Haines and Taylor
Obstetrical and Gynaecological Pathology

EDITED BY

H. Fox

THIRD EDITION

VOLUME 1

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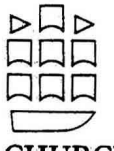

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Preface

This is the third edition of Haines and Taylor's text on Gynaecological Pathology. It is readily admitted, however, that this edition departs so radically from the format of its two predecessors that it represents a new entity rather than a simple revision and updating. Despite this lack of any evolutionary continuity, I wished to retain the names of Claude Taylor and Magnus Haines in the title as a tribute to two men who did much to establish the scientific respectability and intellectual credibility of gynaecological pathology in Great Britain.

The primary aim of the book is to give a full account of the pathology of both gynaecological and obstetrical disorders. There are, of course, many other texts devoted to this topic, but it has appeared to me that few have given sufficient attention to obstetrical pathology. The clinical chimerism of obstetrics and gynaecology should be, but is often not, reflected in pathological texts, and it is hoped that the detailed attention given in this volume to obstetrical pathology will help to correct the imbalance which has tended to lead to a relative neglect of this topic.

The chapters in this multi-author book vary in length and in style, and there is some repetition between the various contributions. All these features are usually considered to be defects in the format of a multi-author volume resulting from a laxity of editorial control. These apparent faults are, however, the direct result of editorial decisions based upon my own concept of the strengths and weaknesses of a large and complex multi-author volume.

Thus I did not impose any minimum or maximum limits on the number of words allowed for each contribution. This decision was based on two factors, of which the first was my confidence in the ability of the invited contributors to decide for themselves the number of words required for a comprehensive consideration of their subject. A second factor was my belief that decisions as to chapter length in multi-author volumes often reflect editorial interests and thus result in an arbitrary and biased view of the relative importance of various topics: this has often resulted in certain aspects of gynaecological pathology, such as the consideration of vulvar, vaginal and tubal disease, receiving relatively inadequate attention, a fault which I hope is rectified in this volume. I have also not insisted upon any unity of style, approach or presentation from the various contributors. The major merit of literary style in a scientific text is that it allows for a lucid and easily comprehensive exposition: I therefore limited my stylistic interventions to the clarification of any obscure passages, and have not attempted to submerge the individualism or flair of my contributors by the editorial imposition of the dead hand of stylistic conformity. I have allowed, and even encouraged, some degree of repetition between chapters. This is because I felt that a book of this length is unlikely to be read in its entirely at a single sitting and that, each chapter should therefore be able to stand as a discrete entity which could be read as a review of a particular topic without the frequent necessity of following cross references to other chapters. My aim was, therefore, to ensure that each chapter was comprehensive, complete in itself and retained the authentic voice of the author.

Certain omissions and commissions in this book require comment. No chapter on gynaecological cytopathology has been included, largely because I felt this to be a subject worthy of a volume in its own right and one which could be considered only in a superficial and sketchy manner when restricted by the confines of a single chapter. By contrast I specifically asked for a rather lengthy description of the embryology and anatomy of the female genital tract; this is perhaps unusual in a textbook of pathology, but reflects my view that many gynaecological lesions can only be fully understood when placed in the context of a sound knowledge of female genital tract development and structure. Some aspects of perinatal pathology have also been included in this book, but these represent, to my mind, only those aspects of this topic which are logical extensions of obstetrical pathology. I have also included discussions of such subjects as the pathology of infertility, the pathology of contraception, the histogenesis of ovarian tumours, the immunopathology of the female genital tract and reproductive immunology: to some, these topics may appear to be out of place in a text devoted primarily to histopathology but their inclusion reflects my feeling that the pathologist must be concerned with all aspects of

disorders of the female genital tract and should not be restricted by the limits of the microscope. There has also been a deliberate inclusion of two chapters on abnormalities of sexual differentiation. This was because I wished to have a general overview of this topic which could be set in apposition to chapters on normal development and on malformations of the female genital tract, together with a separate chapter devoted principally to gonadal pathology in patients with abnormal sexual development.

In most general hospitals, biopsies and surgical specimens from gynaecological and obstetrical patients constitute approximately one third of the total workload of departments of surgical pathology. It is hoped that this book will, despite its imperfections, be of assistance to the pathologist in dealing with this massive inflow of material. I hope also that this volume will indicate some of the scientific and intellectual satisfaction that can be gained from a study of this branch of pathology.

Manchester, 1987 H. F.

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Contents

1

John M. McLean

Embryology and anatomy of the female genital tract and ovaries

Human life and development begin at fertilization when the spermatozoon and ovum fuse to form the zygote or conceptus. Each of the participating gametes contributes more than a million genetic units to the single cell zygote in an arrangement unique to that human being. The normal haploid set of 23 chromosomes in each gamete yields a zygote with the diploid set of 46 chromosomes. Six days after fertilization the conceptus begins the process of implantation in the endometrium, which establishes a relationship with the mother essential to its survival. The first eight weeks of gestation constitute the embryonic period during which the essential form of the human infant is established. Indeed the crucial events of human development occur during the first quarter of gestation. Thereafter maturation and growth occur and continue postpartum, throughout childhood and into adulthood.

