Comparative Features of Vertebrate Embryology

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A Practical Approach

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Ronald D. Hood

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CHAPTER 6

Comparative Features of Vertebrate Embryology

John M. DeSesso

CONTENTS

I. INTRODUCTION

Multicellular animals have limited life spans. Consequently, for a species to survive, a mechanism must exist for the successive production of new generations. The solution to this problem lies in the process of reproduction. This process typically involves the presence of two sexes, the production by each sex of specialized cells called gametes, and a complicated series of events resulting in the joining of two gametes to form a new individual. Gametes are referred to as haploid cells because they contain one-half the number of chromosomes found in somatic cells of the particular species. Male gametes (spermatozoa) are generated in the testes and are small, motile cells, millions of which are produced daily. In contrast, female gametes (ova) are large, nonmotile cells that develop in the ovaries. Relatively few ova are produced, and only a few hundred mature during the reproductive lifetime of female mammals.

Fertilization is the union of a single spermatozoon and an ovum. It occurs in the female reproductive tracts of birds and mammals and produces a new single celled organism, the zygote. Fertilization restores the diploid number of chromosomes, so that the zygote has the same amount of genetic material as did the somatic cells of its parents. Fertilization in mammals and birds also determines the sex of the zygote and initiates the process of cleavage. Cleavage is a rapid series of mitotic divisions that allows the relatively large amount of cytoplasm contributed by the ovum to be divided into progressively smaller cells.

In mammals, fertilization occurs in the uterine tube (oviduct). Cleavage divisions occur as the zygote progresses to the uterus, where it will become attached to the maternal uterine wall. During this time, the zygote is surrounded by the zona pellucida, an acellular mucopolysaccharide layer that prevents the zygote from implanting prematurely. When the zygote reaches the uterus, it is a

Table 6.1 Gestational milestones for mammals

	Gestational Milestone[a]				
	A[b]	B	C	D	E
Species	Implantation	Primitive Streak	Early Differentiation	Partial Closure[c]	Usual Parturition
Rat	5–6	8.5	10	15	21–22
Mouse	5	6.5	9	15	19–20
Rabbit	7.5	7.25	9	18	30–32
Hamster	4.5–5	7	8	13	16
Guinea pig	6	12	14.5	~29	67–68
Monkey	9	17	21	~44–45	166
Human	6–7	13	21	~50–56	266

[a] In gestational days; day of confirmed mating is gestational day 0.
[b] Letters refer to positions on Figure 6.4 (conceptual roadmap of embryonic development).
[c] Marks the end of major organogenesis for most organ systems.

cluster of small cells surrounded by the zona pellucida; this cluster is called a *morula*. Subsequently, the zona pellucida thins, ruptures, and eventually disappears, while the morula cavitates to become a sphere of cells surrounding a fluid-filled cavity. At this stage, the zygote is termed a *blastocyst*.

In most mammals that are used in experimental studies, the blastocyst arises between days 5 and 8 of gestation and attaches to the uterine wall during this time (Table 6.1). Two populations of cells are recognized in a blastocyst. They include the outer sphere of cells, called the *trophoblast* that gives rise to the placenta and fetal membranes, and a small cluster of cells on the inside, the *inner cell mass* that gives rise to the embryo proper.

II. COMPARATIVE PLACENTAL CHARACTERISTICS

One of the earliest tasks of the blastocyst is the establishment of a mechanism for maintenance of nutrient supply and disposal of metabolic wastes. This is accomplished through the development of a placenta from the trophoblast. The placenta and fetal (extraembryonic) membranes are temporary organs that form early in development and exist for a brief period compared to the life span of the organism. Because of their importance to embryonic development, however, they will be described in some detail before we return to further discussion of the embryo proper.

The extraembryonic membranes provide nutrition, respiration, metabolic waste elimination, and protection to the embryo and fetus, in addition to assisting in the establishment of embryonic vascularity. The four fetal membranes of vertebrates are the amnion, chorion, allantois, and yolk sac. Not all vertebrate species exhibit all four membranes; for instance, animals that lay eggs in water (*anamniota*) do not possess an amnion.

A placenta is an organ composed of fetal and parental tissues that are intimately apposed for the purpose of physiological exchange.[1] The fetal tissues of the placenta include one or more of the extraembryonic membranes (e.g., yolk sac, allantois), whereas the parental tissue is usually part of the uterus. The types of placentas can be described by the fetal membranes that participate in the apposition of fetal to maternal tissues. In general, the definitive placentas of eutherian mammals are formed from the outermost membrane of the embryonic vesicle (the avascular chorion), which is augmented by, and receives vascularization from, the allantois. This type of placenta is a chorioallantoic placenta. Most marsupial species develop placentas from the chorion, which is vascularized by the yolk sac. This type of placenta is called a *choriovitelline* (or *yolk sac*) placenta. (See discussion of the rodent "inverted" yolk sac placenta below.)

The placenta and fetal membranes are tissues with diverse structures and functions. In addition, these tissues are dynamic and modify both their structures and functions during gestation. Consequently, when assessing the role of the placenta in developmental toxicity, one must be aware not

