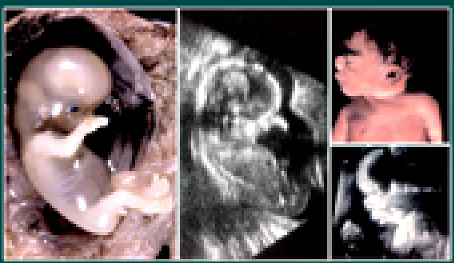
# Embryo & Fetal PATHOLOGY

COLOR ATLAS WITH
*ULTRASOUND CORRELATION*



ENID GILBERT-BARNESS
& DIANE DEBICH-SPICER

CAMBRIDGE www.cambridge.org/9780521825290

## Embryo and Fetal Pathology

### COLOR ATLAS WITH ULTRASOUND CORRELATION

Exhaustively illustrated in color with more than 1000 photographs, figures, histopathology slides, and sonograms, this uniquely authoritative atlas provides the clinician with a visual guide to diagnosing congenital anomalies, both common and rare, in every organ system in the human fetus. It covers the full range of embryo and fetal pathology, from point of death, autopsy and ultrasound, through specific syndromes, intrauterine problems, organ and system defects to multiple births and conjoined twins. Gross pathologic findings are correlated with sonographic features in order that the reader may confirm visually the diagnosis of congenital abnormalities for all organ systems. Obstetricians, perinatologists, neonatologists, geneticists, anatomic pathologists, and all practitioners of maternal-fetal medicine will find this atlas an invaluable resource.

Enid Gilbert-Barness is Professor of Pathology, Laboratory Medicine, Pediatrics and Obstetrics and Gynecology at the University of South Florida and Professor Emeritus of Pathology and Laboratory Medicine and Distinguished Medical Alumni Professor Emeritus at the University of Wisconsin-Madison. She is a leading authority in pediatric pathology with an international reputation for her contributions to the areas of congenital abnormalities, tumor biology, abnormal skeletal growth, sudden infant death syndrome, and many genetic and hereditary disorders.

Diane Debich-Spicer is a pathologists' assistant and highly accomplished medical illustrator. She has had more than twenty years of experience in pediatric pathology.

# Embryo and Fetal Pathology

**COLOR ATLAS WITH ULTRASOUND CORRELATION**

**Enid Gilbert-Barness, MD, MBBS, FRCPA, FRCPath, DSci(hc), MD(hc)**
Tampa General Hospital, University of South Florida
University of Wisconsin School of Medicine

**Diane Debich-Spicer, BS**
Tampa General Hospital, University of South Florida

**Ultrasound contributions from:**
**Mark Williams, MD**
**Kathy B. Porter, MD**
**Susan Guidi, MS, RDMS**

**FOREWORD BY JOHN M. OPITZ, MD, MD(hc), DSci(hc), MD(hc)**
Pediatrics (Medical Genetics), Human Genetics, Obstetrics and Gynecology, and Pathology
University of Utah Medical School

CAMBRIDGE
UNIVERSITY PRESS

CAMBRIDGE UNIVERSITY PRESS
Cambridge, New York, Melbourne, Madrid, Cape Town, Singapore, São Paulo

Cambridge University Press
The Edinburgh Building, Cambridge CB2 2RU, UK

Published in the United States of America by Cambridge University Press, New York

www.cambridge.org
Information on this title: www.cambridge.org/9780521825290



First published in print format 2004

ISBN-13 978-0-511-19581-5 eBook (NetLibrary)
ISBN-10 0-511-19581-8 eBook (NetLibrary)

ISBN-13 978-0-521-82529-0 hardback
ISBN-10 0-521-82529-6 hardback

*To* Lew, Mary, Elizabeth, Jennifer, Rebecca and grandchildren Alexandra, Louis, Christian, James, Thomas, Blake, Spencer, Curtis, Kiara and Rebecca

and

*To* Scott and Andrew

# Contents

# Foreword

With the publication of ***Embryo and Fetal Pathology***, developmental pathology has come full circle. It is no coincidence that the development of this branch of biology was almost exactly congruent with that of morphology. And while morphology, since its founding by Goethe and Burdach, respectively, in 1796 and 1800, continued to grow slowly but steadily, especially after shedding its neo-Platonic philosophical trappings, developmental pathology matured in fits and spurts with some astonishing *hiatus*, which to date remain unexplained by the historians of biology. And while the description of the malformed *fetus*, some of them with remarkable accuracy, antedated the 19th century, it was not until 1802–1805 that we can date a modern (i.e., scientific) analysis of malformations. It was on the 8th of April 1802 that Joannes Fridericus Meckel, *Halensis*, at the age of 21, *publice defendet* his *dissertatio inauguralis "de cordis conditionibus abnormibus"* (on congenital heart defects, published in *Reil's Archive* three years later).

