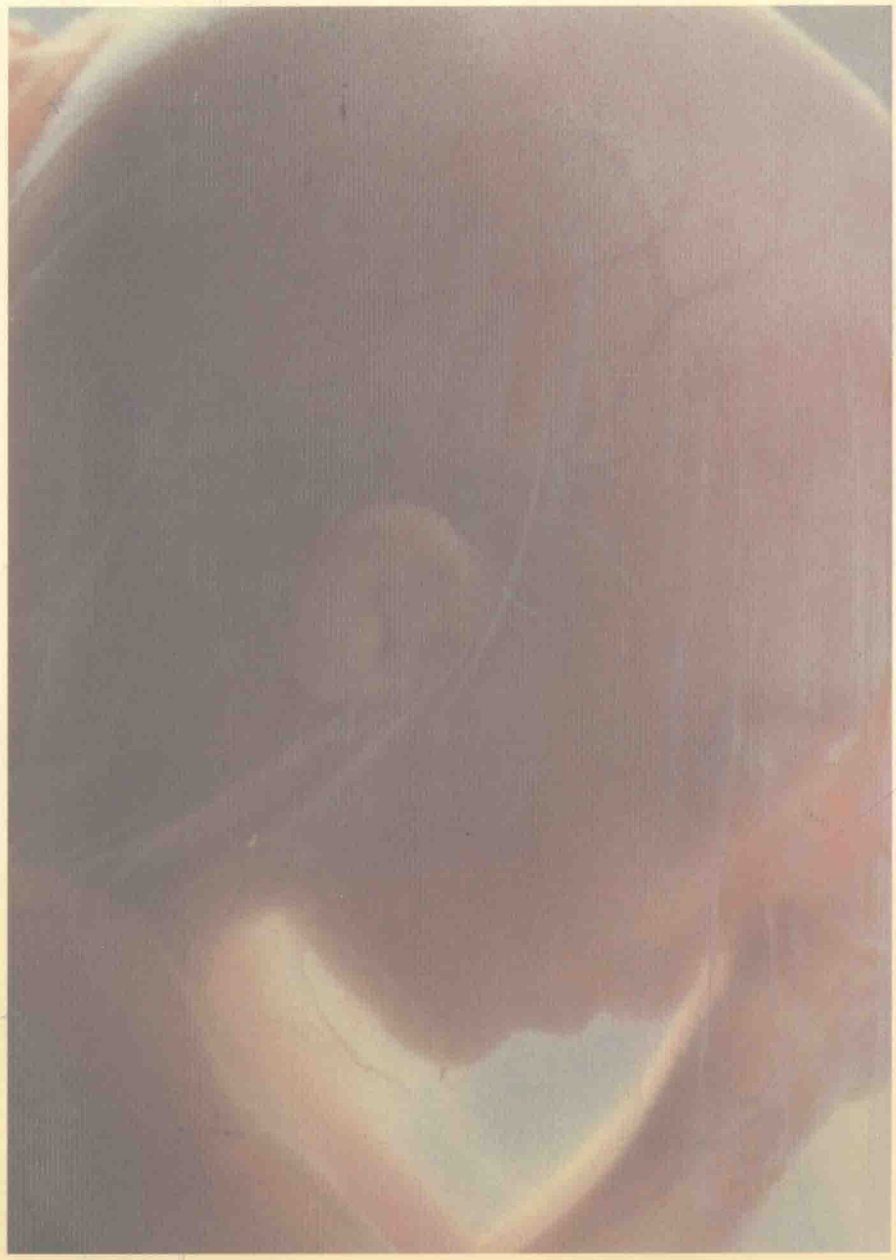
HUMAN EMBRYOLOGY



WILLIAM J. LARSEN

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WILLIAM J. LARSEN, Ph.D.