Because development is a continuous process various means have been used to identify and tabulate the progression of events during normal human embryogenesis. The founder of the Department of Embryology at the Carnegie Institution in Washington, Franklin Mall, was the first to introduce staging into human embryology. Although his successor at the Carnegie Institution, George Streeter, preferred the word 'horizon' to 'stage', their observations form the basis upon which the first eight weeks of human development are described in 23 Carnegie stages. Occasionally the number of paired somites in the embryo has been used as a reference point in embryogenesis but since the first pair appears during Carnegie Stage 9 and the full complement is established during Stage 14, this is only of limited value. Alternatively, embryonic length or age may be used as a means of identifying the developmental stage. Generally the crown-rump length of larger embryos and all fetuses should be stated in preference to, or at least in addition to, the supposed age (O'Rahilly, 1973) but in this account the reference point will be the postovulatory age, i.e. the length of time since the last ovulation, related when appropriate, to the Carnegie Stage. Since ovulation and fertilization are closely related in time the postovulatory interval is an adequate measure of embryonic age. Embryonic age, length and stage are all interrelated. Age, however, conveys an immediate meaning, since it is a familiar yardstick but it must be recognized that prenatal ages are only as useful as postnatal ages, since they are reference points for the usual pattern or range of developmental events.

FERTILIZATION

Fertilization begins when the male gamete makes contact with the female gamete or its investments and ends with the intermingling of maternal and paternal chromosomes at metaphase of the first mitotic division of the zygote (Fig. 1.1). In the event of in vitro fertilization with human gametes pronuclei are formed within 11 hours of first contact (Edwards, 1972). Each female gamete begins its first meiotic division during intrauterine life and completes it at ovulation, while its second meiotic division is completed during the process of fertilization (Uebele-Kallhardt, 1978). This protracted reduction division delivers 22+ X chromosomes to the newly-formed zygote which also receives 22+ X or 22+ Y chromosomes from the male gamete. The resulting chromosomal complement of the zygote is 44+ XX or 44+ XY and thus its genetic or chromosomal sex is established.

Sex chromosomes

While studying spermatogenesis in the insect *Pyrrochoris apterus* the German cytologist Henking (1891) observed one of the chromosomes to remain undivided. This chromosome was therefore present in only half of the spermatozoa produced by the adult male insect. When it was later suggested (McClung, 1902) that this chromosome might have a sex-determining role, it had already been designated the X chromosome (McClung, 1899) and so it has remained. Thus the male *Pyrrochoris apterus* with only one sex chromosome is XO and the female with two sex chromosomes is XX. Stevens (1905) subsequently noted a variant of the two types of spermatozoa. In the common mealworm beetle

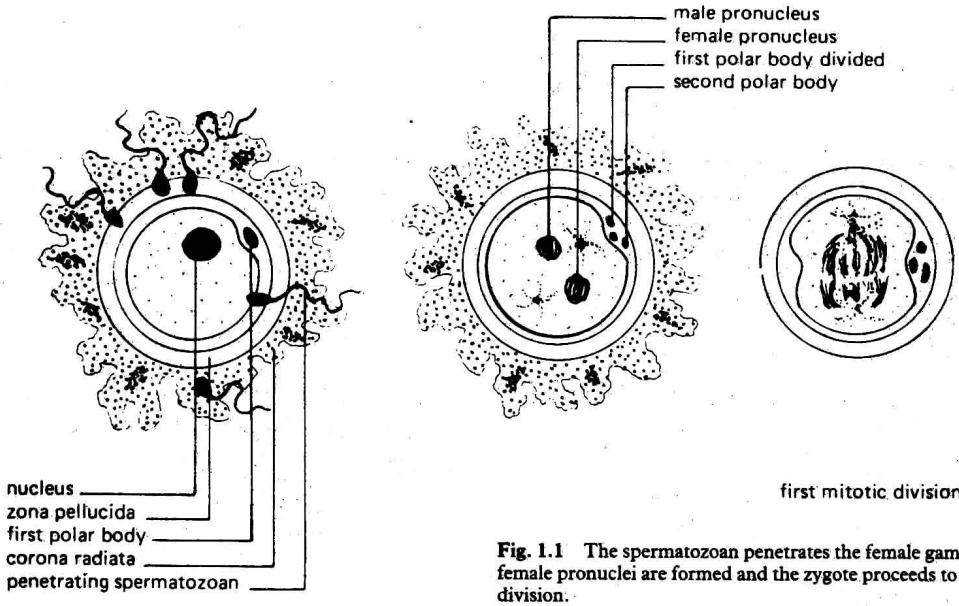

Fig. 1.1 The spermatozoan penetrates the female gamete, the male and female pronuclei are formed and the zygote proceeds to its first mitotic division.

