KEITH L. MOORE
T.V.N. PERSAUD

THE DEVELOPING HUMAN

Clinically Oriented Embryology

8th Edition

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In Memory of Marion Moore

Marion was my best friend, confidant, colleague, and wife for 57 years. She was the mother of our five children and grandmother of our nine grandchildren. Her assistance with the editing and preparation of earlier editions of this and other books was invaluable. Marion, you will always be in our thoughts and in our hearts. You will be surely missed but never forgotten.

Keith L. Moore

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Preface

We are now entering an era of outstanding achievements in the fields of molecular biology and human embryology. The sequencing of the human genome has been achieved, and several mammalian species, including the human embryo, have been cloned. Scientists have isolated human embryonic stem cells, and suggestions for their use in treating certain intractable diseases continue to generate widespread debate. These remarkable scientific developments have already provided promising directions for research in human embryology, which will have an impact on medical practice in the future.

The eighth edition of *The Developing Human* has been thoroughly revised to reflect our current understanding of some of the molecular events that guide formation of the embryo. The book also contains more clinically oriented material than previous editions. These sections are highlighted in color to set them apart from the rest of the text. In addition to focusing on clinically relevant aspects of embryology, we have revised the clinically oriented problems with brief answers and added more case studies that emphasize that embryology is an important part of modern medical practice.

This edition includes numerous new color photographs of embryos (normal and abnormal). Many of the illustrations have been improved using three-dimensional renderings and more effective use of colors. There are also many new diagnostic images (ultrasound and MRI) of embryos and fetuses to illustrate three-dimensional aspects of embryos. An innovative set of animations that will help students to understand the complexities of embryological development now comes with this book.

The coverage of teratology has been increased because the study of abnormal development is helpful in understanding risk estimation, the causes of anomalies, and how malformations may be prevented. Recent advances in the molecular aspects of developmental biology have been highlighted throughout the book, especially in those areas that appear promising for clinical medicine or have the potential for making a significant impact on the direction of future research. With this is mind, we have added a chapter, contributed by Dr. Jeffrey T. Wigle and Dr. David D. Eisenstat, on some common signaling pathways during development.

We have continued our attempts to give an easy-to-read account of human development before birth. Each chapter has been thoroughly revised to reflect new findings in research and their clinical significance. The chapters are organized to present a systematic and logical approach that explains how embryos develop. The first chapter introduces the reader to the scope and importance of embryology, the historical background of the discipline, and the terms used to describe the stages of development. The next four chapters cover embryonic development, beginning with the formation of gametes and ending with the formation of basic organs and systems. The development of specific organs and systems is then described in a systematic manner, followed by chapters dealing with the highlights of the fetal period, the placenta and fetal membranes, and the causes of human congenital anomalies. At the end of each chapter there are references that contain both classic works and recent research publications.

Keith L. Moore
Vid Persaud

Acknowledgments

The Developing Human is widely used by medical, dental, and other students in the health sciences. The suggestions, criticisms, and comments we received from instructors and students around the world have helped us to improve this work. In a book such as this, the illustrations are an essential feature. Many colleagues have generously provided us with photographs of clinical cases from their practice.