Professor, Department of Anatomy and Cell Biology
Faculty Member, Developmental Biology Graduate Program
University of Cincinnati College of Medicine
Research Faculty, Perinatal Research Institute
Children's Hospital and
University of Cincinnati College of Medicine
Cincinnati, Ohio

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Preface

A torrent of new findings and techniques has revolutionized embryology. As a result, this discipline is relevant not only to understanding adult structure but also, increasingly, to a physician's direct practice. I have written *Human Embryology* to meet the needs of first-year medical students in gross anatomy and neuroanatomy courses and to offer them a glimpse of some of the exciting applications that are currently in use or on the horizon. This text is used at the University of Cincinnati in conjunction with the 12 embryology lectures given in the gross anatomy course. It will also interest other readers, including premedical undergraduates, graduate students in developmental biology programs, nursing students, and allied health students in disciplines such as the burgeoning field of genetic counseling.

I researched this book intensively in an attempt to make it wholly up-to-date. In the course of that process, I learned a great deal that has renewed my own fascination with embryology, including the truth behind a number of venerable chestnuts that have been passed down in generations of embryology texts. It is my hope that the students who read this text will be as enthralled by modern embryology as I am.

This text uses a modular design that allows students to review the material in several ways and that will let instructors tailor the book to their specific needs. The first six chapters describe gametogenesis, fertilization, and the initial weeks of development; Chapters 7 through 14 deal with the individual organ systems; and the last chapter covers aspects of fetal development. Each chapter opens with a summary that gives a condensed version of the material in the chapter. In accordance with a frequent demand of my students, these summaries are supplemented by full-page timeline illustrations that graphically display the timing of the events described. The main portion of each chapter is devoted to a concise descriptive embryology of its subject. Other topics, such as theoretical discussions and descriptions of congenital anomalies, are segregated in special Clinical Applications and Experimental Principles sections where they will not clutter the essential story. I have worked hard to make the descriptions of morphogenetic processes complete as well as concise, because I know from experience that gaps in the explanation make these processes difficult to visualize and, hence, to remember. The text headings are written in sentence style so as to encapsulate the main points of the chapter.

Good, three-dimensional illustrations are obviously central to an embryology text. Once a chapter has been mastered, the reader ought to be able to review it by thumbing through the pictures and skimming the captions. Within the limits of space and expense, I have tried to illustrate enough critical stages of each process to obviate "leaps of faith." In the interests of clarity, I have converted all length, somite number, and stage designations to approximate gestation time in days and weeks. However, a complete table relating Carnegie stages, embryo length in millimeters, and numbers of somites is provided on pages xv through xvii. Structures are usually shown in their real context in the embryo, rather than left to float on the page, and color is used abundantly to indicate the derivation of structures and tissues. Where possible, I have included scanning electron micrographs to show how the structures in question actually look.

Although the Clinical Applications and Experimental Principles sections relate to the descriptive text, they are free-standing and can be assigned or omitted

at will. Topics such as multifactorial inheritance, sensitive periods, teratogenicity, and prenatal diagnosis, as well as a selection of congenital abnormalities, are covered in the Clinical Applications sections. These sections will sharpen the interest of first-year students by showing the relation of embryology to clinical practice. Some of them will also prove useful in later training. A student studying Hirschsprung's disease in a second-year pathology course, for example, can refer to the section on the pathogenesis of the underlying parasympathetic anomaly, and a student on a third-year clinical rotation can review the common cardiac anomalies.

Even a cursory reading of the short Experimental Principles sections will show how the information in the descriptive embryology sections was obtained and will give a glimpse of the frontiers of diagnosis, therapy, and research. Some of these sections are not essential to a first-year student, but others are of fundamental utility, such as the discussion of induction in Chapter 4 and the section on the pathogenetic bases of cardiac anomalies in Chapter 7. These sections may also be used to support the multidisciplinary approaches currently employed in some schools.

The past decade has witnessed a revolution in the diagnosis and treatment of congenital diseases. Many diseases can be identified in utero, and fetal operations may soon be routine. However, the revolution is only beginning: The studies now being carried out on novel molecular techniques, such as gene therapy, are thrusting us abruptly into a new age of prenatal medicine. Techniques to cure such diseases as congenital immuno-deficiency syndromes and cystic fibrosis are being tested in animal models, for example. Because of this prospect of therapeutic payoff, the molecular basis of development has become a highly funded topic in medical research. Here in the United States, the number of grant applications submitted to the Molecular Genetics section of the National Institute of Child Health and Human Development is increasing at an unprecedented rate. It will not be possible to develop appropriate applications for these new molecular techniques, however, without input from classical experimental and descriptive embryologic research. That task of integration and application—as well as the daunting social and ethical challenges that the new prenatal and genetic techniques will bring in their train—will fall largely to the students who are now studying medicine, nursing, developmental and molecular biology, and genetic counseling.

