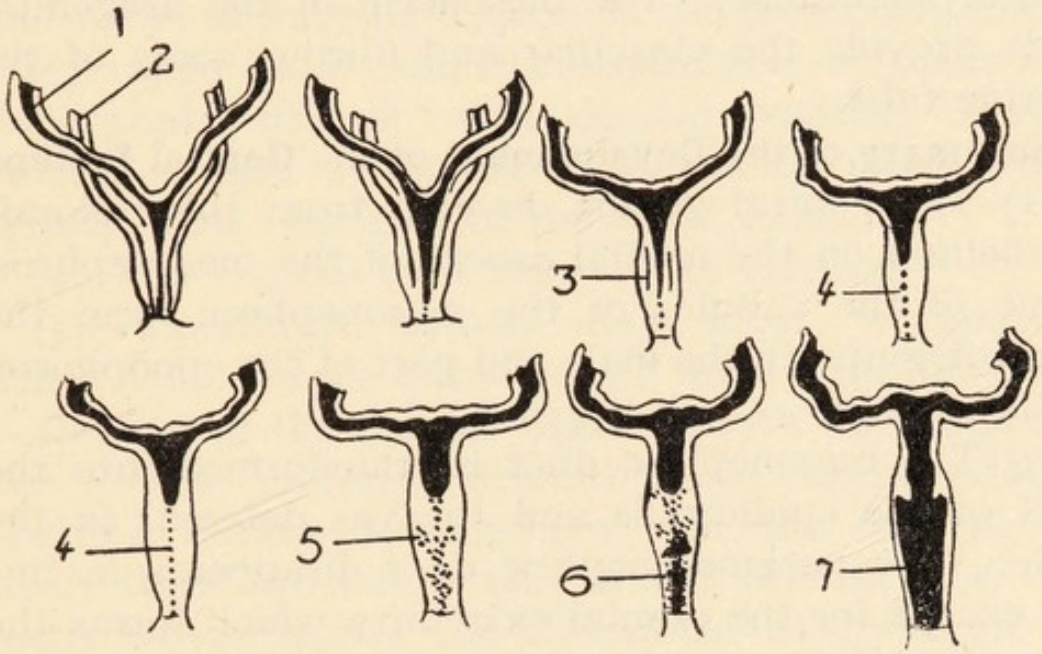

FIG. 38.—DIAGRAMS TO SHOW THE DEVELOPMENT OF THE FEMALE GENITAL TRACT.

Note that the vagina is derived from a solid cord of cells the core of which breaks down.

1, Paramesonephric duct; 2, mesonephric duct; 3, duct of Gartner; 4, vaginal cord; 5, proliferation of vaginal cord; 6, degeneration commencing at the peripheral end of cord; 7, formed vagina.

the fornices which are thus the last part of the vagina to arise. The lower end of the vaginal cord is somewhat bulbous where it indents the dorsal wall of the urogenital sinus to form the Müllerian tubercle. After perforation of this in the canalization of the vagina, the hymen is left as the remnant of the former partition. Irregularity in the breakdown of the tissue of the tubercle results in the various forms of hymen. It should be noted that during development

there is an "eversion" of the urogenital sinus so that the vaginal orifice approaches the body surface. The vestibule of the vagina represents, in the adult, the original tubular urogenital sinus. The mesodermal tissue of the genital cord becomes transformed into the fibrous tissue and muscular coats of the uterus and vagina. The lateral part of it becomes the broad ligament which has added to it the urogenital mesentery. The mesoderm of the urogenital folds provide the muscular and fibrous coats of the uterine tube.

Summary of the Development of the Genital System.—(1) The genital glands develop from the cœlomic epithelium on the medial aspect of the mesonephros. Some of the tubules of the mesonephros form the vasa efferentia in the male and part of the epoöphoron in the female.

(2) The mesonephric duct is transformed into the duct of the epididymis and the vas deferens in the male. The paramesonephric duct disappears in this sex except for the cranial extremity which forms the appendix of the testis, and the caudal end, which may contribute to the uterus masculinus.

(3) The paramesonephric ducts in the female give rise to the paired uterine tubes. Their median fused parts form the uterus, while the vagina results from the canalization of a solid cord of cells extending from the cervix uteri to the dorsal wall of the urogenital sinus. The origin of this cord is disputed.

(4) The mesonephric duct largely disappears in the female. A little of the cranial end is incorporated in the epoöphoron, and a varying segment of the caudal part may constitute the duct of Gartner.

(5) The hymen is the remains of the partition between the bulbous lower end of the vaginal cord and the lumen of the urogenital sinus. Its lower

surface is therefore clothed with epithelium derived from sinus entoderm.

Anomalies of Development of the Genital System.—(1) Absence of the testes or ovaries is a rare condition, due to failure of development of one or both genital ridges.

(2) Fused testes is also a rare anomaly.

(3) Anomalies of the uterus and vagina arise from non-union in varying degree, of the paired primordia. They range from complete duplication of the uterus (bicornuate uterus) with double vagina, through various stages of bipartite uterus to cases which merely show retention of the fœtal form.

(4) The vaginal cord may fail to canalize.

(5) Imperforate hymen may occur, a condition which often passes unrecognised until after puberty.

Descent of the Genital Gland.—Both the testis and the ovary undergo descent from their primary position during development. In the case of the testis there are two stages in the process: (*a*) The testis moves within the abdominal cavity from the fronto-medial aspect of the mesonephros to the deep inguinal ring. (*b*) Later, the gland passes through the inguinal canal to the scrotum.

The first phase of descent is commonly agreed to be due to growth changes in the dorsal abdominal wall, which increases in length rapidly while the testis grows slowly. The gonad thus appears to migrate caudally, and by the end of the third month is lying in the false pelvis near the deep inguinal ring.