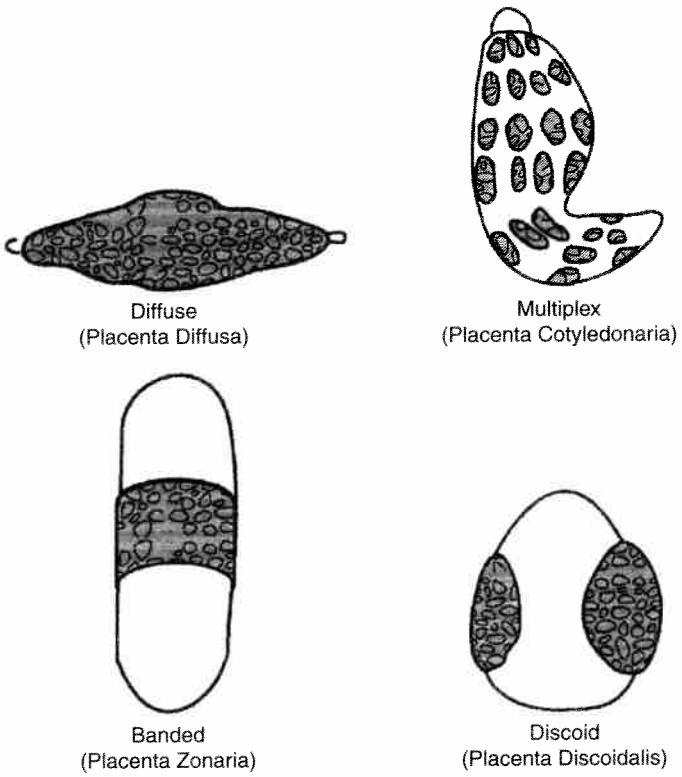

Figure 6.1 Types of placentas, classified by shape. The images depict the outer surface of the chorion, the fetal membrane that is apposed to the maternal reproductive tract. The white territories represent the smooth portions (chorion laeve); the gray regions represent the part of the chorion (chorion frondosum) that is modified to increase the surface area between embryo and mother. Note that banded placentas may exist as complete bands (illustrated) or as partial belts. Note also that discoid placentas may exist as single placentas, as in humans, or as paired structures, as in rhesus monkeys (illustrated).

only of interspecies differences in placental structure and function, but also of differences in the structure and function of the same placenta at different times in gestation.

Placentas are classified according to their gross appearance, their mode of implantation, their type of modification of the chorionic surface to increase surface area, and the intimacy of embryonic invasion into maternal tissues.[2,3] Because these differences can influence the efficiency or rate of transfer of materials between mother and embryo, they will be described briefly.

The outermost fetal membrane is the chorion. To the naked eye, it appears either as a smooth membrane (chorion laeve) or as a roughened or fuzzy membrane (chorion frondosum). The distribution of the villous areas of the chorion may take on one of four shapes (see Figure 6.1).

1. Diffuse (placenta diffusa): Villi are maintained over the entire chorion (e.g., pigs,* horses, humans [early in gestation], lemurs).
2. Multiplex (placenta cotyledonaria): Villi are grouped in discrete rosettes (cotyledons) that are separated by regions of smooth chorion (e.g., cattle, sheep, deer, ruminants).
3. Banded (placenta zonaria): Villi assume a girdle-like configuration around the middle of the chorionic sac (e.g., carnivores — dogs, cats [complete band], bears [less than half]).
4. Discoid (placenta discoidalis): Villi are grouped into one or two disk-shaped regions (e.g., insectivores, bats, rodents, nonhuman primates, definitive human placenta).

* Villi in the pig are actually plicate elevations.

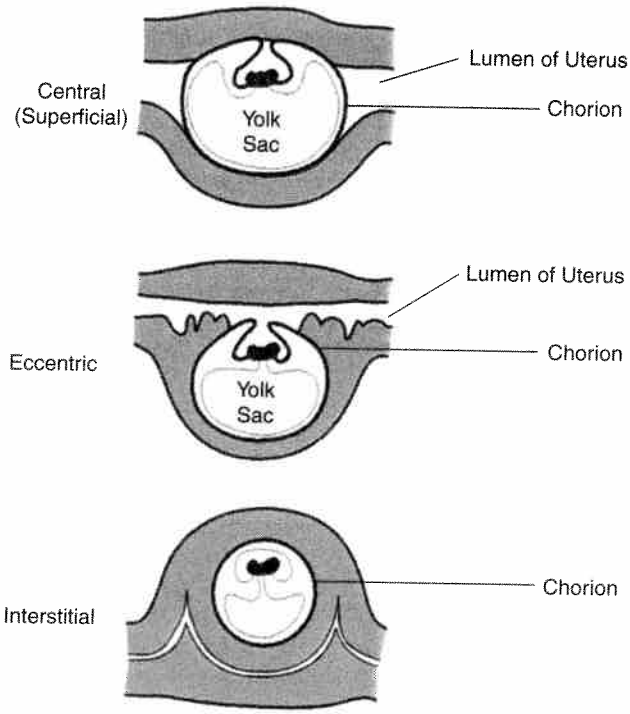

Figure 6.2 Types of placentas, classified by mode of implantation. The depth of implantation into the uterine wall increases from central, in which the conceptus essentially lies in the uterine lumen, to interstitial, in which the conceptus resides completely within the uterine wall and the uterine lumen is obliterated.

The relationship of the chorionic sac to the uterine wall and lumen can be described in terms of the extent or the depth of embryonic implantation into the uterine wall, and three general types of implantation can be distinguished[4] (see Figure 6.2).

1. Central (superficial): The chorionic sac remains in contact with the main uterine lumen (e.g., ungulates, carnivores, monkeys).
2. Eccentric: The chorionic sac lies in a pocket or fold that is partially separated from the uterine lumen (e.g., rodents — early in gestation).
3. Interstitial: The chorionic sac penetrates the uterine mucosa and loses contact with the uterine lumen (e.g., guinea pigs, human beings, rodents — late in gestation).

In rodents, the uterine lining of a pregnant female assumes a characteristic topography while awaiting the arrival of the blastocysts. The uterine mucosa appears scalloped, with evenly spaced indentations (or implantation chambers) along the long axis of each uterine horn. One blastocyst will come to occupy each implantation chamber in such a manner as to make the relationship between the chorion and the uterine lining eccentric. With further development, the rodent embryo will completely embed itself into the uterine wall, making the relationship interstitial.

The modifications of the chorionic surface to increase the area of contact between the chorion frondosum of the embryo and the maternal reproductive tract also demonstrate species differences.[3,5]

Plicate: The surface of the chorion exhibits elevated ridges or folds (e.g., pigs).

Villous: The chorionic surface exhibits fingerlike projections of embryonic tissue that project into maternal blood. The maternal circulatory pattern is described as entering lacunae, or pools, in which the villi are bathed (e.g., primates).

Labyrinthine: The chorionic surface exhibits anastomosing cords or trabeculae of embryonic tissue through which maternal blood flows. The maternal circulatory pattern is described as labyrinthine (e.g., insectivores, rodents, bats).

Great species differences also exist with respect to the layers of embryonic and maternal tissues that are interposed between their respective circulations. The invasiveness of the trophoblast can be gauged by the amount of maternal tissue that is eroded.[2,3,6,7] The three most common placental types, as classified by extent of invasiveness, are described below (see Figure 6.3).