William J. Larsen, Ph.D.

Now the Mother Earth
And the Father Sky
Meeting, joining one another,
Helpmates ever, they

All is beautiful
All is beautiful
All is beautiful, indeed.

And the white corn
And the yellow corn
Meeting, joining one another
Helpmates ever, they

All is beautiful
All is beautiful
All is beautiful, indeed.

(From *Song of the Earth* [Navajo], George W. Cronin (ed): Songs of the Southwest. In: American Indian Poetry: An Anthology of Songs and Chants. Liveright, New York, 1934, with permission.)

Acknowledgments

This project has reinforced my faith in the generosity and commitment to education of my colleagues around the world. Innumerable people have contributed illustrations, criticism, discussion, and encouragement during the exhausting process of research and writing. Dr. Arthur Tamarin granted me complete access to his lifetime's worth of scanning images of primate embryos, many of which are used in this book. I am particularly grateful for his support throughout this project. Dr. Karen Holbrook graciously assembled numerous photos for the chapter on development of the integument, and Dr. Kathryn Tosney provided several illustrations of somites and neural tube development. Drs. Thomas Poole, Douglas Coffin, Gary Schoenwolf, Gillian Morriss-Kay, Antone Jacobson, Douglas Melton, J.M. Icardo, J.M. Hurle, M.H. Kaufman, Barry Bavister, Dorothy Boatman, Mary Hendrix, Vincent Gattone II, Robert Kelley, and Dennis Morse all made major contributions. I am also grateful to Dr. David Phillips, who provided several micrographs, and to Dr. Greg Fedele, who devised the concept and many of the initial sketches for the illustrations in Chapters 2 and 3.

I have many individuals to thank for their critical contributions to the text, including the body of reviewers who read original drafts of various chapters. I want to thank Emma Lou Cardell especially, whose editorial talents improved the writing of every chapter in this book. Dr. Peter Stambrook made many suggestions, provided references, and edited several of the experimental sections. Dr. Thomas Doetschman gave me guidance on the sections dealing with transgenic animal studies. I thank Dr. Antone Jacobson for his discussions and advice regarding development of the head and neck. Dr. Douglas Melton gave me advice on the sections on induction, Drs. Jim Hall and Sarah Pixley reviewed chapters on the nervous system, and Dr. Bob Brackenbury critiqued the discussion of axonal pathfinding in Chapter 13. I am also grateful to Dr. Tomas Pexieder for extensive discussion and review of the chapter on the heart; to Dr. David Schwartz for helpful discussion regarding the clinical section in Chapter 8; to Drs. Robert Kelly, K.V. Hinrichsen, and William Scott for critiqueing the chapter on limb development; and to Drs. C. Willhite, Ernest Zimmerman, and Dahlila Irving for reviewing the section on craniofacial abnormalities. Dr. Tariq Siddiqui kindly read and edited Chapter 15 and many of the clinical discussions.

I have been very fortunate in coming to know Dr. Peter Dignan, Director of Human Genetics at Children's Hospital in Cincinnati. Dr. Dignan gave me frequent advice and criticism and is the major source for the clinical photographs used in this book. I am very thankful for the opportunity to know Dr. Dignan as a friend and colleague. I must also thank Dr. Shirley Soukup, Dr. James McAdams, Dr. Janet Streif, and Dr. David Billmire for their guidance and for providing clinical illustrations.

The text owes much to the dedication and skill of Mr. William Lindesmith and Ms. Vicki Killion of the University of Cincinnati Health Sciences Library, who conducted literature searches and provided copies of countless publications. Their raillery made some things that could have been unpleasant, unexpectedly pleasant.

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I am grateful to Churchill Livingstone for its support and sincerely thank its staff, especially my development editor, Ms. Margot Otway, for her guidance and editing, her mastery of command and control under occasionally formidable circumstances, her patience, and her exquisite good humor. I am also very thankful for the thoughtful advice and counsel of my editor, Mr. William Schmitt.