A fibro-muscular band, the gubernaculum, runs from the lower pole of the testis to the anterior abdominal wall in the urogenital fold. It can be traced on through the layers of the anterior abdominal wall to the scrotum. An evagination of the peritoneum, the processus vaginalis, occurs along the

track of the gubernaculum, commencing about the end of the third month. During the seventh month the testis passes along the inguinal canal lying behind the peritoneum of the processus vaginalis to reach its adult position in the scrotum. During this descent the gubernaculum shortens. It was formerly thought that atrophy and contraction of the gubernaculum drew the testis downwards from the abdominal cavity. Hunter (1926) is of the opinion that the gubernaculum acts as a kind of anchor to prevent the testis moving cephalad with the developing kidney, the testis remaining at the deep inguinal ring until the intra-abdominal pressure is raised to a

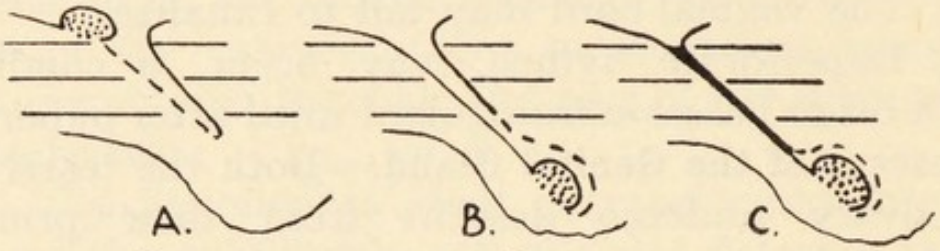

FIG. 39.—DIAGRAMS OF THE DESCENT OF THE TESTIS.

A, Position of testis at the deep inguinal ring with the cone-shaped processus vaginalis. B, Testis immediately after descent into the scrotum. C, Testis after obliteration of the processus, leaving only the tunica vaginalis.

certain point by the growth and enlargement of the abdominal viscera, and that it is finally forced away from the intra-abdominal position, along a pre-formed inguinal canal, to its normal adult position in the scrotum. The cavity of the portion of the processus vaginalis between the testis and the deep inguinal ring becomes obliterated, leaving the lower portion persisting as the tunica vaginalis.

Anomalies in the Descent of the Testis.—(1) The testis may be retained within the abdominal cavity or it may undergo only partial descent, remaining in the inguinal canal. Many of such testes may be induced to complete the process of descent by the administration of androgens.

(2) The testis may descend to an abnormal position (ectopia testis). It may be found in the perineum, the thigh, between the layers of the abdominal musculature or in a pre-penile position. These locations are considered to be associated with the development of abnormal bands of the gubernaculum.

(3) Failure of obliteration of the processus vaginalis gives rise to a congenital inguinal hernia.

In the female the ovary descends to just below the pelvic brim and lies on the posterior surface of the broad ligament. A gubernaculum develops as in the male, except that it is fused, a short distance caudal to the ovary, with the supero-lateral angle of the developing uterus. This fusion divides the gubernaculum into two parts; a proximal, which becomes the round ligament of the ovary, and a distal, which is converted into the round ligament of the uterus.

The External Genitalia.—The external genitalia develop on the ventral surface of the body wall around the anterior, or urogenital portion of the cloacal membrane. In the mid-line a genital tubercle is formed while the urogenital membrane is bounded laterally by labio-scrotal swellings. When the membrane breaks down, a median shallow urethral groove appears extending on to the ventral surface of the genital tubercle, and this is flanked by urethral folds. The external (phallic) portion of the urogenital sinus is represented by this elongated groove which is continuous caudally with the opening of the pelvic portion.

The Male Genitalia.—The urethral folds meet and fuse in the middle line to form a canal continuous with the opening of the urogenital sinus. The fused edges form a median raphe. The glans penis is marked out at the extremity of the genital tubercle by a coronal sulcus at which the anterior opening of the urethra is now situated. An ectodermal cord of

cells sinks into the substance of the glans and becoming canalized completes the formation of the penile urethra. During this time, the scrotal swellings have migrated caudally towards the root of the penis and becoming approximated to each other, form the scrotum. The prepuce develops as a fold of tissue at the coronal sulcus, which grows distally over the surface of the glans (Hunter, 1935). The bulbo-urethral glands arise as evaginations from the hinder end of the entodermal penile urethra.

The Female Genitalia.—The genital tubercle becomes transformed into the clitoris, the distal extremity being marked off by a coronal sulcus. The labial swellings migrate somewhat caudally and join behind the urogenital opening to form the posterior commissure, the remainder of them forming the labia majora. The urethral folds remain separate as the labia minora, the urethral groove and the urogenital sinus as far as the Müllerian tubercle becoming the vestibule of the vagina. The greater vestibular glands arise as entodermal outgrowths from this vaginal vestibule.

Summary of the Development of the External Genitalia.—(1) A genital tubercle forms at the anterior end of the elongated opening of the urogenital sinus. This opening is bounded laterally by labio-scrotal swellings.

(2) A urethral groove runs backwards in the midline from the genital tubercle. Urethral folds arise on each side of this.

(3) The labio-scrotal swellings form, as their name implies, either the halves of the scrotum, or the labia majora.

(4) The penile urethra is a composite structure being derived from :

(*a*) an entodermal segment formed by the fusion of the urethral folds ;

(*b*) an ectodermal part formed by canalization of an epithelial cord in the glans penis.

(5) The urethral folds do not fuse in the female but are transformed into the labia minora.

(6) The bulbo-urethral glands in the male, and the greater vestibular glands in the female, arise as entodermal outgrowths from the lower part of the urogenital sinus.

Anomalies of the External Genitalia.—(1) Double penis, a rare condition, is due to longitudinal division of the genital tubercle.

(2) Hypospadias is a condition in which the urethra opens on the under surface of the penis. It is caused by failure of fusion of the urethral folds.

(3) Epispadias is an uncommon anomaly in which there is a urethral groove on the upper surface of the penis. It is said by Wyburn (1937) to be caused by a minor failure of the mesoderm to develop in the region of the genital tubercle.

(4) Stenosis of the urethra is due to failure of the urethral cord to acquire a lumen.

(5) Phimosis is a condition of the prepuce in which there is an abnormally small opening.

(6) Hypertrophy of the labia minora and/or clitoris may be found.