1. Epitheliochorial: The least invasive type of placenta. No maternal tissue is destroyed. The six layers separating the maternal bloodstream from the embryonic bloodstream are maternal capillary endothelium, maternal uterine connective tissue, uterine epithelium, trophoblast, embryonic connective tissue, and embryonic capillary endothelium (e.g., pigs, horses).
2. Endotheliochorial: The trophoblast invades the endometrium and connective tissue, allowing the trophoblast to approach the maternal capillaries. The four layers interposed between maternal and embryonic circulations are maternal capillary endothelium, trophoblast, embryonic connective tissue, and embryonic capillary endothelium (e.g., dogs, cats).
3. Hemochorial: The trophoblast eliminates all maternal tissue, allowing the trophoblast to come into direct contact with the maternal blood. The three layers that separate the maternal from the embryonic circulation are trophoblast, embryonic connective tissue, and embryonic capillary endothelium (e.g., lagomorphs, bats, rodents, primates).

The gestational periods of rodents and lagomorphs (rabbits and guinea pigs) are brief (16 to 68 days). Consequently, development in these species occurs rapidly. Because the definitive chorioallantoic placenta is not established until a competent embryonic circulatory system is operative (at about the 20 somite stage), these species develop an early placenta that uses the membranes of their rather large yolk sacs. This early placenta is frequently termed the "inverted" yolk sac placenta because portions of the outer yolk sac membranes attenuate and become discontinuous at the plane of apposition to the uterine wall, leaving the epithelium of the inner yolk sac membrane in virtual contact with the uterine lumen and epithelium. The inverted yolk sac placenta ferries nutritive substances to the embryo by a *histiotrophic* process that entails the pinocytosis by yolk sac epithelial cells of maternally derived macromolecules found in uterine secretions and the subsequent breakdown of those macromolecules within lysosomal vacuoles, followed by diffusion into the embryo. In contrast to the inverted yolk sac placenta, the chorioallantoic placenta accomplishes the exchange of nutrients, gases, and metabolic wastes between mother and embryo by means of a *hemotrophic* interchange of solutes between the respective circulations. Such a direct exchange can move materials between mother and embryo more efficiently and rapidly in the chorioallantoic placenta than can the multistep, lysosome-dependent process of the inverted yolk sac placenta.

While the importance of the rodent inverted yolk sac placenta is greatly diminished after the establishment of the chorioallantoic placenta, it does remain functional throughout gestation. For purposes of temporal comparison, the rat inverted yolk sac placenta develops about gestational day 6.5 to 7, whereas the rat chorioallantoic placenta is established at approximately gestational day 11 to 11.5. Inverted yolk sac placentas do not develop in humans or other primates. Table 6.2 summarizes the placental, uterine, and other gestational characteristics of humans and six commonly used experimental mammals.

Since the placenta is the interface between the embryo and the maternal environment, it is the site of absorption, transfer, and metabolism of nutrients and foreign compounds. In the not so distant past, the placenta was believed to be a barrier that prevented the movement of all unwanted xenobiotic (foreign) compounds into the embryo. The thalidomide tragedy of the late 1950s and early 1960s dispelled that idea. The placenta was reconceptualized as a sieve that retarded or eliminated the transfer of molecules that weighed greater than around 1000 Da or were highly charged, highly polar, or strongly bound to (serum) proteins. Currently, however, it is recognized

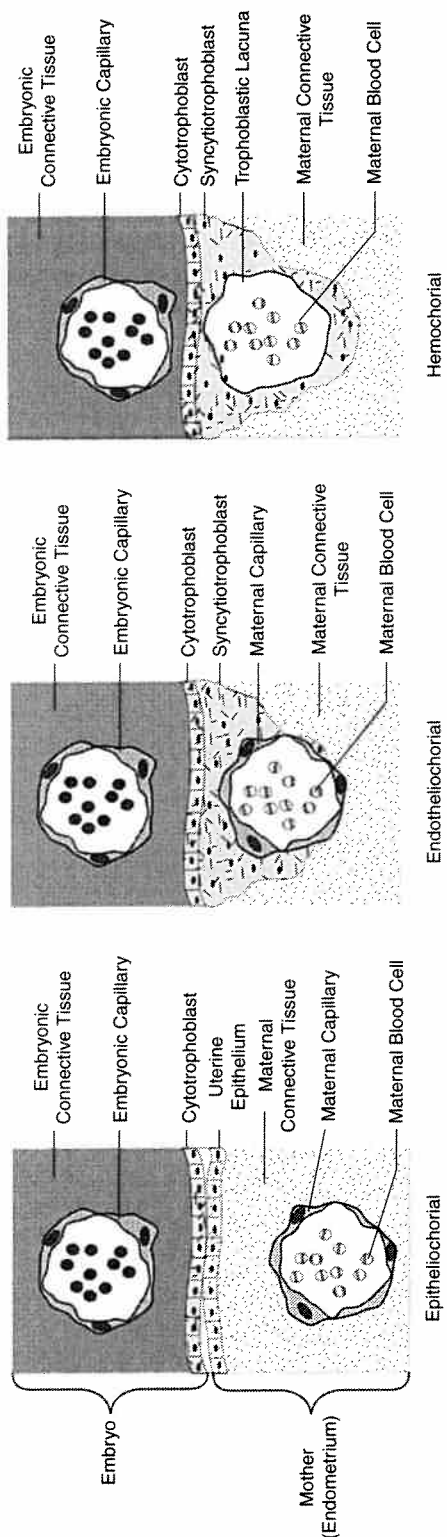

Figure 6.3 Types of placentas, classified by extent of invasiveness. The three most common placental types are depicted in a series that illustrates the progressive loss of tissue layers between the maternal and embryonic vascular systems. Six layers are interposed between the two circulations in the epitheliochorial placenta, four layers in the endotheliochorial placenta, and three layers in the hemochorial placenta.