What happened between 1802 and 1805 in Meckel's life was of the utmost importance for the subsequent development of the field, for it was during that time that the prodigiously gifted, young Meckel – working with Cuvier in Paris – became master of comparative anatomy but with the difference that, while Cuvier ignored embryonic and fetal stages and considered malformations irrelevant, Meckel did not. Indeed, it was Meckel's attention to prenatal stages of life, whether normal or abnormal, that led to the formulation of the concepts of vestigia (persistence of embryonic/fetal stages) and atavisms (recurrence of an ancestral stage) and an initial recapitalulationist attempt to relate evolution and development.

And while, in the words of Virchow, Meckel, during his short life of 52 years, accomplished the best and most in what was in Virchow's days called the science of Teratology, the oblivion that befell his work after his death was so complete that the science was independently reinvented several times in the subsequent century, beginning with Rokitansky, Isidore Geoffroy St.-Hilaire, Taruffi, Dareste, and, finally, Ballantyne. Ernst Schwalbe began his *Morphologie der Missbildungen des Menschen und der Tiere* (Morphology of malformations of humans and animals) in 1906 and finished Parts I (on the science of malformations or Teratology) and II (conjoined twinning, 1907) himself before enlisting the collaboration of coworkers who completed the work after Schwalbe's death; lastly, under Georg Gruber's editorship, the last fascicle (on the malformation of the male genitalia) appeared in 1958. John W. Ballantyne of Edinburgh completed the second part of his *Manual of Antenatal Pathology and Hygiene* (The Embryo) in 1904.

Thereafter, virtually no text for the medical profession comprehensively addressed the science, that is, the causes and pathogenesis of human malformations. I for one received no instruction on the subject in medical school; the somewhat idiosyncratic text by Willis (*The Borderland of Embryology and Pathology*, 1958) with its denunciation of atavisms did not appear until the year before my medical school graduation. After Lejeune's discovery of trisomy "21" in Down syndrome in 1959, there was a sudden and highly productive renaissance of the study of human developmental anomalies – in my case, facilitated by a marvelous undergraduate education in embryology and the evolutionary aspects of development (under Emil Witschi). I had met Josef Warkany in Dr. Witschi's office and, during my first year of residency, was struggling with a decision of whether to continue my training as a teratologist in Cincinnati under Warkany, or as a clinical geneticist in Madison with David Smith and Klaus Patau. I applied to both institutions; a few minutes after I accepted the position in Madison, late at night shortly before the first of July 1961, the chair of Pediatrics in Cincinnati called and was disappointed at my unreasonable decision. In retrospect, it was a fortunate decision because my training placed heavy emphasis on genetics and cytogenetics at a time when medical morphology was barely beginning a rebirth and was not considered a science fit for a respectable geneticist. Nevertheless, after David Smith's departure for the University of Washington in Seattle, pediatric/clinical genetics continued to grow in Madison complemented by a supportive and productive anatomical genetics program where we were privileged to dissect the first few 18- and 13-trisomy infants previously studied by Drs. Smith, Patau, and Pallister (in far-off Montana). The field was stimulated by continuing discoveries in cytogenetics, biochemical genetics, and animal genetics (e.g., Hans Grüneberg in the mouse, Curt Stern and Ernst Hadorn in *Drosophilia*).

And then in 1970, *mirabile cum dictu*, Enid Gilbert was appointed Professor of Pediatric Pathology at the University of Wisconsin, and my life has not been the same since then. Now it was finally possible for me, under the guidance of this enormously experienced, wise, and gentle colleague, to complete my training in developmental pathology and for us to develop together a research, service, and training program combining anatomy, genetics, embryology, and experimental approaches. It must be remembered that Enid was not only the consummate pediatric and fetal pathologist, but also a marvelous teratologist who conducted pioneering studies on the production of cardiovascular malformations in chicks with a successful and well-funded research team. Enid's knowledge in all of these fields was then already so legendary that her future husband, Lew Barness, stumped when asked to come up with a (correct) diagnosis in a CPC exercise, thought to be really clever in reading through Enid's bibliography for her favorite subject in the field to which he had narrowed his nosology (a storage disorder), at which point, he threw his hands up in wonder saying: "... why she has written on *all* of them."