Correlation of Timing Systems Used For Human Embryos (Weeks 1 Through 8)

Week	Day	Length (mm)[a]	Number of Somites	Carnegie stage	Features *(chapters in which features are discussed)*[b]
1	1	0.1–0.15	—	1	Fertilization *(1)*
	1.5–3	0.1–0.2	—	2	First cleavage divisions occur (2–16 cells) *(1)*
	4	0.1–0.2	—	3	Blastocyst is free in uterus *(1)*
	5–6	0.1–0.2	—	4	Blastocyst hatches and begins implanting *(1, 2)*
2	7–12	0.1–0.2	—	5	Blastocyst fully implanted *(1, 2)*
	13	0.2	—	6	Primary stem villi appear *(2)*; primitive streak develops *(3)*
3	16	0.4	—	7	Gastrulation commences; notochordal process forms *(3)*
	18	1–1.5	—	8	Primitive pit forms *(3)*; neural plate and neural folds appear *(3, 4)*; vasculature begins to develop in embryonic disc *(8)*
	20	1.5–2.5	1–3	9	Caudal eminence and first somites form *(3)*; neuromeres appear in presumptive brain vesicles *(4, 13)*; primitive heart tube is forming *(7)*
4	22	2–3.5	4–12	10	Neural folds begin to fuse; cranial end of embryo undergoes rapid flexion *(4, 13)*; respiratory diverticulum appears *(6)*; myocardium forms and heart begins to pump *(7)*; hepatic plate appears *(9)*; first two pharyngeal arches and optic sulci form *(12)*
	24	2.5–4.5	13–20	11	Primordial germ cells begin to migrate from wall of yolk sac *(1)*; cranial neuropore closes *(4)*; buccopharyngeal membrane ruptures *(12)*; optic vesicles develop *(12)*
	26	3–5	21–29	12	Caudal neuropore closes *(4)*; cystic diverticulum and dorsal pancreatic bud appear *(9)*; urorectal septum begins to form*(9, 10)*; upper limb buds appear *(11)*; pharyngeal arches 3 and 4 form *(12)*

[a]Length is the greatest length of embryo.
[b]Timing of some events will differ slightly in some embryos.

Week	Day	Length (mm)[a]	Number of Somites	Carnegie stage	Features (*chapters in which features are discussed*)[b]
4	28	4–6	30+	13	Dorsal and ventral columns begin to differentiate in mantle layer of spinal cord and brain stem *(4, 13)*; septum primum and muscular ventricular septum begin to form in heart *(7)*; spleen appears *(9)*; ureteric buds appear *(10)*; lower limb buds appear *(11)*; otic vesicle and lens placode appear *(12)*; motor nuclei of cranial nerves appear *(13)*
5	32	5–7	—	14	Spinal nerves begin to sprout *(5)*; semilunar valves begin to form in heart *(7)*; lymphatics and coronary vessels appear *(8)*; greater and lesser stomach curvatures and primary intestinal loop form *(9)*; metanephros begins to develop *(10)*; lens pit invaginates into optic cup; endolymphatic duct appears *(12)*; secondary brain vesicles begin to form; cerebral hemispheres become visible *(13)*
	33	7–9	—	15	Atrioventricular valves and definitive pericardial cavity begin to form *(7)*; cloacal folds and genital tubercle appear *(10)*; hand plate develops *(11)*; lens vesicle forms and invagination of nasal pit creates medial and lateral nasal processes *(12)*; cranial nerve motor nuclei appear in ventral column of brain stem; sensory and para-sympathetic cranial nerve ganglia begin to form; primary olfactory neurons send axons into telencephalon *(13)*
6	37	8–11	—	16	Gut tube lumen becomes occluded *(9)*; major calyces of kidney begin to form and kidneys begin to ascend; genital ridges appear *(10)*; foot plate forms on lower limb bud *(11)*; pigment appears in retina; auricular hillocks develop *(12)*

[a]Length is the greatest length of embryo.
[b]Timing of some events will differ slightly in some embryos.