Hermaphroditism.—Hermaphroditism is a condition in which the individual possesses the genital organs of both sexes. In the human it may be either true hermaphroditism or false hermaphroditism. The former condition is excessively rare, the subject having the genital glands of both sexes with external genitalia which may be of male, female or mixed type. False hermaphroditism is much more common and here the individual has genital glands of one sex with external genitalia and secondary sex characters of the other. Thus in one type, testes are present but the external genitalia are retarded in development

and resemble those of the female. An opposite type will show an enlarged clitoris and perhaps fused labia minora, resembling thus a male while ovaries are also present.

CHAPTER XIII

THE MUSCULAR AND SKELETAL SYSTEMS

THERE are three types of muscle cells present in the adult—smooth, cardiac, and skeletal. The mesoderm is the source of all these, except for the muscles of the iris and those associated with the sweat glands.

Smooth muscle fibres develop from the visceral mesoderm through the intermediary of a myoblast. This cell contains an oval nucleus embedded in a granular cytoplasm. In the further stages of development of this cell, the granules are seen to become arranged in rows, and then these granules fuse to become myofibrillae, the cell nucleus retaining a central position. Connective tissue and reticular fibrils develop to bind the smooth muscle fibres into bundles.

Cardiac muscle fibres develop in a very similar manner in the myo-epicardial mantle, but at an early stage the individual cells lose all trace of cell autonomy and unite to form a syncytium. The myofibrils of cardiac muscle develop a cross-striation like those of voluntary muscle.

The skeletal muscle fibres are derived from mesodermal cells of the somites or from the branchial arch mesoderm. The nuclei of the myoblasts occupy a central position as in the early developmental stages of other types of muscle, and fibrillae arise in the cytoplasm. These fibrillae become cross-striated and increase in number very rapidly so that the nucleus is crowded to one side of the cell. While this process

goes on the nucleus divides repeatedly so that the mature striated muscle cell is multi-nucleated.

The Somites.—The somites are laid down on either side of the neural tube as a series of hollow masses of mesoderm (p. 19). In further development the greater part of the medial and ventral walls of each somite are carried medially to form a sclerotome from which the axial skeleton is formed. Cells proliferating from the deep aspect of the remainder

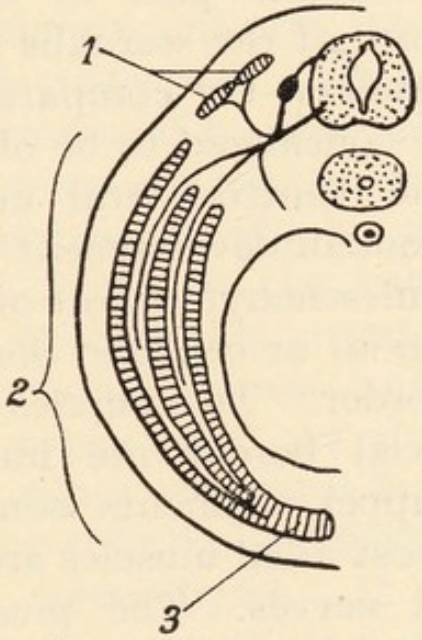

FIG. 40.—THE DEVELOPMENT OF THE MUSCLE SHEETS.
1, Dorsal muscle mass; 2, ventro-lateral sheet; 3, rectus sheet.

of the somite become the myotome, while the rest of the original mass is termed the dermatome. The latter becomes the corium and superficial fascia of the corresponding body segment.

Each myotome is a rectangular block of tissue, and very early the segmental nerve growing outwards from the neural tube establishes connection with it. The myotome now divides into a dorsal and a ventro-lateral part, the segmental nerve dividing correspondingly into posterior and anterior primary rami. The ventro-lateral part of each myotome sends out an extension into the ventral and lateral parts of the

body wall. These ventral processes split into three layers which represent the three sheets of muscle in the abdominal wall, and the external intercostal, internal intercostal, and innermost intercostal muscles of the thoracic wall. The ventral ends of the three laminae become fused to form a rectus sheet on each side of the middle line. These rectus columns are represented in the adult by the rectus abdominis, the infra-hyoid, and some of the supra-hyoid, musculature. The thoracic part of it is occasionally present in the form of the sternalis muscle.

The Limb Muscles.—On comparative grounds the limb muscles are considered to be of segmental origin arising from the ventro-lateral extensions of the somites, but in human development they differentiate *in situ* from the mesenchymal core of the limb. Each limb has a pre-axial or cephalic border, and a post-axial or caudal border. The muscles arising in relation with the pre-axial border are innervated by the nerves of the upper segments contributing to the limb, while the post-axial muscles are supplied by the lower segmental nerves. The musculature of the entire limb is split into a dorsal extensor and ventral flexor group of muscles, and this is reflected in a splitting of the segmental anterior primary rami in the root plexus. Subsequent migration and fusion of the primitive muscle masses of the limbs gives rise to the more complex adult pattern of the brachial and lumbo-sacral plexuses.

Histogenesis of Bone.—There are two modes of development of bone, the intramembranous and the endochondral. The first indication of membrane bone formation is a condensation of mesenchyme cells to form a sheet. Fibres of collagen are laid down between the cells which become reoriented in rows along bundles of these fibres. The individual cells now begin to function as osteoblasts, and to

deposit an osseous matrix among the fibres. The mesenchyme around this centre of ossification becomes highly vascular and penetrates between the spicules of newly formed bone. At the same time the more peripheral mesenchyme becomes transformed into a layer of cells which may be termed the periosteum. This contains osteoblasts in its deeper parts which lay down a compact layer of subperiosteal bone. Eventually a bony sponge-like structure is formed, limited by compact bone externally and having within it the primary marrow cavity. Numerous osteoclasts (multi-nucleated giant cells) appear in the primary marrow, and by their absorptive powers remodel the bone as successive layers of compact bone are laid down externally by the deep layer of the periosteum. Some of the osteoblasts become entangled in the bone as this process goes on. They lie in little spaces called lacunae, and may themselves now be termed osteocytes. As the bone increases in thickness the outer periosteal layer is constantly being reinforced by cells derived from the surrounding undifferentiated mesenchyme. It should be emphasized that, in the growth of a simple membrane bone like the parietal, deposition of new bone on the outer surface is always accompanied by a co-ordinated resorption of bone on the inner surface, and this resorptive activity is always associated with the presence of osteoclasts.