***Embryo and Fetal Pathology*** could not have been published at a more propitious time. At the beginning of this year the National Institute of Child Health and Human Development of the United States will support five centers to conduct exemplary, multidisciplinary studies to determine the causes of stillbirth. Surely, ***Embryo and Fetal Pathology*** will be the resource *par excellence* to guide those of us in the five centers, and *all* other pediatric/fetal pathologists throughout the world, to do the analyses most likely to yield the data needed to inform parents on pathogenesis, cause and recurrence risk pertaining to the death of their infant.

Meckel apologized that his "Beyträge" – contributions to pathologic anatomy of 1811 – were not illustrated, probably *the* crucial factor for that work's oblivion. He tried to amend in 1817 with the publication of his *Tabulae Anatomico-Pathologicae* which covered only the heart. Probably there is no more visually aesthetic science in biology than development and developmental pathology and the Gilbert-Barness text ***Embryo and Fetal Pathology*** is superbly illustrated (with the assistance of Diane Debich-Spicer) with more than 1000 images. Meckel could not have imagined the means available to us now to visually assess the structural and functional status of the embryo and fetus. But ***Embryo and Fetal Pathology*** is a model of coordinating information from ultrasonography, indeed, all means of prenatal diagnosis (with the expert collaboration of Mark Williams, Kathy Porter, and Susan Guidi), anatomy, embryology, radiology, molecular biology, and genetics to assist in our goal of assessing the fetus.

The stepchild of the 19th- and early 20th-century fetal pathology was the placenta and its relationship to fetal pathology; even now, we do not routinely give the placentas the same meticulous attention we pay to the fetus. Thus, Chapter 5 in ***Embryo and Fetal Pathology*** is called to particular attention of all students of human development for its detailed analysis of placental ontogeny, structure, and function.

There are two books Meckel would have considered fundamental in the progress of developmental history and pathology – he was ready, far, far ahead of his contemporaries for the *Origin of Species*... and he would have considered ***Embryo and Fetal Pathology*** the fulfillment of all of his efforts to unite comparative anatomy, embryology, "heredity," pathology, and the relationship of all animals on this earth, whether normal or abnormal. I feel humbly and profoundly gratified to greet and introduce this *opus maximus* of my friend and most distinguished collaborator, Dr. Enid Gilbert-Barness.

John M. Opitz
Lacosalensis, Utah
December 2003

# Preface

This Atlas represents almost 50 years of study of embryos, fetuses, and perinatally dead infants. It includes more than 200 ultrasound images essential to modern diagnosis and important in the correlation with pathologic examination and for genetic counseling. In the past, products of conception frequently have been discarded or given only a cursory pathologic examination; however, in recent years it has become important to carefully examine these specimens and study embryonic tissue to accurately determine the nature and cause of prenatal death.

The Atlas includes more than 2000 illustrations in color, with a brief text of essential concepts and comments. Generous use of tables is made to replace more extensive text and important references are given at the end of each chapter.

A catalog of genetic syndromes with updated references is available through OnLine Mendelian Inheritance in Man OMIM (http://www3.ncbi.nlm.nih.gov/omim/). In general, OMIM does not provide specific testing sites but often discusses the potential for molecular testing and gives references that can be used to contact experts in the field.

It is our hope that this volume will be a useful reference for obstetricians engaged in fetal–maternal and reproductive medicine, geneticists, pediatricians – neonatologists, in particular, and pathologists who have an interest in pediatric and genetic pathology.

Enid Gilbert-Barness, MD
Diane Debich-Spicer, BS

# Acknowledgments

The authors wish to express their thanks and deep gratitude to their many friends and colleagues who have been so generous with their time, encouragement, and support of this work, and to those who have contributed illustrations. In particular, we especially thank Carlos Abramowsky, Jeanne Ackerman, Jeff Angel, Sonja Arnold, John Balis, Lewis Barness, Stephen Brantley, Irwin Browarsky, M. Michael Cohen Jr., John Curran, Monica Drut, Philip Farrell, Jamie Frias, Americo Gonzalvo, Robert Gorlin, Susan Guidi, Silvaselvi Gunasekaran, James Huhta, Stanley Inhorn, Craig Kalter, Judith Krammer, Atilano Lacson, Renata Laxova, Jane Messina, Santo Nicosia, William O'Brien, John M. Opitz, Kathy Porter, Helga Rehder, Allen Root, Karen Schmidt, David Shields, Jürgen Spranger, George Tiller, Mark Williams, and Gabriele ZuRhein. We most sincerely appreciate the untiring dedication of Kathleen Lonkey in the preparation of the manuscript – without her expertise this book would not have been possible. We also thank Margaret Petro and Gerda Anderson, Tampa General Hospital librarians, whose help has been inestimable. To the editors Catherine Felgar and Eleanor Umali, we are profoundly indebted.