We are indebted to the following colleagues (listed alphabetically) for critical reviewing of chapters, making suggestions for improvement of this book, or providing new figures: Dr. Judy Anderson, Department of Human Anatomy and Cell Science, University of Manitoba, Winnipeg, Manitoba; Dr. Stephen Ahing, Department of Dental Diagnostic and Surgical Sciences, Faculty of Dentistry, University of Manitoba, Winnipeg, Manitoba; Dr. Kunwar Batnagar, School of Medicine, University of Louisville, Louisville, Kentucky; Dr. David L. Bolender, Department of Cell Biology, Neurobiology, and Anatomy, Medical College of Wisconsin, Milwaukee, Wisconsin; Dr. Boris Kablar, Department of Anatomy and Neurobiology, Dalhousie University, Halifax, Nova Scotia; Dr. Albert Chudley, Departments of Pediatrics and Child Health, Biochemistry and Medical Genetics, University of Manitoba, Winnipeg, Manitoba; Dr. Blaine M. Cleghorn, Faculty of Dentistry, Dalhousie University, Halifax, Nova Scotia; Dr. Marc Del Bigio, Department of Pathology, University of Manitoba, Winnipeg, Manitoba; Dr. Stephen E. Dolgin, Division of Pediatric Surgery, Mount Sinai School of Medicine, New York, New York; Dr. Raymond Gasser, Department of Cell Biology and Anatomy, Louisiana State University School of Medicine, New Orleans, Louisiana; Dr. Barry Grayson, Institute of Reconstructive Plastic Surgery, New York University Medical Center, New York, New York; Dr. Byron Grove, Department of Anatomy and Cell Biology, University of North Dakota, Grand Forks, North Dakota; Dr. Brian K. Hall, Department of Biology, Dalhousie University, Halifax, Nova Scotia; Dr. Mark W. Hamrick, Department of Cellular Biology and Anatomy, Medical College of Georgia, Augusta, Georgia; Dr. Christopher Harman, Department of Obstetrics, Gynecology, and Reproductive Sciences, University of Maryland, Baltimore, Maryland; Dr. Dagmar Kalousek, Department of Pathology, University of British Columbia, Vancouver, British Columbia; Dr. Tom Klonisch, Department of Human Anatomy and Cell Science, University of Manitoba, Winnipeg, Manitoba; Dr. David J. Kozlowski, Department of Cellular Biology and Anatomy, Medical College of Georgia, Augusta, Georiga; Dr. Peeyush Lala, Faculty of Medicine, University of Western Ontario, London, Ontario; Dr. Deborah Levine, Beth Israel Deaconess Medical Center, Boston, Massachusetts; Dr. Edward A. Lyons, Department of Radiology, University of Manitoba, Winnipeg, Manitoba; Professor Bernard J. Moxham, Cardiff School of Biosciences, Cardiff University, Cardiff, Wales; Dr. John Mulliken, Department of Surgery and Craniofacial Center, Harvard Medical School, Boston, Massachusetts; Dr. Valerie Dean O'Loughlin, Department of Anatomy and Cell Biology, Indiana University, Bloomington, Indiana; Dr. Maria Patestas, Des Moines University, Des Moines, Iowa; Professor T.S. Ranganathan, Department of Anatomical Sciences, St. George's University, Grenada; Dr. Gregory Reid, Department of Obstetrics, Gynecology and Reproductive Sciences, University of Manitoba, Winnipeg, Manitoba; Dr. Norman Rosenblum, The Hospital for Sick Children and Department of Pediatrics, University of Toronto, Toronto, Ontario; Dr. J. Elliott Scott, Department of Oral Biology, Faculty of Dentistry, University of Manitoba, Winnipeg, Manitoba; Dr. Robert Semo, Department of Obstetrics and Gynecology, University of California, San Diego, California; Dr. Joseph Siebert, Research Associate Professor, Children's Hospital and Regional Medical Center, Seattle, Washington; Dr. Kohei Shiota, Department of Anatomy and Developmental Biology, Kyoto University, Kyoto, Japan; Dr. Gerald Smyser, Altru Health System, Grand Forks, North Dakota; Dr. Pierre Soucy, Division of Paediatric General Surgery, Children's Hospital of Eastern Ontario, University of Ottawa, Ottawa, Ontario; Dr. Richard Shane Tubbs, Children's Hospital, University of Alabama at Birmingham, Birmingham, Alabama; Professor Christoph Viebahn, Department of Anatomy and Embryology, Göttingen University, Göttingen, Germany; Christopher von Bartheld, Department of Physiology and Cell Biology, Medical School of Nevada, Reno, Nevada; Dr. Michael Wiley, Division of Anatomy, Department of Surgery, University of Toronto, Toronto, Ontario; and Dr. Donna L. Young, Department of Biology, University of Winnipeg, Winnipeg, Manitoba.

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Keith L. Moore
Vid Persaud

Contents

1 Introduction to the Developing Human

Human development is a continuous process that begins when an **oocyte** (ovum) from a female is fertilized by a **sperm** (spermatozoon) from a male. Cell division, cell migration, programmed cell death, differentiation, growth, and cell rearrangement transform the fertilized oocyte, a highly specialized, totipotent cell, a **zygote**, into a multicellular human being. Although most developmental changes occur during the embryonic and fetal periods, important changes occur during later periods of development: infancy, childhood, adolescence, and early adulthood *Development does not stop at birth*. Important changes, in addition to growth, occur after birth (e.g., development of teeth and female breasts).