Table 6.2 Comparative reproductive and placental features in selected experimental mammals and humans

Feature	Rat	Mouse	Rabbit	Hamster	Guinea Pig	Rhesus Monkey	Human
Estrus cycle (days)	4–6	3–9	None	4	16	28 (menstrual cycle)	28 (menstrual cycle)
Ovulation stimulus	Spontaneous	Spontaneous	Coitus	Spontaneous	Spontaneous	Spontaneous	Spontaneous
Uterus	Bicornuate	Bicornuate	Duplex	Bicornuate	Bicornuate	Simplex	Simplex
Usual no. of offspring	6–14	8–16	6–9	5–10	3–4	1	1
Gestation (days)	22	19	30–32	15–16	67–68	166	266
Implantation type	Eccentric — early Interstitial — late	Eccentric — early Interstitial — late	Superficial	Interstitial	Interstitial	Superficial	Interstitial
Classification by fetal membranes that contribute to placenta	*Early* Inverted yolk sac *Definitive* Chorioallantoic	*Early* Inverted yolk sac *Definitive* Chorioallantoic	*Early* Inverted yolk sac *Definitive* Chorioallantoic	*Early* Inverted yolk sac *Definitive* Chorioallantoic	*Early* Inverted yolk sac *Definitive* Chorioallantoic	Chorioallantoic	Chorioallantoic
Placental shape	Discoid	Discoid	Discoid	Discoid	Discoid	Bidiscoid	Discoid
Internal placental structure	Labyrinthine	Labyrinthine	Labyrinthine	Labyrinthine	Labyrinthine	Villous	Villous
Placental relation to maternal tissues	Hemotrichorial	Hemotrichorial	Hemodichorial	Hemotrichorial	Hemomonochorial	Hemomonochorial	Hemomonochorial

that there exists a broad diversity of mechanisms for transporting molecules through the placenta. The transport mechanisms[8–10] include both simple diffusion for most molecules (e.g., urea, oxygen, carbon dioxide) and carrier-mediated transport. The carrier-mediated mechanisms include active transport (e.g., for sodium/potassium, calcium, amino acids), facilitated diffusion (e.g., for D-glucose), and receptor-mediated endocytosis (e.g., for immunoglobulins, vitamin B-12). Thus, given the multiplicity of available transport mechanisms, when any substance is presented to the placenta, the question concerning entry into the embryo should not be whether placental transfer occurs, but rather by what mechanism and at what rate will transfer occur. The closest phenomenon to a barrier function is the expression in trophoblast cells of the multidrug resistance (*mdr*) gene family, which encodes a p-glycoprotein on the surface of the trophoblast membrane of conceptuses[11–13] exposed to certain xenobiotics. This phenomenon serves to limit the exposure of embryos to selected molecules.

In addition to transferring nutritive molecules to the embryo, the placenta may metabolize substances, whether they are nutrients or xenobiotic compounds.[9,10,14] For example, in cattle and sheep, the placental trophoblast converts maternally delivered glucose to fructose, which is in turn transferred to the embryo. In those species, an intravenous dose of glucose to the pregnant female causes a dramatic rise in fetal plasma fructose concentrations, rather than a rise in fetal plasma glucose. This illustrates the concept that placentas are not merely sieves but have the ability to alter some of the types of molecules that traverse them.

Placentas also contain various enzymes that are capable of metabolizing xenobiotics.[15–17] These enzymes include reductases, epoxide hydrases, cytochrome P-450 monooxgenases, glucuronidases, and others. These enzymes are not present at all times during gestation but make their appearances as the placenta (and embryo) mature. The presence (or absence) of these enzymes reflects the genotype of the embryo rather than that of the mother. Placental enzymes can be induced by inducers of monooxygenases, such as phenobarbital, benzo(*a*)pyrene, and 3-methylcholanthrene. In addition, the formation of reactive intermediates from xenobiotic compounds by placental enzyme preparations has been demonstrated *in vitro* (e.g., see Chapter 12 of this volume).

Placental toxicity, per se, is rarely cited as a primary mechanism for developmental toxicity. This does not mean that the importance of the placenta in development is not recognized, nor does it mean that placental dysfunction can be discounted as playing a critical role in development.[10,14,17–20] That the placenta plays a role in developmental toxicity is not in dispute; rather, it has proved difficult to determine whether developmental toxicity arises as a result of direct placental toxicity or from combined effects on the materno-feto-placental unit. Examples of developmental toxicity that have been ascribed to some combination of mother, fetus, and placenta include reductions in utero-placental blood flow subsequent to hydroxyurea,[21,22] altered transport of nutrients by azo dyes,[23,24] immunotoxicants,[25,26] lectins,[71] and hemoglobin-based oxygen carriers,[72] as well as pathological changes observed in the trophoblast after exposure to placental toxicants, such as cadmium.[27,28]

III. EMBRYOLOGICAL PROCESSES

Development from zygote to embryo to fetus to independent animal is a dynamic and carefully orchestrated phenomenon that involves numerous simultaneous processes that occurs in specific sequences and at particular times during both gestation and the postnatal period. This is especially true for rodents, wherein many of the organ systems of neonates have attained only the state of maturation found in late second or early third trimester human fetuses.[29] While it is imperative that developmental schedules be maintained, each embryo develops at its own rate, and there is some room for adjustment to the schedules. That is, some developmental events may be delayed to a certain extent without adverse consequences. Thus, the gestational ages given for developmental events are merely averages of the observed events. Embryos within the same litter of polytocous species are frequently at different developmental stages, especially during early embryogenesis. This may have resulted from different times of fertilization as well as from differences in the rate at which each embryo progresses through its own developmental schedule.

While many of the details concerning the development of embryos from various species (e.g., length of gestation, size of fetuses, time at which developmental landmarks appear) differ, the sequence of developmental events and many other features and processes are remarkably consistent across species. The following paragraphs will provide an overview of the consistencies and similarities of processes that take place in all embryos.

The blastocyst is a small organism, the cells of which have relatively few distinguishing morphological characteristics when observed with a microscope. There are two geographically distinct areas, the trophoblast and the inner cell mass. Not only does the blastocyst grow larger in size, but also the cells that comprise the blastocyst must become different in structure and in function as development of the individual progresses. As mentioned previously, the trophoblast forms the fetal membranes, whereas the inner cell mass gives rise to the embryo proper.

The cells of the inner cell mass quickly segregate into a two-layered disk that unequally transects the blastocyst cavity. One layer of cells (epiblast) is associated with the developing amniotic cavity; the other layer (hypoblast) is associated with the developing yolk sac cavity. The epiblast in turn rearranges by a process of cellular migration (variously called *invagination*, *ingression*, or *gastrulation*)[30–33] into the three germ layers (ectoderm, mesoderm, and endoderm), as well as the notochord. The hypoblast gives rise to the epithelial lining of the yolk sac, but does not contribute to the embryo proper.