Tenebrio molitor she observed that spermatozoa had either ten large chromosomes or one small and nine large chromosomes. Since adult female cells possessed 20 large chromosomes and adult male cells one small and 19 large chromosomes, she suggested that the character of the spermatozoan determined the sex of the progeny. About the same time Wilson (1906) made identical observations and referred to the small chromosome as the Y chromosome. Thus in *Drosophila melanogaster*, so beloved of geneticists, males are XY and females XX. The Y chromosome, however, was not considered to have any male determining function, since in Drosophila, flies with XXY chromosomes are normal fertile females while those with XO chromosomes are sterile males (Bridges, 1916). Indeed the chromosomal constitution of the human male was thought to be XO (Von Winiwarter, 1912; Oguma & Kihara, 1923) until the Y chromosome was demonstrated in man (Painter, 1924).

Before the introduction of modern cytological techniques observations on human chromosomes were not wholly reliable. With the use of dividing cells in tissue culture, however, Tjio & Levan (1956) established the human diploid number of chromosomes as 46. This was confirmed by Ford & Hamerton (1956) who also provided unequivocal evidence of the presence of an X and a Y chromosome in human male cells. These new techniques not only established the normal male and female sex chromosome constitutions they also revealed a number of sex chromosome abnormalities associated with familiar clinical syndromes. The XXY sex chromosome pattern in Klinefelter's syndrome (Jacobs & Strong, 1959) and the XO pattern in Turner's syndrome (Ford et al, 1959) suggested that, contrary to the situation in Drosophila, the human Y chromosome was male determining and the number of X chromosomes had no major effect on the process of sex determination.

Sexual differentiation and determination

Procreation by sexual means allows an infinite range of genetic variation, the opportunity of its unique expression and its subsequent conservation for future generations. Sex exists partly because of its powerful evolutionary advantages, although it is far from clear why there are only two sexes in vertebrates (Austin et al, 1981). Gonochorism, whereby males and females develop as separate individuals, may arise by the operation of environmental factors such as temperature in reptiles or host size in nematodes (Bull, 1981). It is generally, although not unanimously, accepted that environmental sex determination was the first and primitive mechanism for producing two sexes and that this was later replaced by the XX/XY genotypic mechanism (Witschi, 1929; Ohno, 1967; Mittwoch, 1971. 1975). The majority of mammalian species conform to the XY male/XX female system with the Y chromosome being male-determining (Vorontsov, 1973). In contrast the sex chromosome pattern in birds is ZZ male/ZW female with the W chromosome being female determining (Owen, 1965). Reference to sex determining chromosomes draws attention to the problem of distinguishing between determination and differentiation during embryogenesis. Determination describes events which irrevocably commit cells to a certain

course of development and differentiation describes the processes whereby these cells achieve this development. Since the sex of an individual is established at fertilization this may be regarded as the definitive act of determination with all that follows being processes of embryonic differentiation.

This is a sequential process whereby the genetic or chromosomal sex of the zygote determines the gonadal sex of the embryo which itself regulates the differentiation of the internal and external genital apparatus and hence the sexual phenotype of the individual. At puberty the development of secondary sexual characteristics reinforces the phenotypic manifestations of the sexual dimorphism which achieves its biological fulfilment in successful procreation. Both male and female embryos possess the same indifferent gonadal and genital primordia which have an inherent tendency to feminize unless there is active interference by masculinizing factors. An ovary differentiates unless the indifferent embryonic gonad becomes a testis under the influence of a testis organizing factor regulated by the Y chromosome. Female differentiation of the internal and external sexual organs occurs in the absence of a testis whether or not ovaries are present. The sexual dimorphism that results from sexual differentiation in placental mammals is mediated by the testis and its secretions. Furthermore this male differentiation takes place in an environment of high oestrogen and progestagen concentrations. By contrast, in birds it is the W chromosome of the heterogametic female (ZW) which imposes ovarian differentiation on the indifferent gonad and the ovarian secretions which induce feminization of the internal and external sexual organs. The homogametic avian zygote develops the male phenotype in the absence of any hormonal stimulus (Mittwoch, 1981).

In man, these differentiating processes are regulated by at least 30 specific genes located in sex chromosomes or autosomes that act through a variety of mechanisms, including organizing factors, sex steroid and peptide secretions and specific tissue receptors (Grumbach & Conte, 1981).