Endochondral ossification is seen typically in the long bones of a limb. Here the mesenchymal cells first become an axial condensation which is then transformed into the cartilaginous fore-runner of the bone. The question now arises, if these axial mesenchymal cells are already pre-determined for chondrification, or simply indifferent cells which have taken up axial positions. Murray (1936) discussing this point, quotes an experiment by Fell, who

cultivated fragments of teased mesenchyme from the limb buds of four-day chick embryos *in vitro*. Some of the fragments produced cartilage while others did not. The conclusion was that as all the fragments had been treated in the same way lying side by side in the same medium, the differences in differentiation must have been intrinsic—*i.e.*, that the mesenchyme which had chondrified had contained tissue predetermined for that process.

After the cartilaginous model of the bone has been formed changes take place in the surrounding perichondrium. The outer cells of this membrane become the fibrous layer of the future periosteum, while those of the inner layer differentiate to form osteoblasts which lay down compact bone on the outer surface of the shaft. The cartilage cells in the centre of the shaft become enlarged and calcium salts are deposited in the matrix around them. Vascular tissue derived from the deep layer of the periosteum penetrates into spaces in the matrix which have been formed by resorption, and this vascular tissue may be termed the primary bone marrow. Osteoblasts in the primary bone marrow deposit bone on the remains of the calcified cartilage. Giant cells (osteoclasts) later appear and collect along the surface of the spicules of primary bone. Remodelling of the central parts of the bone takes place so that a medullary cavity of increasing size is formed ; this process is accompanied by a co-ordinated deposition of subperiosteal bone on the outer surface of the shaft.

The Skeletal System.—The skeleton may be considered as consisting of two morphological parts : (*a*) an axial skeleton made up of the vertebrae, ribs, sternum and skull ; (*b*) an appendicular skeleton, which is composed of the pectoral and pelvic girdles with the limb bones.

The Axial Skeleton.—The vertebrae are derived from the sclerotomes. These are masses of cells which surround the notochord and are derived from the primitive mesodermal segments (p. 19). Each sclerotome is divisible into a dense caudal part and a less dense cranial part. The cranial part of one sclerotome fuses with the caudal part of the preceding one to give rise to the primordium of a vertebral centrum. The segmental spinal nerves lie between these vertebral primordia which are thus intersegmental in position. The denser part of each centrum gives rise to two outgrowths: one passes dorsally around the neural tube to meet its fellow of the opposite side to form the neural arch; a second grows ventrolaterally as the costal process, but this only reaches its full development in the thoracic region where it forms a free rib. As the costal elements grow ventrally in the thoracic region they presently turn and grow medially. Their medial extremities become connected by a longitudinal bar, the sternal bar. There will be thus paired sternal bars which fuse in the midline from above downwards, forming in succession, the manubrium, the body of the sternum, and the xiphoid process. It must be understood that all the elements described are at first simply condensations of the mesoderm. These later chondrify and then ossify. The mesodermal tissue intervening between the primordia of the vertebral centra becomes transformed into the fibrocartilaginous intervertebral discs, in the centre of which notochordal tissue persists in modified form as the nucleus pulposus.

The Skull.—The skull consists essentially of two parts. There is first, a series of bones which form a protective investment for the brain and the organs of special sense (the neuro-cranium), and second, the bones of the jaws, or viscerocranium. Some of these

bones develop in cartilage, others are formed in membrane, while yet a third group are compound, having some portions which ossify in membrane and others which pass through a cartilaginous stage.

The Neurocranium.—The entire neurocranium of the human embryo is first indicated by a mesodermal condensation around the anterior end of the neural tube. In general, the basal part of this becomes transformed into a series of cartilages which later ossify, while the remainder forms a set of roofing bones for the skull ossifying directly from membrane.

The cartilaginous part of the skull (chondrocranium) is first seen as a pair of bars lying on either side of the cranial end of the notochord. These are the parachordal cartilages and they terminate anteriorly just behind the hypophysis. The two cartilages enlarge and come together in the middle line surrounding the notochord and forming what is known as the basal plate. A second pair of cartilages appears flanking, and in front of the hypophysis. These are the trabeculae, and their caudal ends eventually fuse with the basal plate which also becomes supplemented at its posterior extremity by the union with it of three or four occipital sclerotomes. Laterally the basal plate fuses with the cartilaginous otic capsule. An opening between this and the first occipital sclerotome represents the jugular foramen. The hinder end of the basal plate gives rise to the basi-occipital, while cartilaginous centres representing the ex-occipital and supra-occipital form in the mesodermal condensation lateral and dorsal to the developing hind brain. The anterior end of the basal plate forms the post-sphenoid. The pre-sphenoid element is formed from the trabecular bars. Centres of chondrification in the mesoderm lateral to these denote the orbito-sphenoid and the ali-sphenoid. The first of these extends medially around the optic

nerve and forms the lesser wing of the sphenoid. The second is separated from the orbito-sphenoid by the third, fourth, sixth, and first two divisions of the fifth cranial nerve, that is, the structures passing through the primitive sphenoidal fissure. The second