Specific tissues of the body are derived from each germ layer. The ectoderm will give rise to the nervous system, skin, and adnexal dermal organs, including teeth, nails, hair, and both sweat and mammary glands. The derivatives of the mesoderm include cartilage, bone, muscle, tendons, connective tissue, kidneys, gonads, and blood. The endoderm gives rise to the linings of the alimentary, respiratory, and lower urinary tracts. The notochord serves as a primitive supporting tissue for the embryo and actively participates in the organization of the embryo. It degenerates, leaving no derivative except for the nucleus pulposus of each intervertebral disk.

The primordia of the organ systems are formed from combinations of tissues derived from the germ layers. To execute this process efficiently and accurately, many controls operate to maintain embryonic schedules and to control the fates of populations of cells, although there is some room for flexibility in these schedules and fates.

To help understand how the development of the embryo proper unfolds in an orderly fashion, two important concepts will be explained. These relate to the potential fate of a given cell (embryonic cellular potency) and its state of differentiation. Briefly, *embryonic cellular potency* is the total range of developmental possibilities (i.e., all possible adult tissues) that an embryonic cell is capable of manifesting under any conditions. In contrast, *differentiation* is the process whereby an embryonic cell attains the intrinsic properties and functions that characterize a particular tissue. Differentiation is a progressive, continuous phenomenon that involves at least three steps: (1) determination, during which stable biochemical changes occur within cells, but the changes are not apparent microscopically, (2) cytodifferentiation, during which those biochemical changes manifest themselves, resulting in the characteristic cytological and histological features that distinguish cell or tissue types from one another, and (3) functional differentiation, during which the cell or tissue begins to act in a physiologically mature role (e.g., insulin synthesis and release by pancreatic islet cells).

An embryonic cell's potency and its state of differentiation are reciprocal characteristics. Cells in the early stages of development, such as the blastomeres, the cells of the morula, or those of the inner cell mass of the blastocyst, are not differentiated; they are morphologically similar, and they have the potential to become nearly any type of embryonic cell. The pluripotent cells of the inner cell mass constitute the population of embryonic stem cells, which hold the promise of cures for many debilitating diseases.[73] As development proceeds, however, developmental decisions are made concerning the fate of each cell. Thus, at later periods of gestation the cells have become different from one another. One cell may have become an endoderm cell lining the liver parenchyma, while another may be a mesoderm cell that is providing smooth muscle in the walls of a blood vessel. The possible ultimate fates available to an endoderm cell are not the same as those of a

mesoderm cell. Thus, the cells have restricted their potential. Also, they look different from one another because their state of differentiation has increased.

Cells become increasingly differentiated with increasing gestational age, and their embryonic potential decreases, as depicted in Figure 6.4. For both of these processes to occur in the proper sequence to result in a well-formed, normal individual, mechanisms must be available to keep populations of cells on schedule. A primary means for accomplishing this is the process of tissue interactions. As an example of tissue interactions, we discuss embryonic induction.[34]

Embryonic induction requires two populations of cells of developmentally dissimilar origin that attain proximity to one another. Developmental information of a directive nature is released or transferred from one population of cells (the inducer) for a finite period. The receiving population of cells must be competent (i.e., able to react to the directive message) for a limited period. The change that is evoked in the competent tissue must be progressive, stable, and maturational. One important thing to note about this process is that the ability of one population of cells to send a message and the second to receive and respond to the message is limited to a finite period (or window) that is intrinsic to each cell population. It is the transfer of developmental information through these open "windows" that maintains the embryo on its schedule. Genetic control over the timing and location of inducing and competent tissues is likely related to the sequence of expression and spatial delimitation within the embryo of genes controlling the synthesis of transcription factors and developmental control genes, such as the homeobox genes.[35–37]

The nature of the message substance or inducer has been investigated for many years. It is not known what the medium of the message is in all cases. In some cases, the message appears to require direct contact between the cells; in others it appears to be the release of a chemical substance into the extracellular space. In still other cases, a combination of the two appears to be required. For our purposes, however, the nature of the message is not as important as the fact that appropriate communication between the populations of cells has occurred in a timely fashion.

It is important to recognize that, for a given cell, the information required to direct its differentiation (e.g., manufacture of cellular structural proteins, receptor molecules, and extracellular matrix molecules) resides within the genetic material of its own nucleus, whereas the information required to maintain developmental schedules usually comes from environmental stimuli (e.g., inducer molecules as well as permissive and instructive signal molecules that are manufactured and released by other embryonic cells). Successful development of an organism requires timely interactions between (normal) environmental stimuli and embryonic genes as they are expressed or repressed throughout development.[38] It should not be surprising, then, that abnormalities in either an embryo's genetic material (i.e., mutations or chromosomal aberrations) or its environment can lead to developmental anomalies.

The subcellular and molecular interactions that direct or contribute to the execution of these developmental processes (differentiation, induction, pattern formation), as well as to their control by gene expression, are active areas of research that are beyond the scope of this brief overview. The reader is referred to more detailed texts and articles that capture this information.[32,33,39]

To respond to challenges external to the embryo or to untoward intrinsic influences on development, the embryo can possibly undergo internal rearrangements of its schedule or populations of cells, thus maintaining normal, orderly development. This process has been termed *embryonic regulation*. Regulation is an important concept because it demonstrates that the process of embryonic development is a dynamic progression that is able to adjust to changing conditions.