Week	Day	Length (mm)[a]	Number of Somites	Carnegie stage	Features (*chapters in which features are discussed*)[b]
6	41	11–14	—	17	Bronchopulmonary segment primordia appear *(6)*; septum intermedium of heart is complete *(7)*; subcardinal vein system forms *(8)*; finger rays are distinct *(11)*; nasolacrimal groove forms *(12)*; cerebellum begins to form *(13)*; melanocytes enter epidermis; dental laminae form *(14)*
7	44	13–17	—	18	Skeletal ossification begins *(4, 11)*; Sertoli cells begin to differentiate in the male gonad *(10)*; elbows and toe rays appear *(11)*; intermaxillary process and eyelids form in face *(12)*; thalami of diencephalon expand *(13)*; nipples and first hair follicles appear *(14)*
	47	16–18	—	19	Pericardioperitoneal canals close *(6)*; septum primum fuses with septum intermedium in heart *(7)*; minor calyces of kidney are forming; urogenital membrane ruptures *(10)*; trunk elongates and straightens *(15)*
8	50	18–22	—	20	Primary intestinal loop completes initial counterclockwise rotation *(9)*; in males, paramesonephric ducts begin to regress and vasa deferentia begin to form *(10)*; upper limbs bend at elbows *(11)*
	52	22–24	—	21	Hands and feet approach each other at the midline *(11)*
	54	23–28	—	22	Eyelids and auricles are more developed *(12)*
	56	27–31	—	23	Chorionic cavity is obliterated by the growth of the amniotic sac *(6)*; definitive superior vena cava and major branches of the aortic arch are established *(8)*; gut tube lumen is almost completely recanalized *(9)*; primary teeth are at cap stage *(14)*

[a]Length is the greatest length of embryo.

[b]Timing of some events will differ slightly in some embryos.

(Columns 1 through 5 from O'Rahilly R, Müller F. 1987. Developmental Stages in Human Embryos. Carnegie Institute Wash. Publ. No. 637, with permission.)

Contents

CHAPTER

1

Gametogenesis, Fertilization, and the First Week

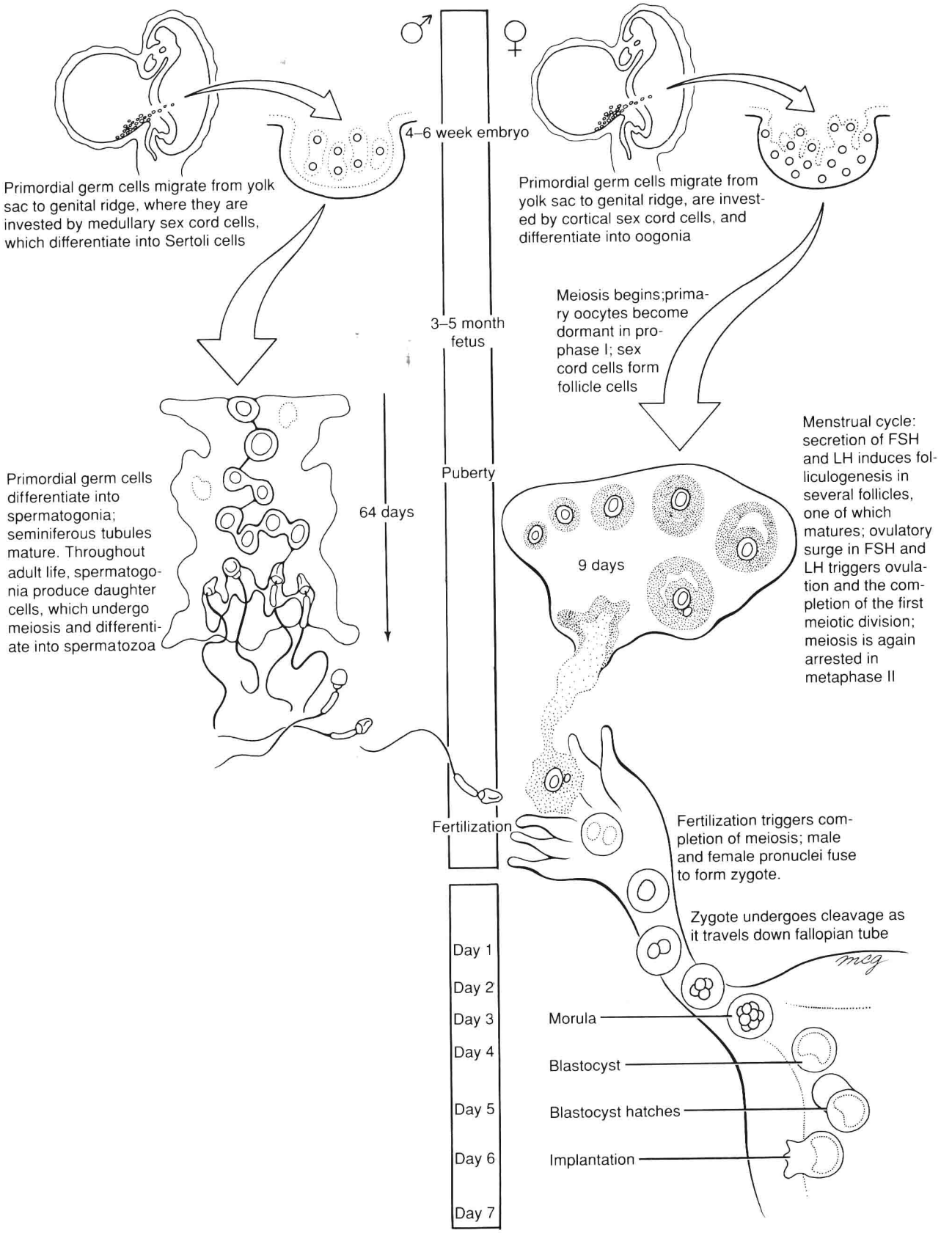
Origin of the Germ Line; Meiosis; Gametogenesis in the Male and Female; the Menstrual Cycle; Fertilization; Cleavage