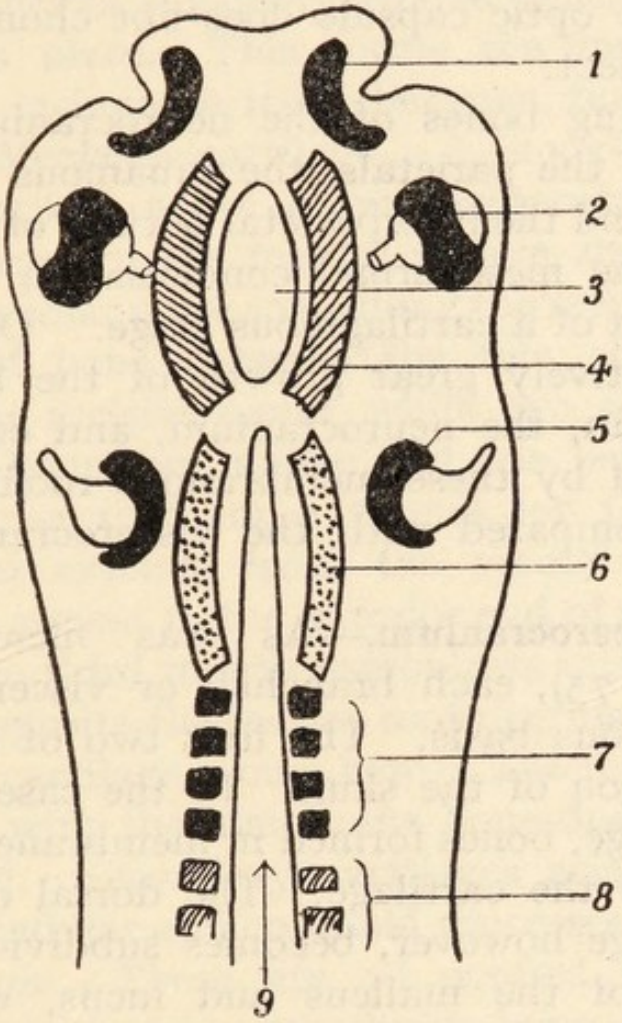

FIG. 41.—THE PRIMORDIAL CHONDROCRANIUM.

1, Nasal capsule; 2, optic capsule; 3, hypophyseal foramen; 4, trabecular cartilage; 5, otic capsule; 6, parachordal cartilage; 7, occipital segments; 8, cervical segments; 9, notochord.

division of the fifth nerve is later encircled by bone so passing through a separate foramen rotundum in the adult skull. The ali-sphenoid gives rise to much of the greater wing of the sphenoid. Chondrification around the otocyst with subsequent ossification, forms the primordium of the petro-mastoid portion of the temporal bone. Chondrification also takes

place in the mesoderm around the olfactory placodes so forming the nasal capsules which unite with each other, and posteriorly fuse with the trabeculae. The ethmoid and the cartilaginous portion of the nasal septum represent the nasal capsules in the adult. The optic capsule does not chondrify in the human subject.

The roofing bones of the neurocranium, that is, the frontal, the parietals, the squamous parts of the temporals and the interparietal portion of the occipital ossify in the mesodermal condensation without the intervention of a cartilaginous stage. Owing mainly to the relatively great growth of the brain before birth in man, the neurocranium, and especially the part formed by these membranous roofing bones, is large as compared with the viscerocranium of the infant.

The Viscerocranium.—As was mentioned previously (p. 75), each branchial or visceral arch has a cartilaginous basis. The first two of these aid in the formation of the skull. In the case of the first arch cartilage, bones formed in membrane supplement and replace the cartilage. The dorsal extremity of this cartilage however, becomes subdivided into the primordia of the malleus and incus, which ossify during the fourth month, while the adjacent part of the second arch cartilage likewise ossifies to form the stapes and the styloid process.

The Mandible.—The mandible is developed mainly from ossification in the dense mesodermal condensation on the outer side of the first arch cartilage (Meckel's cartilage). The following account of its formation is based on the description given by Fawcett (1924).

The inferior dental branch of the mandibular division of the trigeminal nerve lies parallel with, and on the outer side of the cartilage. Opposite the

junction of the middle and anterior thirds of this, the nerve divides into mental and incisive branches. Bone makes its first appearance at the eighth week in the tissue at the angle between these two branches and grows rapidly backward underneath the mental nerve which thus lies in a groove. Inbending of the anterior border of this bony groove under the incisive nerve takes place. This forms the inner alveolar wall which insinuates itself between the developing teeth and Meckel's cartilage. A hook-like process over the mental nerve grows backwards from the anterior border of the mental groove and fuses with the outer alveolar plate so forming the mental foramen. A bridge of bone between the two alveolar walls closes in the incisive canal while two shelf-like projections of bone, one above and one below Meckel's cartilage, fuse to form a tunnel for the cartilage. This tunnel extends from the second milk molar tooth germ almost to the anterior end of the cartilage. Early in the third month osteoblasts invade Meckel's cartilage opposite the incisor tooth germs and ossification in the cartilage occurs here. The remainder of it in relation with the membrane bone degenerates and is absorbed. Secondary cartilages arise in relation with the condylar and coronoid processes and possibly at the angle. These are all ossified by extension from the neighbouring membrane bone.

There is another membranous ossification in the dorsal part of the mandibular arch which forms the tympanic part of the temporal bone.

The Maxillary Processes.—It will be remembered that the first branchial arch bifurcates anteriorly, the upper portion being called the maxillary process. A number of membrane bones form in this. Superficially there are the premaxilla, the maxilla, the zygomatic, and the squamous portion of the temporal. More deeply, there develop the palatine and the vomer.

The bony centres for all these make their appearance relatively early in development during the eighth week.

The Appendicular Skeleton.—The mesenchymal core of the limb bud from which the bones arise, becomes divided into segments as chondrification takes place. Reference has already been made to experimental work on the growth of bone (p. 159) and the results of similar investigations show that any embryonic bone normally grows to form its *general* adult pattern in response to *intrinsic* factors; *extrinsic* factors may later modify somewhat details of the predetermined bony form.

The bones of the limbs, and of the limb girdles, pass through a cartilaginous stage before ossification occurs. The clavicle is an exception to this rule. It ossifies, for the most part, in membrane, the centre for it, detectable at the sixth week, being the first to appear in the embryonic body.

Anomalies of Development of the Skeleton.—(1) Variations in the number of vertebræ are not uncommon. For example, thirteen thoracic vertebræ may be present instead of the normal twelve; the lumbar series may be reduced to four or increased to six; the sacrum may show six segments instead of five.

(2) Rachischisis. In this condition the halves of the neural arches fail to unite in part or all of the vertebral column, the contents of the vertebral canal then being exposed. When the cranial vault is also affected the condition is termed craniorachischisis. Associated abnormalities of the central nervous system (which are probably responsible for the bony defect) are mentioned on p. 159.