EARLY EMBRYOGENESIS

Preimplantation phase

The human zygote with its XX or XY sex chromosome constitution is usually conceived in the distal third of the uterine tube (Croxatto & Ortiz, 1975). Various mechanisms are involved in the movement of the zygote towards the uterine cavity which it enters some 80 hours after fertilization (Pauerstein, 1978). During that period mitotic activity generates an increaisng number of cells termed blastomeres, within which the total volume of cytoplasm decreases as cell numbers increase (O'Rahilly, 1973). The age of the conceptus and its cell content and organization on entry to the uterine cavity are thought to be critical to its subsequent successful implantation and development (Hunter, 1982). The birth of normal infants, however, following external fertilization (IVF) of human gametes has shown that the tubal phase of development before entry of the conceptus to the uterine cavity is not essential to normal embryogenesis. Indeed successful pregnancy has been reported with embryo transfer at the two-cell to three-cell stage (Trounson & Conti, 1982).

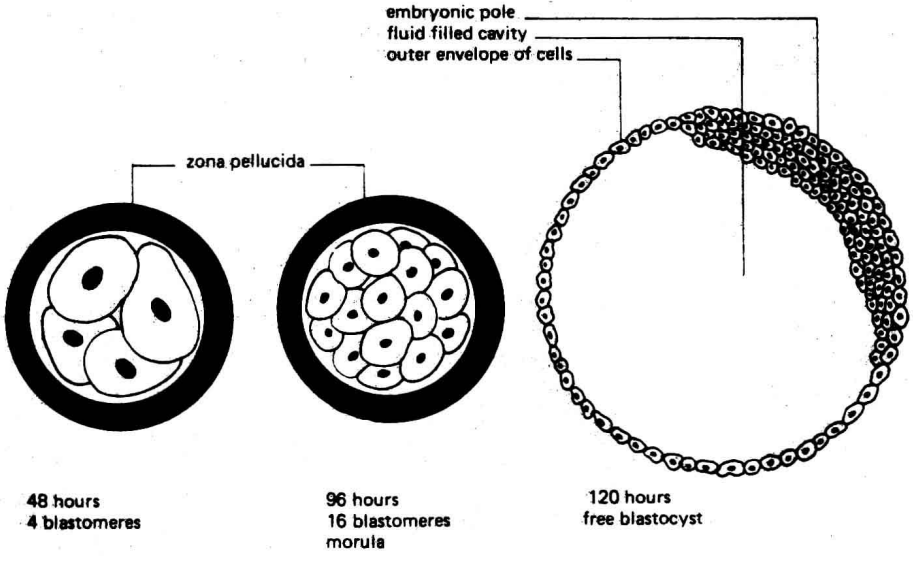

Fig. 1.2 The conceptus, as the morula, is enclosed within an acellular envelope, the zona pellucida. Dissolution of the zona pellucida allows formation of the blastocyst with an embryonic pole, or inner cell mass, and a characteristic fluid-filled cavity.

Carnegie Stage 2 extends from the two cell embryo, through the dissolution of the zona pellucida, to the appearance of the fluid-filled segmentation cavity which identifies the blastocyst. The central cells of the morula (Fig. 1.2) are thought to be embryonic and the peripheral cells trophoblastic (Hertig et al, 1954). The segmentation cavity begins to form when the conceptus has 32 cells (O'Rahilly, 1973) although it has been observed in a 16- to 20-cell embryo after external fertilization (Edwards, 1972). Formation of the blastocyst enables embryonic and trophoblastic cells to be specifically identified. Carnegie Stage 3 embraces the period of development during which the blastocyst (Fig. 1.2) normally lies free within the female reproductive tract. The embryonic cells of the blastocyst are referred to as the embryonic pole or the inner cell mass and it has been suggested (Hertig, 1968) that the precursor cell of the primordial germ cells can be identified within the embryonic pole during this stage, some 108 hours after fertilization.

Implantation

Implantation is a complex process 'by which the conceptus is transported to its site of attachment, held there, orientated properly, and then attached by adhesion, trophoblastic penetration, spread, proliferation, envelopment of vessels and other developments of the placenta, both conceptual and maternal' (Boving, 1963). The embryo adheres to, penetrates and is eventually buried within the endometrium, a process which extends from the sixth to the twelfth postovulatory day and embraces Carnegie Stages 4 and 5 (O'Rahilly, 1973). During this period the outer envelope of cytotrophoblast, forming the wall of the blastocyst, generates syncytiotrophoblast on its external surface (Tao & Hertig, 1965; Enders, 1965) and extraembryonic mesoderm from its internal surface (Hertig & Rock, 1949). The syncytiotrophoblast, cytotrophoblast and extraembryonic mesoderm together form the chorion (Fig. 1.3a). The invasive and endocrine properties of the syncytiotrophoblast are crucial to the survival of the embryo but these aspects of the continuance of pregnancy will not be discussed further in this chapter.