## ONE

# The Human Embryo and Embryonic Growth Disorganization

### STAGES OF EMBRYONIC DEVELOPMENT

Carnegie staging in the development of the human embryo categorizes 23 stages.

#### Fertilization and Implantation (Stages 1–3)

Embryonic development commences with fertilization between a sperm and a secondary oocyte (Tables 1.1 to 1.5). The fertilization process requires about 24 hours and results in the formation of a **zygote** – a diploid cell with 46 chromosomes containing genetic material from both parents. This takes place in the ampulla of the uterine tube.

The embryo's sex is determined at fertilization. An X chromosome-bearing sperm produces an XX zygote, which normally develops into a female, whereas fertilization by a Y chromosome-bearing sperm produces an XY zygote, which normally develops into a male.

The zygote passes down the uterine tube and undergoes rapid mitotic cell divisions, termed cleavage. These divisions result in smaller cells – the **blastomeres.** Three days later, after the developing embryo enters the uterine cavity, compaction occurs, resulting in a solid sphere of 12–16 cells to form the **morula**.

At 4 days, hollow spaces appear inside the compact morula and fluid soon passes into these cavities, allowing one large space to form and thus converting the morula into the **blastocyst** (blastocyst hatching). The blastocyst cavity

**Table 1.1** Human embryonic development and growth

| Period | Conception* (d) | Gestational age** (d) | CR length (mm) | External characterizations | Carnegie staging |
|---|---|---|---|---|---|
| Blastogenesis | | | | | |
| First 2 weeks | 0–14 | 0–28 | 0–0.4 | Unicellular to bilaminar plate | 1–6b |
| Days 14–28 | 15–28 | 29–35 | 0.4–4.6 | Trilaminar embryo to open neural groove | 7–10 |
| Organogenesis | | | | | |
| Second 4 weeks | 22–35 | 36–49 | 4.6–8 | Neural tube closure to limb buds | 11–13 |
| Days 32–56 | 36–60 | 50–75 | 8–30 | Limb growth to fused eyelids | 14–22 |
| Fetal | 61–266 | 75–280 | 35–350 | Fetal maturation | |

* Embryonic development is dated from fertilization.
** Prenatal growth evaluation by ultrasound is dated from day of last menstrual period. This is termed "gestational age."
Adaped from Wilson RD: Prenatal evaluation of growth by ultrasound, *Growth Genetics & Hormones*, v.9(1), 1993.

separates the cells into an outer cell layer, the trophoblast, which gives rise to the placenta, and a group of centrally located cells, the **inner cell mass**, which gives rise to both embryo and extraembryonic tissue.

The **zona pellucida** hatches on day 5 and the blastocyst attaches to the endometrial epithelium. The trophoblastic cells then start to invade the endometrium.

Implantation of the blastocyst usually takes place on day 7 in the midportion of the body of the uterus, slightly more frequently on the posterior than on the anterior wall.

### Gastrulation

Changes occur in the developing embryo as the bilaminar embryonic disc is converted into a trilaminar embryonic disc composed of three germ layers.

**Table 1.2** Measurements of gestation age by ultrasound

| Mean gestational age (wk)* | Mean gestational sac diameter (mm)† | Embryo CR length (mm) | BPD (mm) | Femur length (mm) |
|---|---|---|---|---|
| 5 + 0 | 2 | – | – | – |
| 6 + 0 | 10 | 6 | – | – |
| 7 + 0 | 18 | 10 | – | – |
| 8 + 0 | 26 | 17 | – | – |
| 9 + 0 | – | 25 | – | – |
| 10 + 0 | – | 33 | – | – |
| 11 + 0 | – | 43 | – | 6 |
| 12 + 0 | – | 55 | 17 | 9 |
| 13 + 0 | – | 68 | 20 | 12 |
| 14 + 0 | – | 85 | 25 | 15 |

* From 1st day of last menstrual period  † Daya et al., 1991  ‡ Jeanty, 1983
Adaped from Wilson RD: Prenatal evaluation of growth by ultrasound, *Growth Genetics & Hormones*, v.9(1), 1993.