When an embryo is challenged by an environmental agent, many components contribute to the eventual outcome. Some of these are extraembryonic in nature, whereas others are embryological components. Although the extraembryonic components are not the main thrust of this discussion, they will be addressed briefly because they can affect the rate and quality of embryonic development. First, the nature of the environmental agent itself must be considered. For instance, is it a physical agent or a chemical agent? If it is a chemical agent, then its structure, polarity, and lipid solubility are all important properties to be considered as they affect the amount of uptake of the chemical

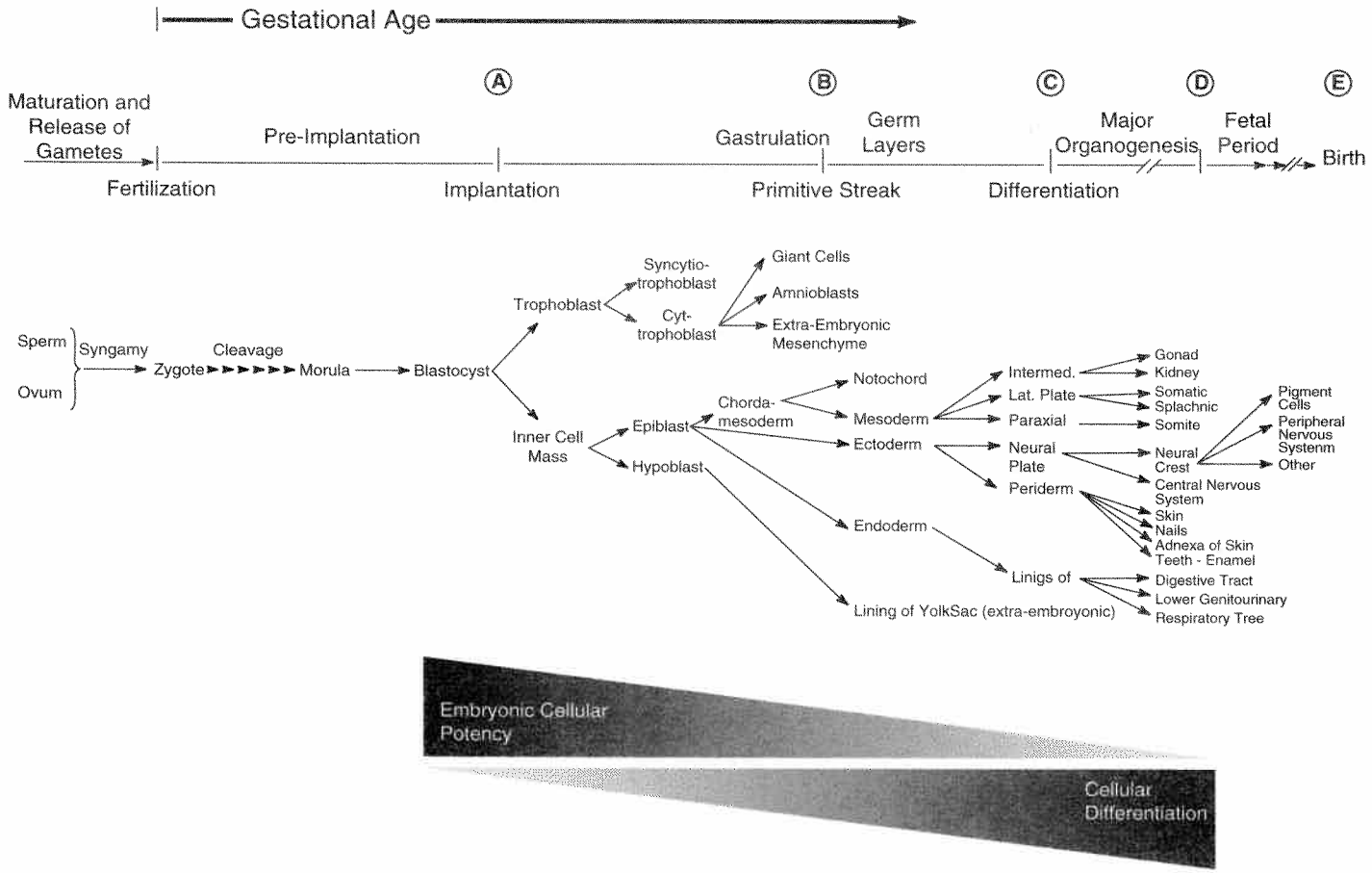

Figure 6.4 Diagrammatic representation of embryonic development. Fertilization is depicted on the left, and developmental maturation proceeds to the right. The dashed arrow represents possible differentiative pathways; the series of arrowheads denotes the rapidly occurring cell divisions during cleavage. Diverging arrows represent developmental decisions made by tissues as they differentiate. With each succeeding developmental decision, a cell's developmental potential decreases, while its state of differentiation increases. The circled letters denote the gestational milestones for the species listed in Table 6.1.

into the mother and the amount that will ultimately reach the embryo. In addition, each environmental agent may be thought to act in a specific way on some aspect of embryonic metabolism, and this specificity may help to determine how the agent interferes with embryonic development.

A second extraembryonic component is the dosage of the particular agent. The dosage is not as simple a component as one might assume; not all doses of proven teratogens cause birth defects. Typically, there is a lower dose range that allows most, or all, embryos to proceed through normal development, whereas higher doses may kill the embryo (and perhaps the mother as well). In between those two doses, there is usually a rather narrow teratogenic range in which sufficient damage is elicited in the embryo to disrupt developmental events without destroying it entirely. In addition, the dosage may be administered either acutely or chronically, and this also will affect the nature of any interference with embryonic development that may occur.

A third extraembryonic component is the physiological state of the mother because she provides the physical environment of the embryo. The state of the mother's nutrition and her general state of health are important, as is her ability to metabolize chemical agents and thereby change the nature of the compound to which the embryo may be exposed.[40] A fourth extraembryonic component is the previously discussed efficiency of the maternal-fetal exchange through the placenta. In summary then, the major nonembryonic considerations are the nature of the teratogenic agent, the dosage of the agent and timing of exposure, the maternal organism, and the effectiveness of maternal-embryonic exchange.