DEVELOPMENTAL PERIODS

It is customary to divide human development into *prenatal* (before birth) and *postnatal* (after birth) periods. The main developmental changes occurring before birth are illustrated in the *Timetable of Human Prenatal Development* (Figs. 1-1 and 1-2). Examination of the timetable reveals that the most visible advances occur during the third to eighth weeks of embryonic development. During the fetal period, differentiation and growth of tissues and organs occur. The rate of body growth increases during this period.

EMBRYOLOGIC TERMINOLOGY

The following terms are commonly used in discussions of developing humans; several of these terms are used in the *Timetable of Human Prenatal Development*. Most terms have Latin (L.) or Greek (Gr.) origins.

Oocyte (*L. ovum*, egg). The female germ or sex cells are produced in the *ovaries*. When mature, the oocytes are called secondary oocytes or mature oocytes.

Sperm (Gr. *sperma*, seed). The sperm, or spermatozoon, refers to the male germ cell produced in the testes (testicles). Numerous sperms (spermatozoa) are expelled from the male urethra during ejaculation.

Zygote. This cell results from the union of an oocyte and a sperm during fertilization. A zygote or embryo is the beginning of a new human being.

Gestational Age. It is difficult to determine exactly when fertilization (conception) occurs because the process cannot be observed in vivo (within the living body). Physicians calculate the age of the embryo or fetus from the presumed first day of the last normal menstrual period. This is the *gestational age*, which is approximately 2 weeks longer than the *fertilization age* because the oocyte is not fertilized until approximately 2 weeks after the preceding menstruation (see Fig. 1-1).

Cleavage. This is the *series of mitotic cell divisions of the zygote* that result in the formation of early embryonic cells, *blastomeres*. The size of the cleaving zygote remains unchanged because at each succeeding cleavage division, the blastomeres become smaller.

Morula (L. *morus*, mulberry). This solid mass of 12 to approximately 32 blastomeres is formed by cleavage of a zygote. The blastomeres change their shape and tightly align themselves against each other to form a compact ball of cells. This phenomenon, **compaction**, is probably mediated by cell surface adhesion glycoproteins. The morula stage occurs 3 to 4 days after fertilization, just as the early embryo enters the uterus.

Blastocyst (Gr. *blastos*, germ + *kystis*, bladder). After 2 to 3 days, the morula enters the uterus from the uterine tube (fallopian tube). Soon a fluid-filled cavity, the *blastocystic cavity*, develops inside it. This change converts the morula into a blastocyst. Its centrally located cells, the *inner cell mass* or *embryoblast*, is the embryonic part of the embryo.

Implantation. The process during which the blastocyst attaches to the *endometrium*, the mucous membrane or lining of uterus, and subsequently embeds in it. The preimplantation period of embryonic development is the time between fertilization and the beginning of implantation, a period of approximately 6 days.

Gastrula (Gr. *gaster*, stomach). During gastrulation (transformation of a blastocyst into a gastrula), a three-layered or trilaminar embryonic disc forms (third week). The three germ layers of the gastrula (ectoderm, mesoderm, and endoderm) subsequently differentiate into the tissues and organs of the embryo.

Neurula (Gr. *neuron*, nerve). The early embryo during the third and fourth weeks when the neural tube is developing from the neural plate (see Fig. 1-1). It is the first appearance of the nervous system and the next stage after the gastrula.

Embryo (Gr. *embryon*). The developing human during its early stages of development. The *embryonic period* extends to the end of the eighth week (56 days), by which time the beginnings of all major structures are present. The size of embryos is given as crown-rump length, which is measured from the vertex of the cranium (crown of head) to the rump (buttocks).

Stages of Prenatal Development. Early embryonic development is described in stages because of the variable period it takes for embryos to develop certain morphologic characteristics (see Fig. 1-1). *Stage 1* begins at fertilization and embryonic development ends at stage 23, which occurs on day 56. The *fetal period* begins on day 57 and ends when the fetus is completely outside the mother.

Conceptus (L. *conceptio*, derivatives of zygote). The embryo and its adnexa (L., appendages or adjunct parts) or associated membranes (i.e., the *products of conception*). The conceptus includes all structures that develop from the zygote, both embryonic and extraembryonic. Hence, it includes the embryo as well as the embryonic part of the placenta and its associated membranes: amnion, chorionic (gestational) sac, and umbilical vesicle or yolk sac (see Chapter 7).