The process of germ layer formation, called gastrulation, is the beginning of embryogenesis (formation of the embryo).

Gastrulation begins at the end of the 1st week with the appearance of the hypoblast; it continues during the 2nd week with the formation of the epiblast and is completed during the 3rd week with the formation of intraembryonic mesoderm by the primitive streak. The three primary germ layers are called ectoderm, mesoderm, and endoderm. As the embryo develops, these layers give rise to the tissues and organs of the embryo.

The blastocyst begins to become attached to the uterine lining (the endometrium).

### Implantation

Implantation includes dissolution of the zona pellucida and adhesion between the blastocyst and the endometrium, trophoblastic penetration, and migration

**Table 1.3** Number of somites correlated to approximate age in days

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

**Table 1.4** Summary of embryonic development highlights

| CR length (mm) | Days after ovulation | Carnegie stage | Main external features |
|---|---|---|---|
| 0.1 | 0–2 | 1 | Fertilized oocyte |
| | 4–6 | 3 | Blastocyst |
| 0.2–0.4 | 6–15 | 5 | Trilaminar embryo with primitive streak |
| 1.5–2.0 | 20–22 | 9 | Heart tubes begin to fuse |
| 2.0–3.0 | 22–24 | 10 | Neural folds begin to fuse; heart begins to beat |
| 3.0–4.0 | 24–26 | 11 | Rostral neuropore closing |
| 4.0–5.0 | 26–30 | 12 | Upper limb buds appear |
| 5.0–6.0 | 28–32 | 13 | Four pairs of branchial arches |
| 6.0–7.0 | 31–35 | 14 | Lens pits and nasal pits visible |
| ***Highlights 35–56 days, organogenesis*** | | | |
| 7.0–10.0 | 35–38 | 15 | Hand plates formed; retinal pigment visible |
| 10.0–12.0 | 37–42 | 16 | Foot plates formed |
| 12.0–14.0 | 42–44 | 17 | Finger rays appear; auricular hillocks developed |
| 14.0–17.0 | 44–48 | 18 | Toe rays appear |
| 16.0–20.0 | 48–51 | 19 | Trunk elongating; midgut herniation to umbilical cord |
| 20.0–22.0 | 51–53 | 20 | Fingers distinct but webbed |
| 22.0–24.0 | 53–54 | 21 | Fingers free and longer |
| 24.0–28.0 | 54–56 | 22 | Toes free and longer |
| 28.0–30.0 | 56–60 | 23 | Head more rounded; fusing eyelids |

**Table 1.5** Major landmarks for early development

| |
|---|
| Retinal pigment 35–37 days |
| Separation of common aorticopulmonary trunk (A & PA separate) 42 days |
| Distinct elbow and/or developing eyelids 44 days |
| Scalp vascular plexus 49 days |
| Intestines into umbilical cord 7–10 weeks |
| Perforation of anal membrane 51 days |
| Lack of tail 56 days |
| Fingernails and a well-defined neck 10–12 weeks (a fetus not embryo) |

of the blastocyst through the endometrium. Implantation occurs by the intrusion of trophoblastic extensions, which penetrate between apparently intact endometrial cells.

### Second Week of Development (Stages 4 and 5)

During the 2nd week, a bilaminar **embryonic disc** forms, **amniotic and primary yolk sac** cavities develop, and there are two layers of trophoblast (Figure 1.1).

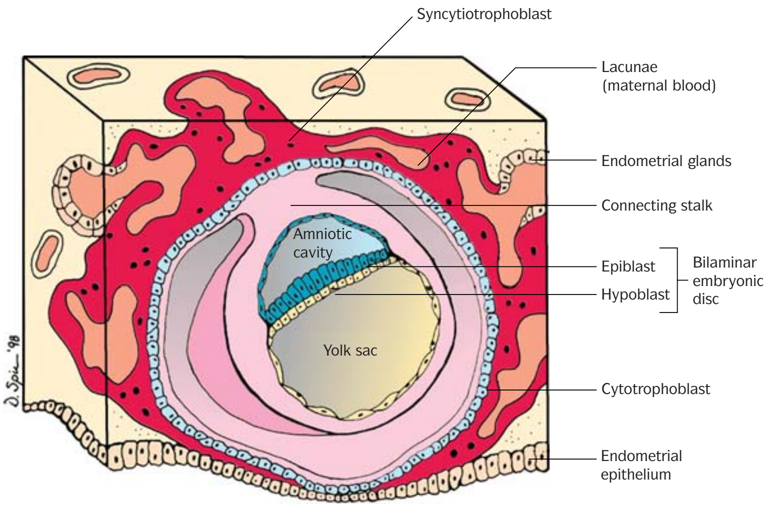
The two-layered disc separates the blastocyst cavity into two unequal parts (a smaller amniotic cavity and a larger primary yolk cavity). The thick layer of embryonic cells bordering the amniotic cavity is called the **epiblast** and a thin layer bordering the primary yolk cavity is called the **hypoblast**.