SUMMARY

The discussion of human embryology could be initiated at any of several points in the human reproductive cycle. In this text, we begin our description of the developing human with the formation and differentiation of the male and female sex cells or **gametes,** which will unite at fertilization to initiate the embryonic development of a new individual. The cell line that leads to the gametes, called the **germ line,** first becomes distinct during the fourth week of embryonic development, as cells called **primordial germ cells** differentiate within the wall of the yolk sac. These cells actively migrate to the posterior body wall of the embryo, where they populate the developing gonads and differentiate into the gamete precursor cells called **spermatogonia** in the male and **oogonia** in the female. Like the normal somatic cells of the body, the spermatogonia and oogonia are **diploid,** that is, they contain a complement of 23 pairs of chromosomes (a total of 46 chromosomes). When these cells produce gametes by the process of **gametogenesis** (called **spermatogenesis** in the male and **oogenesis** in the female), they undergo **meiosis,** a sequence of two specialized cell divisions by which the number of chromosomes in the gametes is halved. The gametes thus contain 23 chromosomes (one of each pair) and are said to be **haploid.** The developing gametes also undergo cytoplasmic modifications, resulting in the production of mature **spermatozoa** in the male and **definitive oocytes** in the female.

In the male, formation of spermatogonia and spermatogenesis take place in the seminiferous tubules of the testes and do not occur until puberty. In the female, in contrast, all the primary oocytes that the individual will ever possess are produced during fetal life. Between the third and fifth months of fetal life, the oogonia commence the first meiotic division. Shortly after beginning meiosis, however, these cells enter a state of dormancy and meiotic arrest which will persist until after puberty. After puberty, a few oocytes and their enclosing follicles resume development each month in response to the monthly production of pituitary gonadotropic hormones. Only one of these follicles matures fully and undergoes **ovulation** to release the enclosed oocyte, and the oocyte itself completes meiosis (thus becoming a mature gamete) only if it is fertilized by a spermatozoon. Fertilization takes place in the oviduct. After the oocyte finishes meiosis, the nuclei of the male and female gametes unite, resulting in the formation of a **zygote** containing a single diploid nucleus. Embryonic development is considered to begin at this point.