There are also important embryological components that affect embryonic outcomes.[41–43] The first of these components is the embryonic genotype and its expression, the theoretical basis of which has been discussed elsewhere[38] and which is the topic of ongoing, in-depth research.[31,33,39] In simplest terms, the embryonic genotype is an important embryonic consideration because it determines the inherent susceptibility of the embryo to exogenous agents at any given time during development. Alterations in a cell's DNA are the cause of mutations. Throughout most of the life span of mammals, DNA is replicated with great fidelity, and alterations to nonreplicating DNA, caused by environmental agents such as irradiation or chemicals, are rapidly repaired. There are two periods, however, when mammals are rather vulnerable to permanent changes in their DNA. One of these periods occurs during cleavage, when cell cycle times are shortest and extremely rapid synthesis of DNA is required. The fidelity of DNA replication diminishes with the continued rapidity of its synthesis. The other period is during the postmeiotic stage of gamete development. The greatest sensitivity occurs in males during spermiogenesis, when spermatozoa are maturing. The maturation of spermatozoa involves a process that drastically decreases the cytoplasm of the cells. In concert with the reduction of nonessential cytoplasm, the enzymes required for DNA repair are lost, leaving the maturing gametes unable to repair DNA damage. These topics have been discussed at length by others.[44,45]

A second important embryonic component is the stage of development of the embryo. In general, the time at which an agent acts on an embryo determines which tissues will be susceptible to the effects of the agent. This means that susceptibility to a particular agent will vary greatly during the course of gestation. Agents that are applied, even at high doses, during the predifferentiation period (from the time of fertilization through formation of the blastocyst) typically produce no teratogenic response, although exposure of females to mutagens within a few hours of mating has been reported to induce malformed offspring in some instances.[46] The reason why young embryos appear to be resistant to the effects of teratogens is not well understood; however, that resistance is probably a result of either the lack of specialization by the cells of the zygote to form specific parts of the organism, thereby retaining their embryonic potency, or a large number of stem cells. As long as all or many cells of the zygote retain a high degree of potency, the destruction or damage of some of those cells can be tolerated because the embryo can still undergo sufficient regulation to allow normal development to proceed. Although it appears that the destruction of a small number of undifferentiated cells in the embryo does not necessarily result in a structural malformation, there does appear to be a critical limit beyond which damaging even nonspecialized cells cannot

be tolerated if the embryo is to live; if that critical limit is exceeded, the zygote will die. Further, nonlethal damage to the genome of pluripotent cells can result in a mosaic of tissues that exhibit increased likelihood of disease or other pathology.[44]

During the period of early organogenesis (when the embryo begins to undergo differentiation and the establishment of the germ layers), the onset of greatest susceptibility to teratogenesis occurs. This is coincident with the processes of gastrulation or invagination. For mammals, this occurs approximately five days postconception in small rodents (e.g., hamsters and mice), and up to 10 to 12 days postconception in primates. Not only is the onset of susceptibility to teratogenesis sudden, but also the majority of teratogenic agents produce their highest incidences of malformations at about this time.[41] Although there are no indications of the definitive organs in the embryo at that time, the cells of the germ layers have become determined (i.e., the morphologically undetectable aspect of differentiation has occurred) and have, therefore, lost some of their embryonic potency. Thus, cells that have become determined are susceptible to teratogenic agents even though their ultimate morphology is not yet evident. For example, rat embryos that have been exposed to x-rays on gestational day 10 exhibit malformations of the kidney at term.[47] This is of interest because the definitive kidney of the rat develops from the metanephros, which does not appear until day 12 of gestation.

This illustrates the concept that it is the stage of development at which an agent is effective, rather than the time at which it is administered, that determines the embryo's susceptibility.[48] This concept is important for those agents that might be stored in adipose tissues of the body. By way of example, this has been used as a basis to allege that the vitamin A derivative, etretinate, may have caused malformations in the offspring of a woman who had terminated its use several months prior to conception.[49]

Not only do embryos themselves have a sudden onset of susceptibility to teratogenesis, but also each organ of an embryo has a sensitive period for teratogenesis.[41,45] This sensitive (or critical) period is the time during which a small dose of a teratogen produces a great percentage of fetuses that will exhibit malformations of the organ in question. The critical period coincides with the early developmental events and tissue interactions that occur within the organ. In general, the susceptibility to teratogenesis decreases as differentiation and organogenesis proceed. This is because the proliferative and morphogenetic activities that characterize the early stages of the formation of tissues and organs become less prominent as the organ develops.

As an embryo progresses through the period of organogenesis, and as differentiation continues, production of a given teratogenic effect requires increasingly higher doses of the teratogen. This means that as organ systems and the embryo itself become progressively more differentiated, they become increasingly resistant to teratogenesis. Most of the organ systems have been laid down by the period of late organogenesis and the early fetal period, and the critical events involved in their formation have been completed. What remains to be accomplished during the remainder of prenatal and postnatal development is the progressive growth and functional maturation of each organ system. Strictly speaking, the majority of gross malformations become increasingly less problematic, although malformations of late-developing organs (e.g., kidneys, genitalia, and brain), altered histodifferentiation, growth retardation, and postnatal functional deficits (including neurobehavioral problems) may still be caused.

IV. COMPARATIVE EMBRYOLOGICAL MILESTONES

Because the primordia of the organ systems of an embryo are laid down in sequence, and not concomitantly at any given time in gestation, each organ system is likely to be at a unique stage of differentiation. For this reason, agents given acutely during a particular period of gestation may cause malformations of one organ system but not of another, or they may cause different malformations of the same organ system. Thus, the pattern of defects caused by any particular teratogen

may change if the time at which the agent is applied or if the time at which the agent is effective occurs successively later in gestation. This has led to the construction of developmental schedules for embryos and, subsequently, both the use and misuse of those embryonic timetables.[50] It is important to realize that embryonic timetables can be used to determine at what developmental time a given organ is formed. From such a table, it is possible to ascertain the earliest and latest gestational times at which a particular organ system is likely to be grossly malformed by a noxious agent. Such embryonic schedules are useful for determining whether an embryo was exposed during or prior to the time of development for a given organ; they cannot identify the exact date at which an embryo was exposed to a particular agent because, as mentioned previously, some agents have delayed effects.