The inner cell mass

The primitive amniotic cavity develops by cavitation within the inner cell mass (Fig. 1.3b) some 7½ days after fertilization (Blechschmidt, 1968; Luckett, 1973). The floor of the amniotic cavity is the epiblast (Hertig, 1968) but in this account it will be referred to as the primary ectoderm. Initially the primary ectoderm consists of variously sized polyhedral cells which either show no precise pattern of arrangement or are in the form of a pseudostratified columnar epithelium showing mitotic figures (O'Rahilly, 1973). The primary endoderm is formed from the cells between the blastocyst cavity and the floor of the amniotic cavity (Heuser & Streeter, 1941). The opposed layers of primary ectoderm and primary endoderm form the bilaminar embryonic disc. The cells of the primary endoderm are small, darkly staining and vacuolated and have no specific arrangement (Hertig & Rock, 1945). The blastocyst cavity is subsequently enclosed by the exocoelomic membrane which is continuous with the primary endoderm at the margins of the embryonic disc. The exocoelomic membrane may arise from primary endodermal cells which migrate around the walls of the blastocyst cavity or it may arise by delamination from the inner aspect of the extraembryonic mesoderm of the chorion (Hertig & Rock, 1945). The exocoelomic membrane and the primary endoderm of the embryonic disc enclose the yolk sac (Fig. 1.3c).

During the thirteenth, fourteenth and fifteenth postovulatory days (Carnegie Stage 6) several significant events

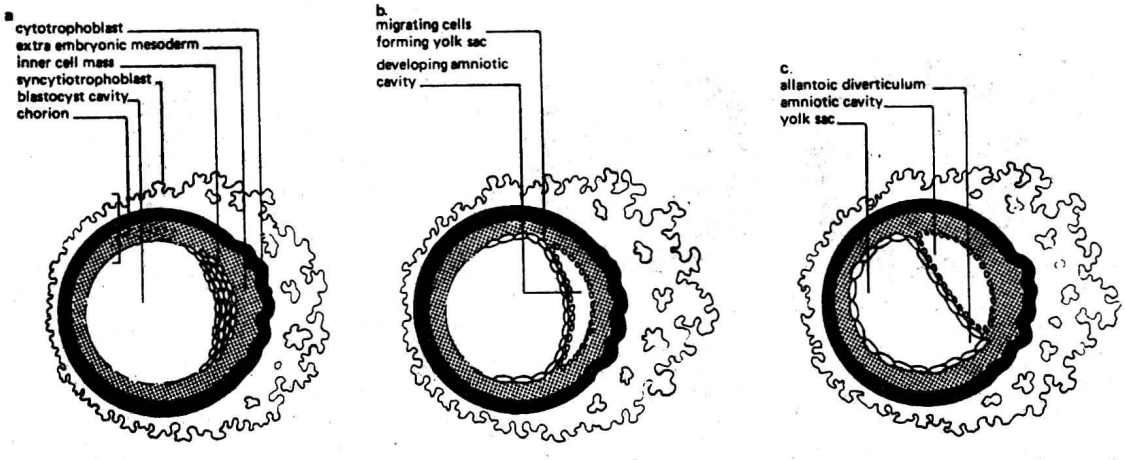

Fig. 1.3 The conceptus continues to differentiate forming (a) the chorion, (b) the amniotic cavity and (c) the yolk sac. The area of contact between amniotic cavity and yolk sac is the bilaminar embryonic disc.

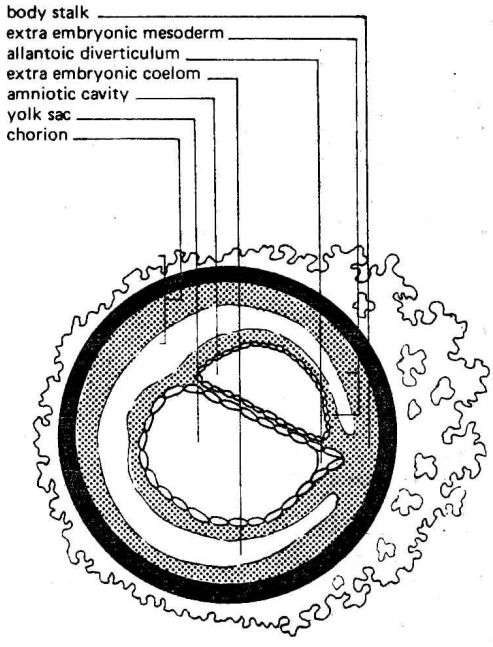

Fig. 1.4 The formation of the extraembryonic coelom establishes the body stalk which attaches the caudal end of the bilaminar embryonic disc to the chorion. An extension of the yolk sac into the body stalk forms the allantoic diverticulum.