(3) Supernumerary ribs may be present, and are produced by excessive growth of the costal elements of the seventh cervical or first lumbar vertebra.

The cervical rib is the common form, and is of clinical importance because of its relation to the lowest trunk of the brachial plexus and to the subclavian artery.

(4) Cleft sternum results from complete or partial failure of union of the sternal bars in the mid-line.

(5) Premature union of one or more cranial sutures produces various abnormal skull forms. Early ossification of the sagittal suture gives rise to a keeled or boat-shaped skull (scaphocephaly) ; if the coronal suture is affected a pointed skull (acrocephaly) results ; plagiocephaly (a twisted skull) is due to early ossification of one-half of the coronal suture or lambdoid suture.

(6) Dysostosis cleido-cranialis. This is a *very* rare condition, of interest mainly because in it there are combined defective ossification of the membrane bones of the skull *and* the clavicle.

(7) Anomalies of the digits may occur. Syndactyly (fusion of digits) and polydactyly (supernumerary digits) are the most common. The importance of genetic factors in the production of digital abnormalities is mentioned in the next chapter.

(8) Congenital clubfoot may be due to some inherent defect in the limb blastema, or it may be the result of persistence of the fœtal position of the limb. The former is the much more likely cause. The association of this condition with other abnormalities, particularly with lumbar rachischisis, should be noted.

(9) Gigantism and dwarfism may be general or local conditions. The general condition is most probably to be ascribed to an endocrine dysfunction associated with some genetic abnormality. In simple cases, there is wide variation from the normal in the period in which union takes place between the diaphyses and epiphyses of the long bones. If union be delayed, growth in length continues for a longer

period than normal and gigantism results. If union occurs prematurely, the opposite condition of dwarfism will be found. There are, however, special forms of dwarfism such as achondroplasia and ateleiosis, which are rather more complicated. The achondroplasiac dwarf is characterised by the possession of short limbs as compared with the trunk; there is disorganisation of the cartilaginous cells at the junction between epiphysis and diaphysis in the long bones of the limbs. The ateleiotic dwarf represents a persistent infantile condition where the epiphyseal cartilages have not united and are inactive.

Local gigantism is an uncommon condition affecting perhaps one or more digits or a region of the body.

CHAPTER XIV

THE TRANSMISSION OF HEREDITARY CHARACTERS

EVERY potential individual, that is, every fertilised ovum, commences development with a complement of hereditary factors (genes) derived from both parents at the time of union of the germ cells in fertilisation. These inherited factors operate during development, both before and after birth, to produce an individual resembling the parents. The environment, both prenatal and post-natal, may influence some of these hereditary characters and modify them, but there are certain characters which cannot be affected by the environment and hence are said to be determined at fertilisation. Examples of these are the blood group to which the person belongs and the colour of the eyes. The study of these hereditary factors, and the laws which govern their transmission from parents to offspring, is known as the science of genetics.

Genetic laws are fundamentally the same for plants and animals, and since many generations of plants and lower animals can be investigated in a relatively short period of time, the study of genetics has largely been based on them. In addition, certain forms possess chromosomes particularly favourable to the genetic analysis of experimental procedures. But in all cases where genetic laws have been tested in lower forms they have been found applicable to human hereditary.

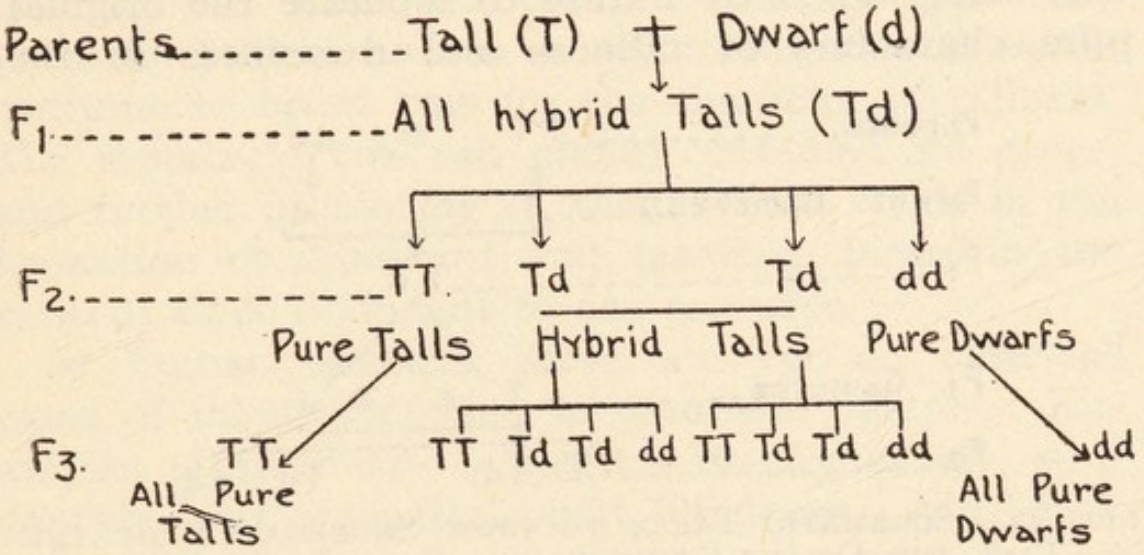

FIG. 42.—SCHEMATIC TABLE SHOWING MENDELIAN INHERITANCE AS APPLIED TO TALL AND DWARF PEAS.
T = tall; d = dwarf.

The fundamental genetic laws are based on the experiments of Mendel (1866) on garden peas. Mendel studied the inheritance of a number of characters of this form, of which tallness and dwarfness may be taken as a typical example. If a tall pea and a dwarf pea were cross-fertilised and the resultant peas planted, all of the plants that grew from them were tall. These he called the first filial generation (F_1). These tall cross-bred plants were allowed to produce peas by self-fertilisation, and when such were sown the second filial generation (F_2) showed some plants that were tall and some that were dwarf,

in the proportion of three tall to one dwarf. Peas derived from self-fertilisation of each of the dwarf plants were then sown, and they produced dwarf plants only; seed from some of the self-fertilised tall plants produced both tall and dwarf offspring, in the proportion of three tall to one dwarf; the remainder of the seed from the tall plants produced nothing but tall offspring in the third (F_3) generation (see Fig. 42 for details).