The newly formed embryo undergoes a series of cell divisions called **cleavage** as it travels down the oviduct toward the uterus. The cleavage divisions subdivide the



Timeline. Gametogenesis and the first week of development.

zygote first into two cells, then into four, then into eight, and so on. These daughter cells do not grow between divisions, so the entire embryo remains the same size. Starting at the 8- to 16-cell stage, the cleaving embryo differentiates into two groups of cells: a peripheral **outer cell mass** and a central **inner cell mass.** The outer cell mass, also called the **trophoblast,** is the main source of the placenta and associated membranes, whereas the inner cell mass, also called the **embryoblast,** gives rise to the embryo proper and its attached membranes. By the 30-cell stage, the embryo, now called a **morula,** begins to form a fluid-filled central cavity, the **blastocyst cavity.** By the fifth to sixth day of development, the embryo is a hollow ball of about 100 cells called a **blastocyst.** At this point it enters the uterine cavity and begins to implant into the endometrial lining of the uterine wall.

The germ cells arise outside the embryo proper

The primordial germ cells originate on the yolk sac and migrate to the posterior body wall

In humans, the cell line that gives rise to the gametes can first be distinguished at 4 weeks as a scattered population of ovoid, poorly differentiated cells in the endoderm of the yolk sac wall (Fig. 1-1A). These cells are called the **primordial germ cells,** and their lineage constitutes the **germ line.** The origin and migration of the germ cells are easily investigated in a number of mammals because the plasma membranes of these cells stain intensely with reagents that localize the enzyme alkaline phosphatase.

Between 4 and 6 weeks, the primordial germ cells migrate by ameboid movement from the yolk sac to the wall of the gut tube and from the gut tube via the mesentery to the dorsal body wall (Fig. 1-1B). In the

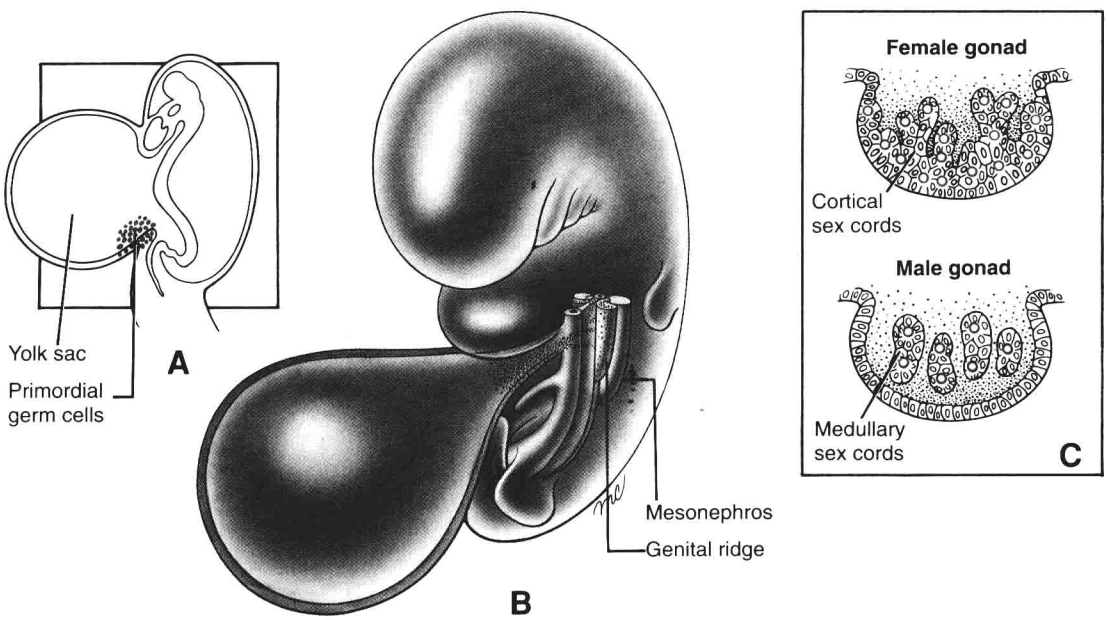


Fig. 1-1. (A) The primordial germ cells differentiate in the endodermal layer of the yolk sac at 4 to 6 weeks of development and migrate to the dorsal body wall. **(B)** Between 6 and 12 weeks, the primordial germ cells induce formation of the genital ridges. **(C)** Sex cord cells differentiate and invest the primordial germ cells. In females, the sex cords of the cortical region survive and become the ovarian follicle cells; in males the medullary sex cords survive and become the Sertoli cells of the seminiferous tubules.