occur within the conceptus. The chorionic cavity or extra-embryonic coelom (Fig. 1.4), which has been forming by resorption of extraembryonic mesoderm, is now readily identified (O'Rahilly, 1973). The amniotic cavity and yolk/sac remain enclosed by extraembryonic mesoderm which extends from the caudal end of the embryonic disc to the chorion proper, thereby forming the primitive bodystalk (Florian, 1930). Blood vessel primordia are present within this primitive bodystalk and indicate the future umbilical vessels (Hertig, 1935). In addition a recess of the yolk sac penetrates into the primitive bodystalk as a narrowing diverticulum (Fig. 1.4) and forms the allatoic or allantoic diverticulum (Florian, 1930). Within the yolk sac endoderm of this region possible primordial germ cells, 'stuffed with glycogen', have been observed in a 13-day-old embryo (Hertig et al, 1958). The primitive streak or groove is also observed during this stage as a proliferation of cells lying in the median plane of the caudal region of the embryonic disc (Heuser & Streeter, 1941). The primitive streak may be observed in the floor of the amniotic cavity (Fig. 1.5a). During this stage of development the bilaminar embryonic disc begins to be converted into a trilaminar disc. This is achieved by the primitive streak generating intraembryonic mesoderm which migrates through the embryonic disc in the plane between ectoderm and endoderm (Fig. 1.5b).

Carnegie Stage 7, from the fifteenth to the seventeenth day, is characterized by the appearance of the notochordal

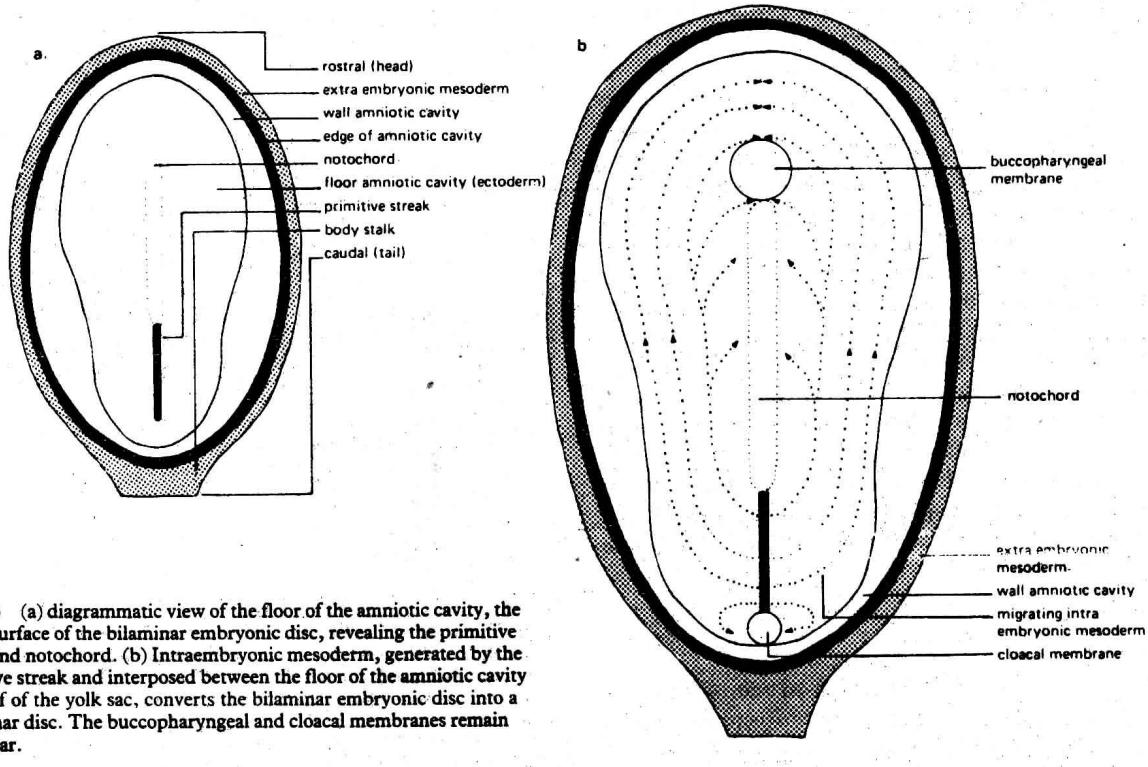

Fig. 1.5 (a) diagrammatic view of the floor of the amniotic cavity, the dorsal surface of the bilaminar embryonic disc, revealing the primitive streak and notochord. (b) Intraembryonic mesoderm, generated by the primitive streak and interposed between the floor of the amniotic cavity and roof of the yolk sac, converts the bilaminar embryonic disc into a trilaminar disc. The buccopharyngeal and cloacal membranes remain bilaminar.