From these experiments it is clear that an attempt was being made by nature to separate the original pure characters of tallness and dwarfness in the

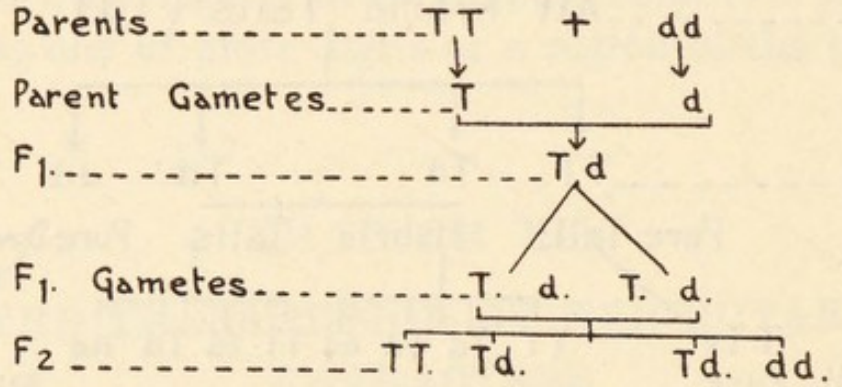

FIG. 43.—SCHEMATIC TABLE TO SHOW SEGREGATION OF THE TALL AND DWARF GENES IN THE GAMETES OF PEAS.
T = tall; d = dwarf.

parent stock from the hybrids. This is known as the law of segregation. The character of tallness, which was found in the F_1 generation, is known as a dominant character since it overshadows the recessive character of dwarfness. These characters are known to be caused by certain elements on the maternal and paternal chromosomes called genes.

Consideration of Fig. 43 will indicate how these dominant and recessive factors become separated out during breeding. The parent stock possessed either the character of tallness or dwarfness in pure form, that is, when self-fertilised they always bred true. The first filial generation (F_1) were all tall since the

gene for dwarfness was present but masked by the dominant tall (T) gene. The gametes (sex cells) of the F_1 generation contained the genes for tallness and dwarfness in equal numbers so that when such plants were self-fertilised the dominant T gene would be present in three out of four of the offspring and they would all be tall plants. In one out of the four, two d (dwarfness) genes would be present and hence these plants would be dwarfs, and on further self-fertilisation would continue to breed truly dwarf. One of the three tall plants would contain only genes for tallness and so on self-fertilisation it would continue to breed true for the character of tallness. The remaining two tall plants contained Td genes, and further inbreeding of them would result in the formation of dominant and recessive forms in the ratio of three dominant to one recessive.

In human genetics there are certain clear-cut cases of inheritance due to dominant factors. Examples of these are congenital brachydactyly, syndactyly, and congenital night blindness. Also black hair colour is dominant over brown hair colour, and so is brown iris colour over blue.

Mendelian laws have been applied to animals and they have been found to hold equally good for them. For example, the colour of the ordinary brownish-grey wild mouse is due to bands of pigment in its hair; black at the base and yellow at the tip. This is known as "agouti" colouration. But in fancy mice there is a variety in which the hair appears black, due to the absence of the yellow tip to the hair. If a pure agouti mouse is crossed with a black or non-agouti, the offspring at F_1 are all agouti in colour—that is, the agouti factor is dominant over the non-agouti, which is the recessive factor. If however these hybrids are inbred, the F_2 generation comes out as 25 per cent. pure agouti, 50 per cent.

hybrid agouti, and 25 per cent. pure non-agouti. This shows the Mendelian ratio of 1 : 2 : 1.

In both the agouti (A) and the non-agouti (b) mice there is a variety with straight hair (S) and a variety with wavy hair (w). If a non-agouti wavy mouse (bw) be crossed with an agouti straight mouse (AS), the F_1 animals will be agouti straight (AbSw) since A is dominant over b, and S over w. Then if these F_1 hybrids are inbred the genes will be segregated out as follows :

Agouti straight (AS) . . .	9
Agouti wavy (Aw) . . .	3
Non-agouti straight (bS) . .	3
Non-agouti wavy (bw) . . .	1

In these experiments two new types have been produced—the agouti wavy and the non-agouti straight. The combinations of dominant and recessive characters which have produced these adult forms are shown in Fig. 44. It will be seen that the AbSw hybrids gave rise to four gametes in equal numbers :

AS : Aw : bS : bw.

These combinations take place in the ova as well as in the spermatozoa and since every kind of ovum is likely to be fertilised by any kind of spermatozoon, there are $4^2 = 16$ possible combinations yielding 9 agouti straight, 3 non-agouti straight, 3 agouti wavy and 1 non-agouti wavy. The several genes of the cross are being segregated out as is shown in Fig. 44. This rule holds good for other possible combinations.

The blood groups A, B, AB and O are transmitted from parents to offspring in accordance with Mendelian laws. The principles involved may be briefly stated as follows :

When red blood corpuscles of one animal species

are mixed with the serum of another species they become clumped together or agglutinated. There is in the serum a substance (an agglutinin) which

Eggs → / Sperms ↓	AS	Aw	bS	bw
AS	AA SS Pure Agouti. Pure Straight.	AASw Pure Agouti. Hybrid Straight.	Ab SS Hybrid Agouti. Pure Straight.	Ab Sw Hybrid Agouti. Hybrid Straight.
Aw	AA Sw Pure Agouti. Hybrid Straight.	AAww Pure Agouti. Pure Wave.	Ab Sw Hybrid Agouti. Hybrid Straight.	Ab ww Hybrid Agouti. Pure Wave.
bS	Ab SS Hybrid Agouti. Pure Straight.	Ab Sw Hybrid Agouti. Hybrid Straight.	bbSS Pure Non Agouti. Pure Straight.	bb Sw Pure Non Agouti. Hybrid Straight.
bw	Ab Sw Hybrid Agouti. Hybrid Straight.	Abww Hybrid Agouti. Pure Wave	bb Sw Pure Non Agouti. Hybrid Straight.	bbww Pure Non Agouti. Pure Wave.