Primordium (L. *primus*, first + *ordior*, to begin). The beginning or first discernible indication of an organ or structure. The terms *anlage* and rudiment have similar meanings. The primordium of the upper limb appears as a bud on day 26 (see Fig. 1-1).

Fetus (L., unborn offspring). After the embryonic period (8 weeks) and until birth, the developing human is called a fetus. During the *fetal period* (ninth week to birth), differentiation and growth of the tissues and organs formed during the embryonic period occur. These developmental changes are not dramatic.

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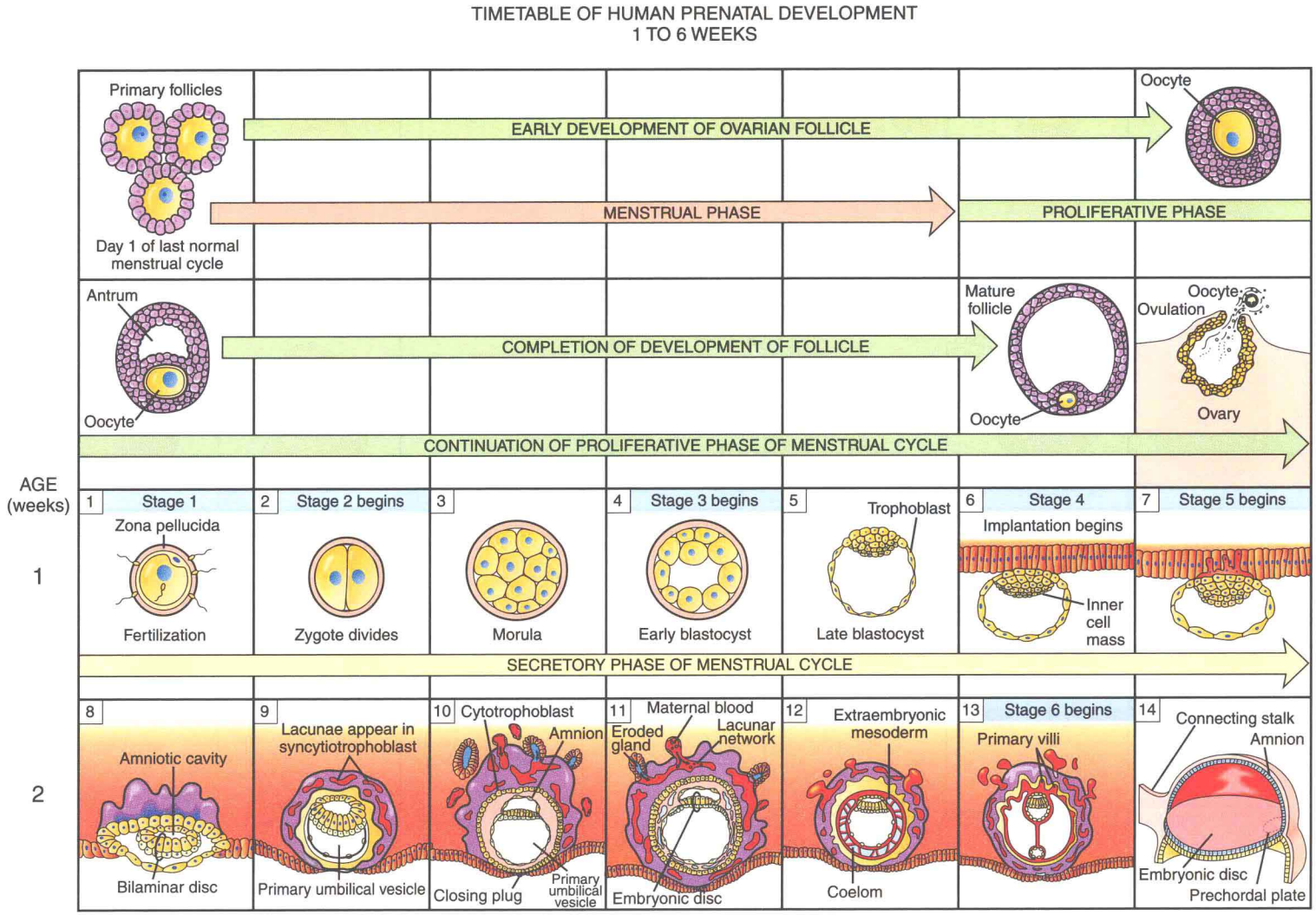
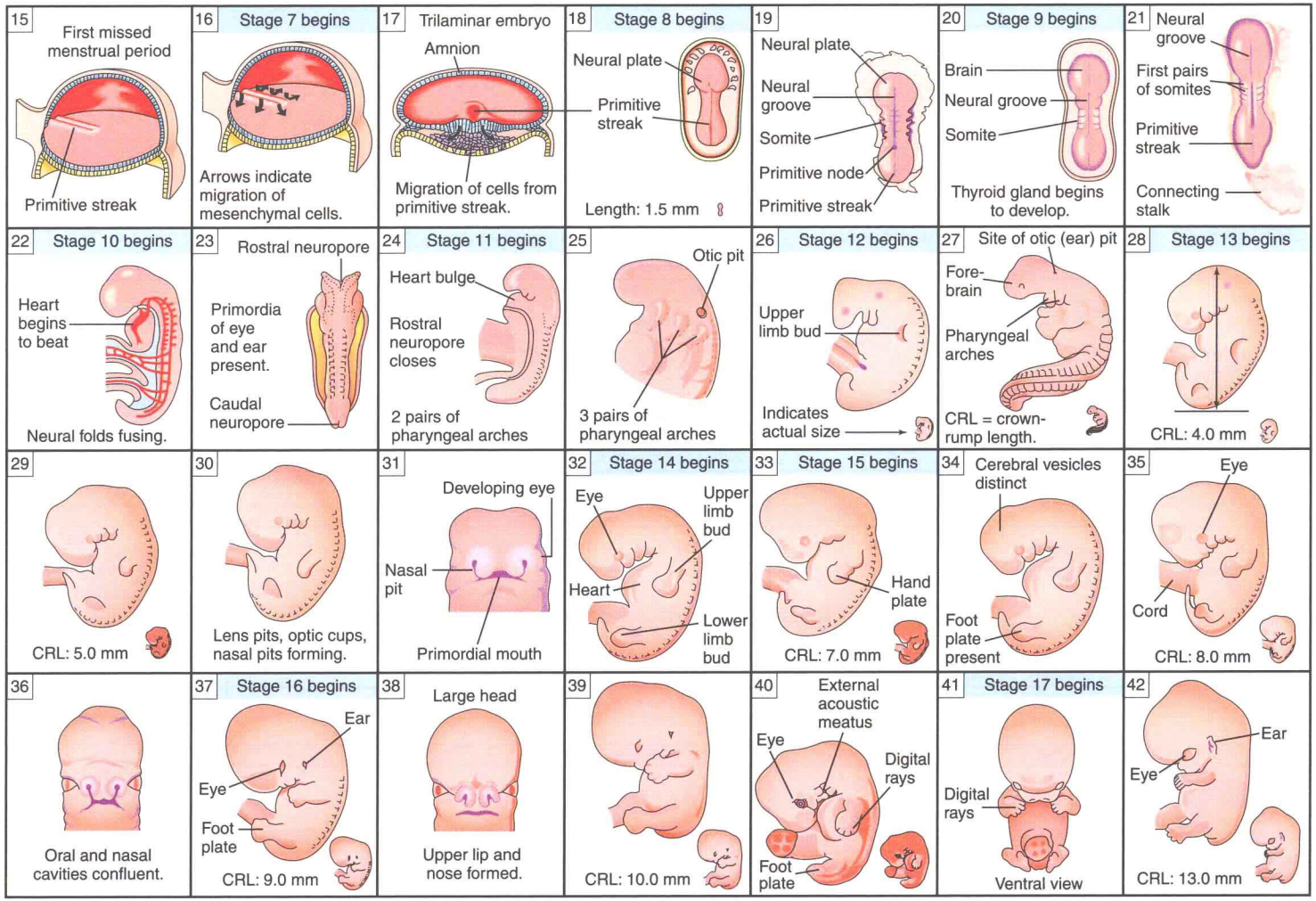