The trophoblast differentiates into two layers, an inner **cytotrophoblast** and an outer **syncytiotrophoblast**. The trophoblast continues to penetrate deeper into the endometrium. At the end of the 2nd week, the site of implantation is recognized as a small elevated area of endometrium having a central pore filled with a blood clot.

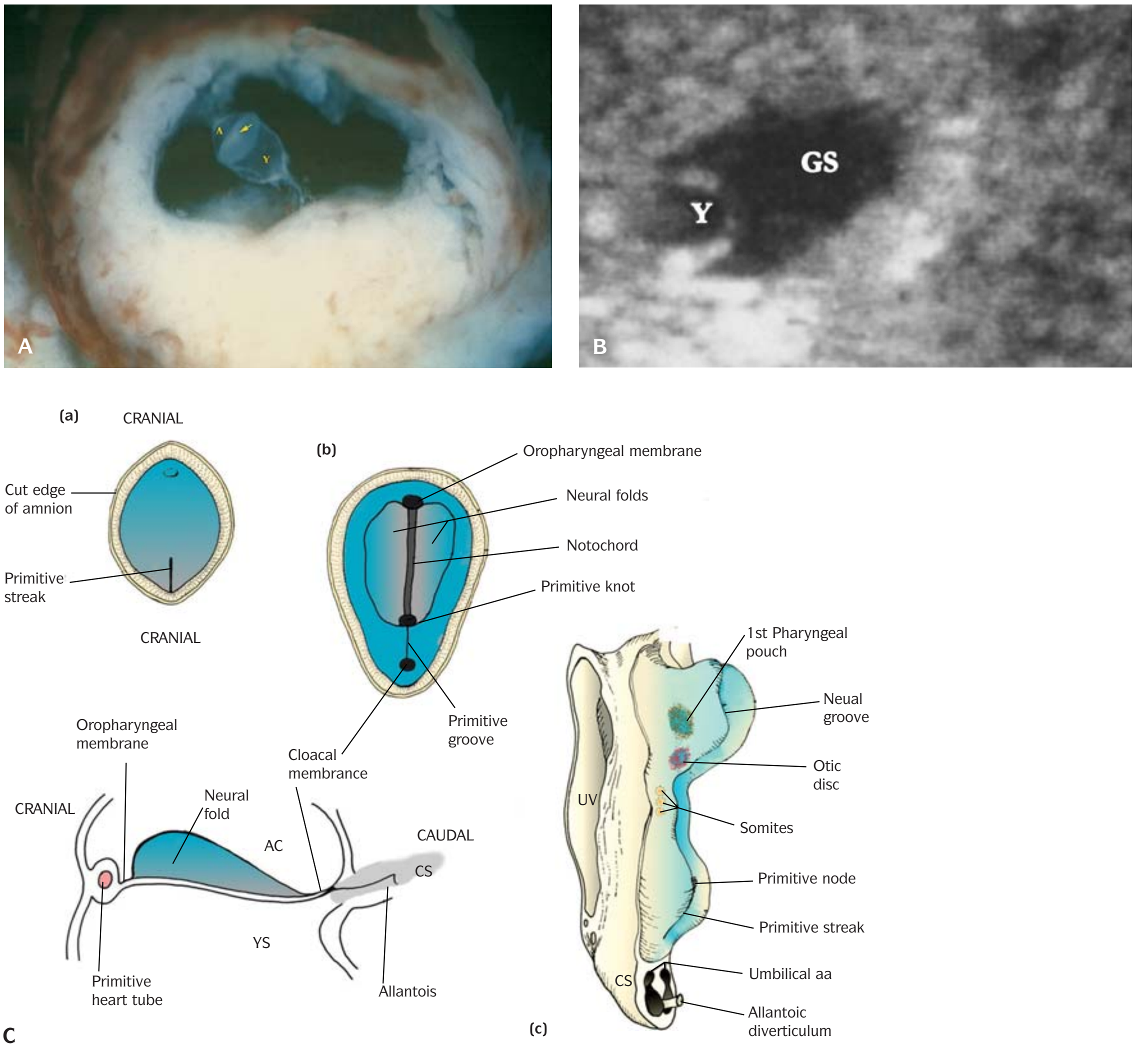
### Third Week of Development (Stages 6–9)

Formation of the primitive streak and three germ layers (ectoderm, mesoderm, and endoderm) (Figure 1.2) occurs during the 3rd week.