FIG. 44.—SCHEMATIC TABLE TO SHOW THE POSSIBLE COMBINATIONS OF THE GENES FOR STRAIGHT HAIR, WAVY HAIR, AGOUTI COLOUR AND NON-AGOUTI COLOUR IN MICE.
A = agouti ; S = straight ; b = non-agouti ; w = wavy.

attaches itself to an agglutinable substance (agglutinogen) in the red cells and clumping occurs. In man, blood cannot be transfused from one person to another unless the two bloods are compatible. The important factor is the agglutinogen in the red

cells of the donor; if that is incompatible with the agglutinin in the recipient's serum, serious consequences will result in transfusion. From the standpoint of heredity the A and the B agglutinogen factors are dominant over the O factor. If a child's blood belongs to either group A or B one or other of its parents must have blood belonging to such a group.

Genes do not always act in the relatively simple manner just described. There may be incomplete

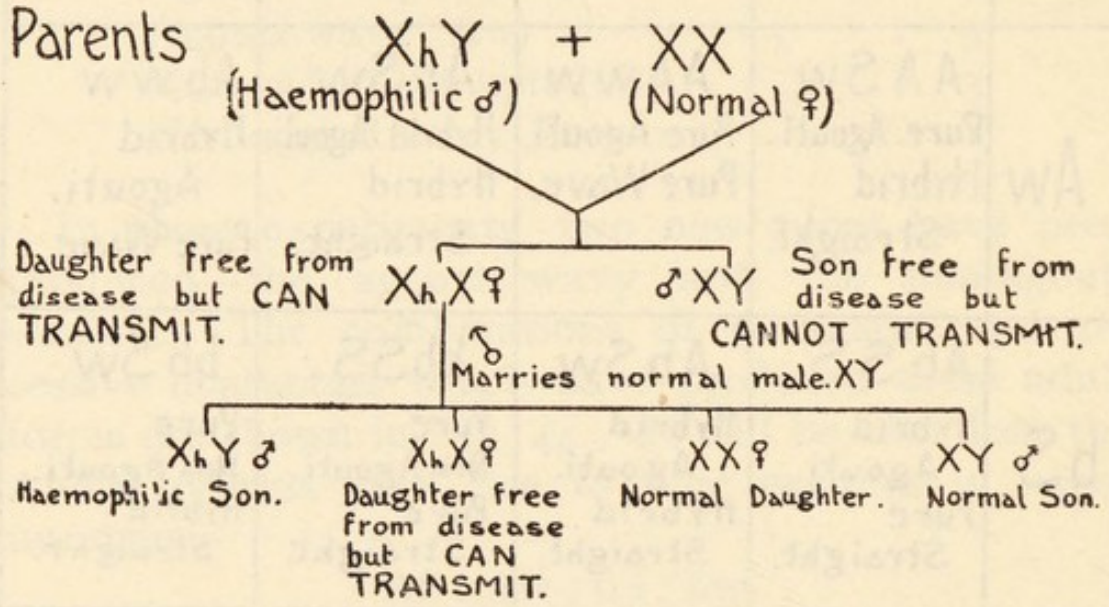

FIG. 45.—SCHEMATIC TABLE TO SHOW THE TRANSMISSION OF HAEMOPHILIAC GENES THROUGH THREE GENERATIONS.

X, female chromosome with non-haemophiliac gene; Xh, female chromosome with haemophiliac gene; Y, normal male chromosome.

action of a gene or there may be a lethal gene present. An example of the latter is the disease in man called Huntingdon's chorea. Here the disease appears first about 35 years of age and the patient rarely lives longer than ten to twelve years after that time. The carrier is eventually killed by his or her predisposition to the disease but only after he or she has passed on the lethal gene to the offspring.

Sex-linked characters are important in certain rare diseases such as haemophilia. The factor here is

transmitted on an X chromosome. If a haemophiliac male marries a normal unrelated female all their daughters must necessarily receive one haemophiliac X chromosome from the father and a normal X chromosome from the mother. The sons all receive a normal Y chromosome from the father and a normal X chromosome from the mother. They therefore do not suffer from the disease, nor can they transmit it to their offspring. But the daughters all have a haemophilac X chromosome, and they will necessarily transmit the disease to 50 per cent. of their sons after marriage with a normal male.

APPENDIX

OSSIFICATION TIMES

The ossification periods have been widely studied, but the work of Hess (1923), although differing in some respects from that usually given in textbooks on osteology, is now recognized as being the most accurate series of observations at present available. These observations may be summarized as follows :

7th week : Mandible, diaphysis of clavicle.
8th week : Diaphysis of humerus, radius, and ulna.
9th week : The terminal phalanges, the 2nd and 3rd basal phalanges, and the 2nd and 3rd metacarpal bones of the hand ; the ilium ; the 2nd and 3rd metatarsals, and the terminal phalanges of the foot bones.
10th week : 1st rib, and the 4th and 1st basal phalanges of the hand.
10th to 12th week : 4th, 5th, and 1st metatarsals.

11th to 12th week : The basal phalanx of the 5th digit, and the middle phalanges of the 2nd, 3rd, and 4th digits of the hand.

13th to 14th week : All the remaining metatarsals and the phalanges of the foot except the last phalanx of the 5th digit.

13th to 16th week : The middle phalanx of the 5th finger.

16th to 17th week : Descending ramus of ischium.

17th to 20th week : Odontoid process of axis.

21st to 24th week : Sternum.

21st to 28th week : Descending ramus of pubis.

21st to 29th week : Calcaneus (os calcis).

24th to 32nd week : Talus (astragalus).

33rd to 36th week : Last phalanx of the 5th digit of foot.

35th to 48th week : Distal epiphysis of femur, and occasionally the proximal epiphysis of tibia.

The wide variation in these figures might be accounted for by the statement of Pryor (1927), that ossification begins at an earlier date in female foetuses than in the male.

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