FIGURE 1-1. Early stages of development. Development of an ovarian follicle containing an oocyte, ovulation, and the phases of the menstrual cycle are illustrated. Human development begins at fertilization, approximately 14 days after the onset of the last normal menstrual period. Cleavage of the zygote in the uterine tube, implantation of the blastocyst in the endometrium (lining) of the uterus, and early development of the embryo are also shown. Beginning students should not attempt to memorize these tables or the stages (e.g., that stage 3 begins on day 4 and stage 5 on day 7). *Continued*



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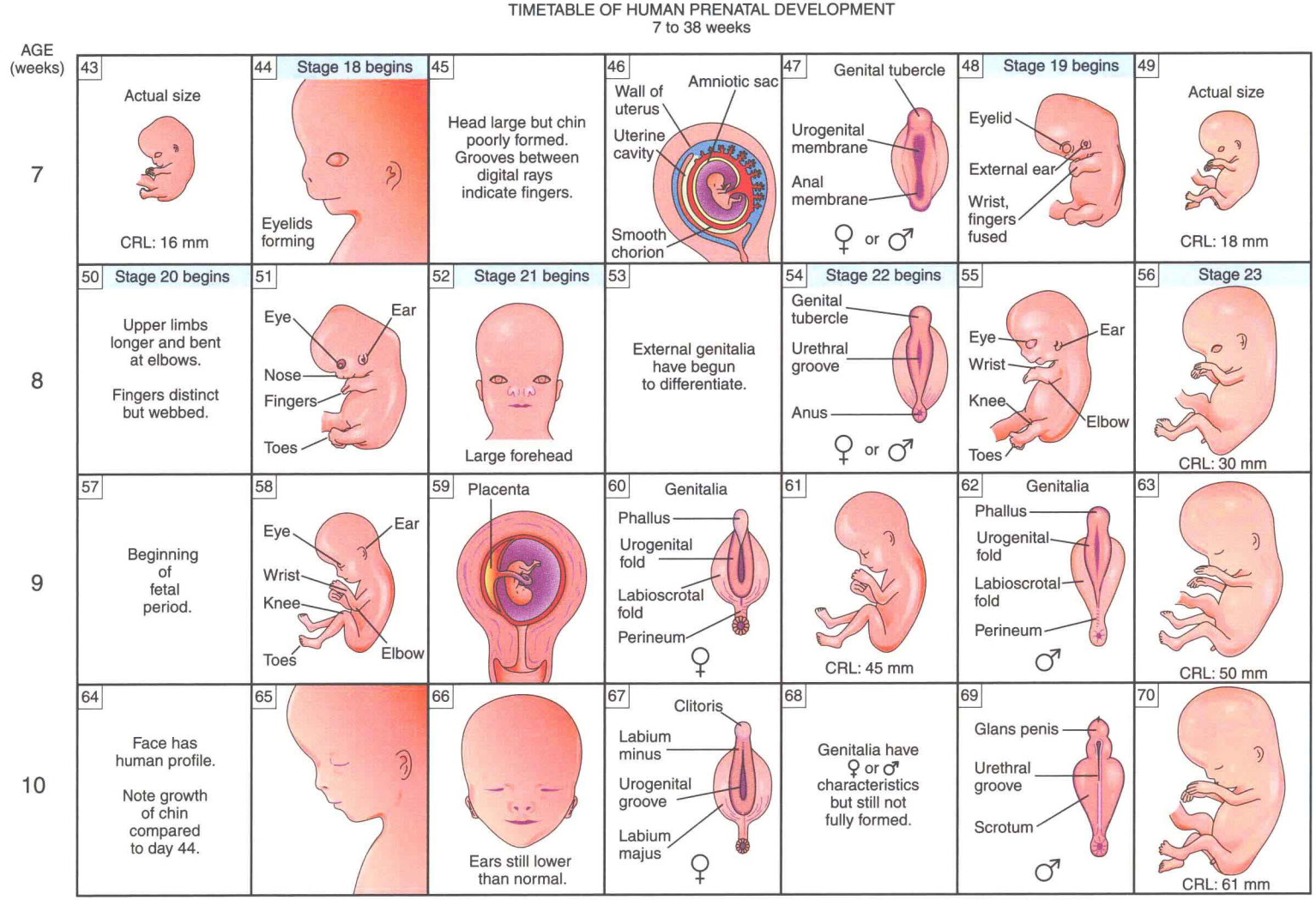