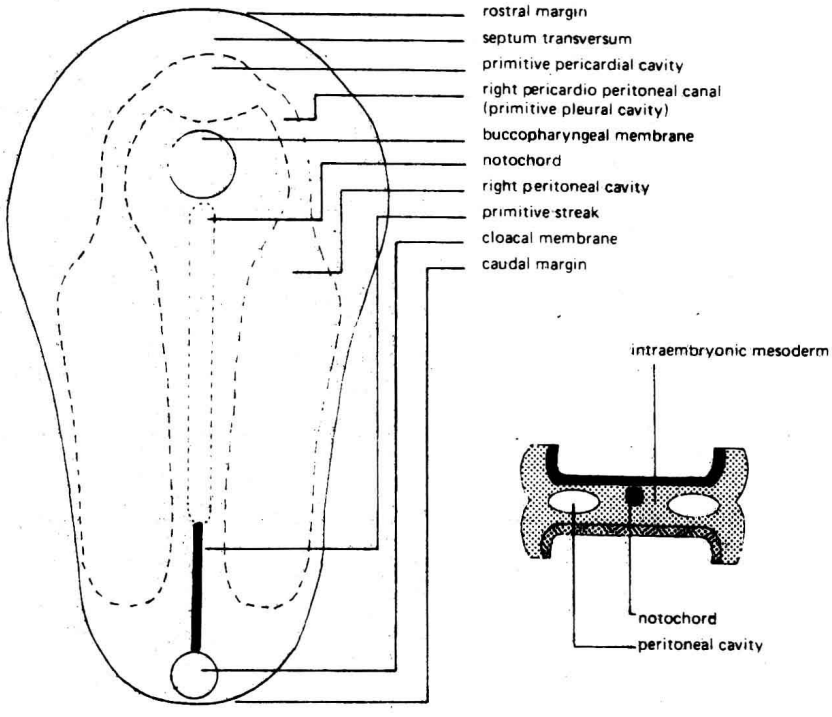

Fig. 1.6 The intraembryonic coelom forms within the intraembryonic mesoderm of the trilaminar embryonic disc.

process, which is a prolongation of the primitive streak in the direction of the future head end of the embryo (Heuser, 1932). During the following two days, Carnegie Stage 8, the intraembryonic mesoderm reaches the margins of the embryonic disc (O'Rahilly, 1973). Two areas of ectoderm endoderm apposition remain, the cloacal membrane and the prechordal plate (Hill & Florian, 1931), which is here referred to as the buccopharyngeal membrane. These two sites are situated in the midline, the buccopharyngeal membrane immediately rostral to the notochordal process and the cloacal membrane immediately caudal to the primitive streak (Fig. 1.5b). As the intraembryonic mesoderm reaches the margins of the embryonic disc its cellular density is greatest near the primitive streak (Jones & Brewer, 1941). Elsewhere isolated spaces are forming within the intraembryonic mesoderm which rapidly coalesce to form an inverted U-shaped intraembryonic coelom (Fig. 1.6) comprising the pericardial cavity, the pleural cavities and the peritoneal cavities in continuity with one another (McIntyre, 1926).

Flexion

Carnegie Stage 9, from the nineteenth to the twenty-first day heralds the onset of that phase of embryogenesis dominated by the formation of the neural folds. The neural plate ectoderm is situated on the dorsal surface of the trilaminar embryo (Fig. 1.7). A midline, longitudinal neural groove appears (Fig. 1.8a) and quickly deepens (Figs. 1.8b

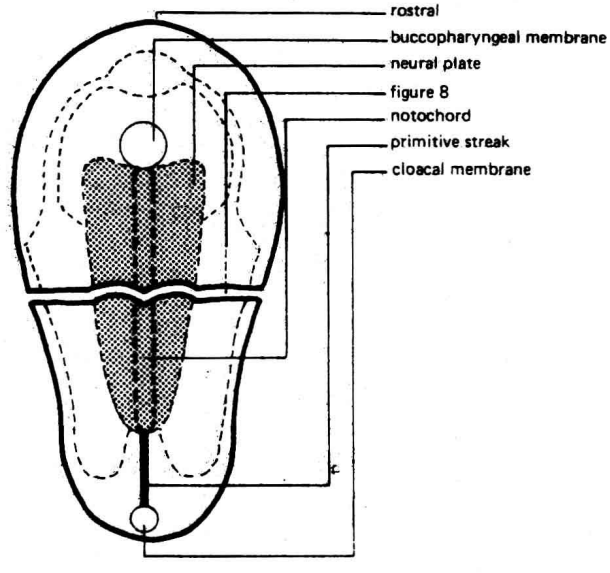

Fig. 1.7 The ectoderm on the dorsal surface of the trilaminar embryonic disc overlying the notochord forms the neural plate.