The **primitive streak** results from a proliferation of ectodermal cells at the caudal end of the embryonal disc. Cells at the primitive streak proliferate to form the embryonic endoderm and mesoderm. The cephalic end of




**1.1.** Bilaminar embryonic disc in the 2nd week of development (stage 5), with amniotic and primary yolk sac cavities.




**1.2.** **(A)** Ectopic pregnancy at day 17 showing an embryonic disc with opacity (arrow) representing the primitive streak. The amniotic cavity (A) and the primary yolk sac cavity (Y) are present. **(B)** Ultrasound of a human embryo at the same stage of development as A (GS, gestational sac; Y, yolk sac). **(C)** Diagram of development of the primitive streak (a), notochord (b), and neural folds (c) in a trilaminar embryo (stages 6–9).

the primitive streak is the primitive node, and this cord of cells is the **notochord**.

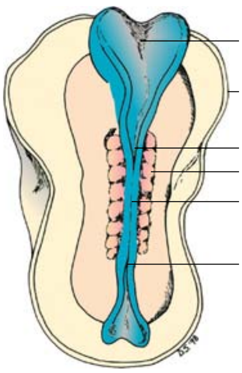
Thickening of ectodermal cells gives rise to the **neural plate**, the first appearance of the nervous system, which becomes depressed below the surface along the long axis of the embryo to form the neural groove. The **neural groove** deepens and its margins elevate to form the **neural folds**. The fusion is completed during the 4th week of development. The neural tube ultimately will give rise to the central nervous system. The cephalic end will dilate to form the forebrain, midbrain, and hindbrain. The remainder of the neural tube will become the spinal cord.

The mesoderm on either side of the midline of the embryo (the paraxial mesoderm) undergoes segmentation, forming **somites**. The first pair of somites arises in the cervical region of the embryo at approximately day 20 of development. From there new somites appear in craniocaudal sequence, approximately three per day, until 42–44 pairs are present at the end of week 5. There are 4 occipital, 8 cervical, 12 thoracic, 5 lumbar, 5 sacral, and 8–10 coccygeal pairs. The first occipital and the last 5–7 coccygeal somites later disappear, while the remainder form the axial skeleton. During this period of development, the age of the embryo is expressed in the number of somites. Each somite differentiates into bones, cartilage, and ligaments of the vertebral column as well as into skeletal voluntary muscles, dermis, and subcutaneous tissue of the skin. The intermediate mesoderm and the lateral mesoderm give rise to portions of the urogenital system. The lateral plate mesoderm is involved in the development of pericardial, pleural, and peritoneal cavities as well as the muscle of the diaphragm.

Mesoderm also forms a primitive cardiovascular system during the 3rd week of development. Blood vessel formation begins in the extraembryonic mesoderm of the yolk sac, the connecting stalk, and the chorion. Embryonic vessels develop 2 days later. The linkage of the primitive heart tube with blood vessels takes place toward the end of week 3, after which blood circulation begins. The beating heart tube begins at 17–19 days.

The embryo changes shape from a disc to a tube with a cranial and a caudal end and the third germ layer, the endoderm, becomes incorporated into the interior of the embryo.

The formation of **chorionic villi** takes place in the 3rd week. The cytotrophoblast cells of the chorionic villi penetrate the layer of syncytiotrophoblast to form a cytotrophoblastic shell, which attaches the chorionic sac to the endometrial tissues.