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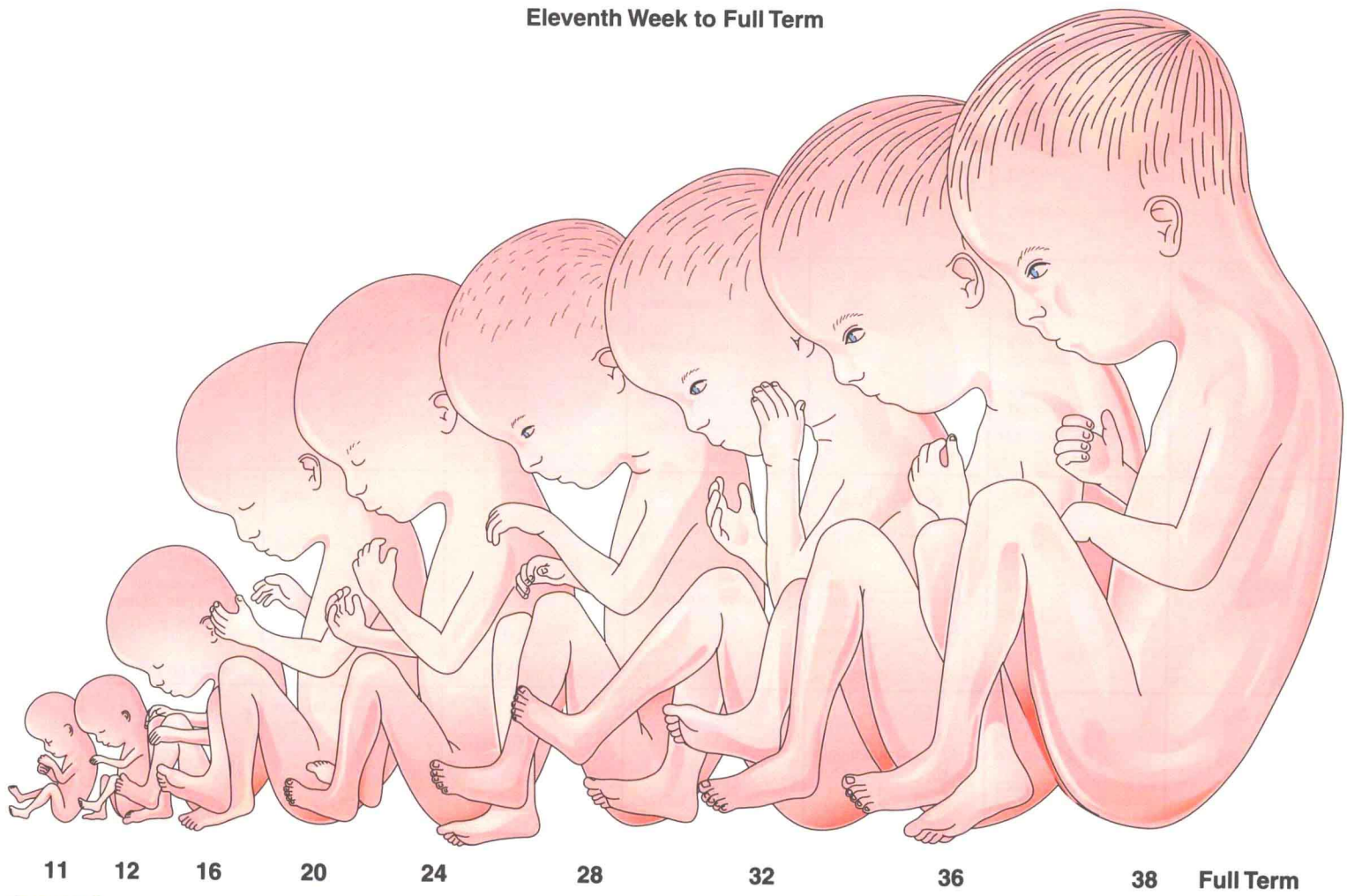

FIGURE 1-2. The embryonic period terminates at the end of the eighth week; by this time, the beginnings (primordia) of all essential structures are present. The fetal period, extending from 9 weeks to birth, is characterized by growth and elaboration of structures. Sex is clearly distinguishable by 12 weeks. Fetuses are viable 22 weeks after fertilization, but their chances of survival are not good until they are several weeks older. The 11- to 38-week fetuses shown are approximately half of their actual sizes. For more information, see Chapter 6.