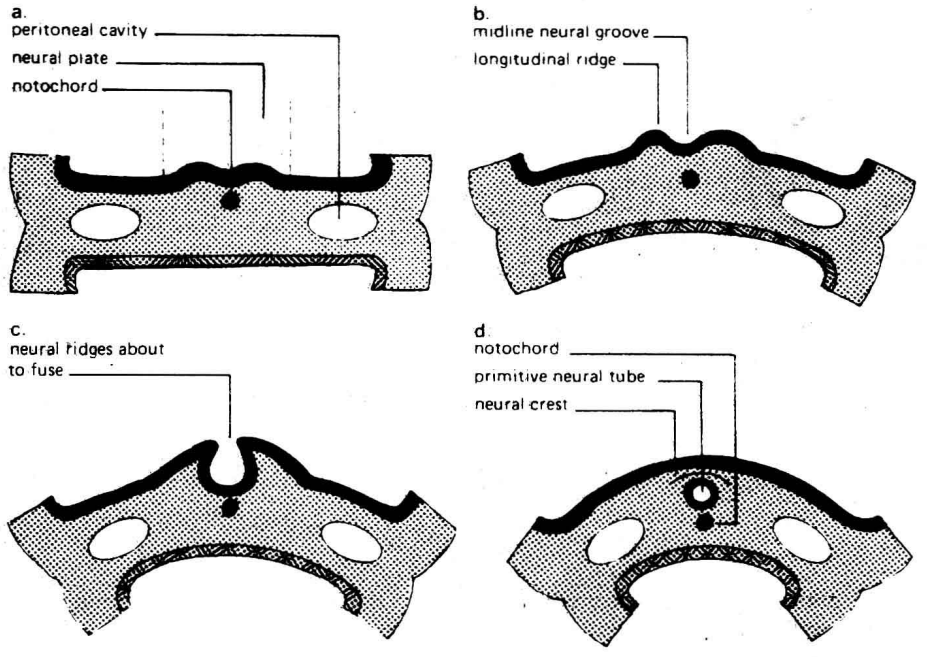

Fig. 1.8 (a) A midline longitudinal groove appears in the neural plate ectoderm. (b) The neural groove deepens with elevation of the neural ridges. (c) The neural ridges approximate and fuse to form the neural tube. (d) As the neural tube is enclosed by the intraembryonic mesoderm the trilaminar embryo folds in the transverse plane displaying a dorsal convexity and ventral concavity.

and 1.8c) but remains open throughout its length. Approximately half of the longitudinal extent of the groove represents the future brain (O'Rahilly, 1973). During the next five days the neural ridges fuse and the primitive neural tube is buried in the underlying intraembryonic mesoderm (Fig. 1.8d). This process of fusion begins in the midembryo region and extends rostrally and caudally until the whole length of the neural tube is closed by the twenty-sixth postovulatory day. During this period the growth of the primitive central nervous system completely transforms the originally flat trilaminar embryonic disc. The growth of the nervous system initially produces a simple dorsal convexity and ventral concavity (Fig. 1.9a). As growth proceeds, the rostral end of the neural tube expands and a greater degree of curvature results. Eventually the portion of the embryo which accommodates the neural tube attains maximum dorsal convexity (Fig. 1.9b) and the once rostral and caudal portions of the embryo are so displaced ventrally that the neural tube is freed from their constraining influences. Unimpeded the neural tube extends rostrally and caudally, overriding the now ventrally displaced original rostral and caudal regions of the embryonic disc which are therefore inverted and reversed in the formation of the head and tail folds (Fig. 1.9c). Neural tube closure and growth has also effected significant folding in the transverse plane, producing the lateral folds (Fig. 1.8d). This process of flexion reorientates the primitive embryonic tissues and structures

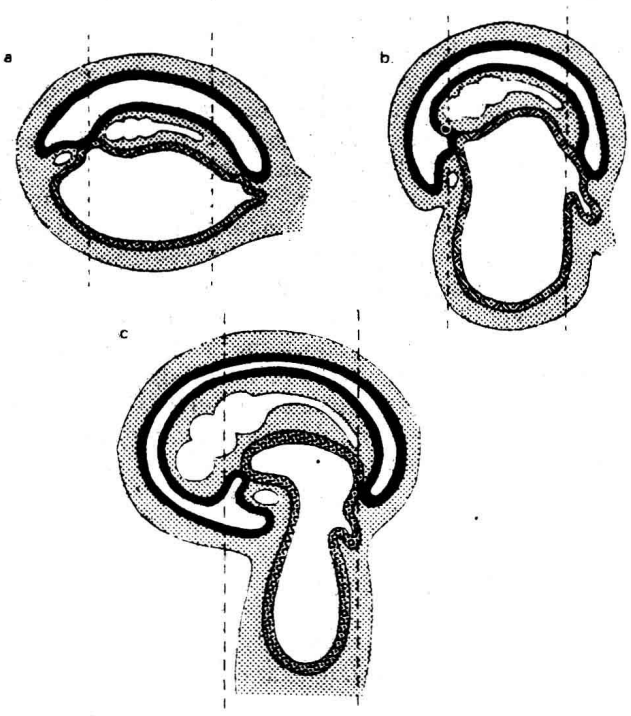

Fig. 1.9 (a) As the neural tube is enclosed within the intraembryonic mesoderm it lengthens, and expands rostrally, causing a dorsal convexity and ventral concavity. (b) Further growth of the neural tube increases this curvature in the longitudinal plane, (c) with the eventual formation of the head and tail folds.