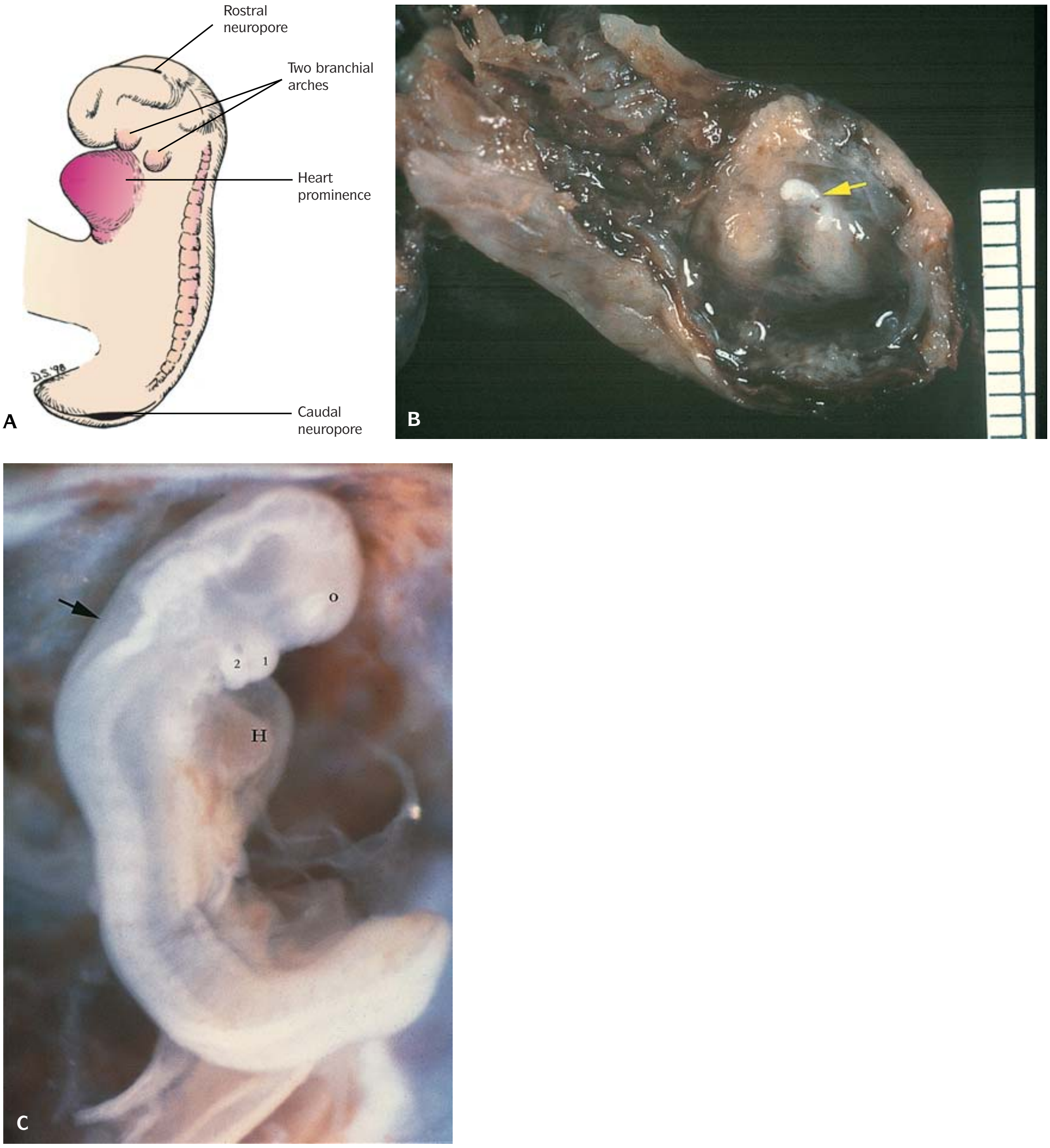



**1.3.** Diagram of human embryo at stage 10. Neural folds are partially fused with the neural tube open at the rostral and caudal neuropore.

### Fourth Week of Development (Stages 10–12: Up to Day 28, End of Blastogenesis)

At this stage, the embryo measures 2–5 mm (Figures 1.3 to 1.6). At *stage 10*, the embryo (at 22–24 days) is almost straight and has between 4 and 12 somites that produce conspicuous surface elevations. The neural tube is closed between the somites but is widely open at the rostral and caudal neuropore. The first and second pairs of branchial arches become visible.

During *stage 11*, a slight curve is produced by folding of the head and tail. The heart produces a large ventral prominence. The rostral neuropore continues to close and optic vesicles are formed.




**1.4.** **(A)** Diagram of a human embryo at stage 11. **(B)** A human embryo at stage 11 (arrow) showing a slight curve. The size should range from 2 to 5 mm. **(C)** Human embryo at stage 11 with a slight curve, two pairs of branchial arches, heart prominence (H), and optic vesicle (O). Rostral neuropore (arrow) continues to close.