The differences among species, especially with respect to the timing of prenatal developmental events, are the subjects of Tables 6.3 to 6.12. The tables present the times of appearance for events in the embryology of various organ systems for selected laboratory animal species. The timing of such events is important if one wishes to investigate the normal development of a particular organ system. Timing is also crucial to studies of the genesis of malformations of an organ, using an animal model, or if one wishes to determine whether treatment with a specific agent is capable of eliciting the malformation of a given organ system. In cases such as the latter, the investigator must know at what gestational time the organ system in question is undergoing organogenesis in the appropriate animal model. Thus, the reader is referred to Tables 6.3 to 6.12 for interspecies comparisons of embryonic events related to development in general (Table 6.3); the circulatory system (Table 6.4); the digestive system (Table 6.5); selected endocrine glands (Table 6.6); the respiratory system (Table 6.7); the nervous system (Table 6.8); selected organs of special sense, i.e., eye, ear, and olfactory region (Table 6.9); the muscular, skeletal, and integumentary systems (Table 6.10); the excretory system (Table 6.11); and the reproductive system (Table 6.12). It is important to reemphasize that development does not end at birth and that it may be important to study events in postnatal animals. When the developmental phases of an organism's life are scaled according to the appearance of developmental landmarks (rather strict chronology) so that the developmental schedules of different species are congruent, they are being compared according to physiologic time. This concept is explained in greater detail elsewhere.[29]

Although avian models are not considered to be relevant for the assessment of human developmental toxicity, data for the chicken are included because of its long-standing use in embryological studies and because of its possible usefulness in assessment of the developmental toxicity of environmental pollutants toward wildlife. More complete texts and monographs should be consulted for the detailed embryology of particular species (e.g., human,[32,33,51,52] rat,[53,54] mouse,[55–57] hamster,[58] rabbit,[53,59] guinea pig,[55,60] rhesus monkey,[61,62] and chicken[63–65]).

Determination of the precise times in gestation for each species at which developmental events take place is difficult for a number of reasons. Even though the process of prenatal development proceeds sequentially, the rate at which it proceeds is neither standardized nor constant, even among offspring within the same litter. Development is based upon the expression of information contained within the genome of embryonic cells, and the timing of that expression is both triggered by and permitted by signals in the environment of those cells. Thus, there can be substantial variation in the time of appearance of rudimentary embryonic structures. This is especially true for those species with longer gestational periods.

The timing of embryonic events is further complicated by the fact that the starting point for timing (the instant of fertilization) is not known precisely. In most cases, the time of copulation is used as a surrogate for the time of fertilization. By convention, gestational age is measured from the time that mating is either observed (rabbits) or deduced from evidence of mating (such as observation of a copulatory plug in mice or rats or finding sperm in a vaginal smear in rats, mice, or hamsters). When mating is deduced, the time of fertilization is usually considered to have occurred at 9:00 a.m. of the day that the observations were made. Thus, by embryological convention, 9:00 a.m. of the day that the observations are made is set as day 0, hour 0 of gestation.

In humans and other primates, gestational age is estimated by ovulation age (or, at times, menstrual age — which is about 14 days longer than ovulation age). This means that the actual time of fertilization may be miscalculated by as much as 12 h in rodents and much longer in primates. For avian embryos, including chickens, development is initiated approximately 24 h prior to laying.

A final impediment to establishing the timing for embryonic events is caused by the sample size (or number of examined specimens) from which the times have been derived. In some species, particularly humans and other primates, the number of available specimens is quite small, leading to variations in the timing of events reported by the source documents. Thus, to group or classify embryos by their stage of development rather than by the time after fertilization, some investigators report other embryonic characteristics, such as crown-rump length, number of somites, or external features, as surrogates for gestational age.[52,53,63,66–70]

The aforementioned challenges to determining timing have led to the inclusion of several entries for many developmental events in Tables 6.3 to 6.12. These tables present the timing of developmental events of seven mammalian species and the chicken, organized by organ system. The entries include the estimated time during gestation and (where appropriate and available) the surrogate descriptors somite number or crown-rump length. Where source data have diverged, the entries are given as ranges. It should be emphasized, however, that even though the timing for the developmental events may be somewhat imprecise for certain events, the order of developmental events within a given organ system rarely changes.

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Table 6.3 Comparative early developmental milestones

	Rat				Mouse			Rabbit			Hamster			Guinea Pig			Rhesus Monkey			Human				Chicken		
Description	Age[a] (d)	Size (mm)	Somites	Ref.	Age (d)	Somites	Ref.	Age (d)	Somites	Ref.	Age (d)	Somites	Ref.	Age (d)	Somites	Ref.	Age (d)	Somites	Ref.	Age (d)	Size (mm)[b]	Somites	Ref.	Age (d/h)	Somites	Ref.
One cell (in oviduct)	1	0.07		1–4,6, 9,12	1		5,7–9				1		42				1		33	1	0.13		61,62			
Two cells (in oviduct)	2	0.08		1–4,6, 9,12	1		5,7–9, 12	0.33		12, 28	1–1.5		42	0.96		49, 56	1		12	2	0.12		62,63	3h[c]		12
Four cells (in oviduct)	3	0.08		1–4,6, 9,12	2.25		12	0.46		12, 28	1.67		12,42	1.25		50	1.5		12	1.5–2	0.12		62,63	3.25h[c]		12
Eight–twelve cells	3.25	0.08		1–4,6, 9,12	2		5,7–9							3.5		56				3	0.1		63			
Morula (in uterus)	3.5	0.08		1–4,6, 9,12	3		5,7–9				3		42				4		177	4			41			
Free blastocyst (in uterus)	5	0.12		1–4,6, 9,12	4		5,7–9, 12				3.5–4		42	4.75		56	5–8		33	5	0.1		63			
Implantation	5.5–6	0.28		10–12	4.5–5		10,34	7–7.5		10, 12	4.5–6		10,12, 42,43	6–6.5		10, 51–53, 56	9		10,12, 46,60	6–7.5			10,12, 64	NA		
Shell membrane formed in oviduct (chick)																								3.5–4.5h[c]		86
Shell of egg formed in uterine portion of oviduct (chick)																								4.5–24h[c]		86
Hypoblast formed	6			1–4, 6,9	4.5		5,7–9, 12				~5		42	6–6.5		51	9		46	7–8	0.5		65			
Primitive streak	8.5–9	1		1–4, 6,9, 10,12			5,7–9, 10,35	7.25		10, 57	6.5–7		10,42	12–13		10,15	15–17		10,33	13.5–17	0.3–1.2		9,10, 35,66	7–19h		10, 86
Neural folds	9	1		1–4, 6,9, 11	7.5		5,7–9	7.75–8.25	1–4	27	7.75	5	44	14–14.5		15,55	20–21	3	33	18–21	1.5–2	1–4	36,37, 41,67, 68,70	22–26h	1	86, 87
First myocardial contractions	9.5	1.5	1–4	1,2,9, 13,14, 18,24, 54	8		24	8.5	9	24, 57	8–8.25	12–13	42,43, 44	16–16.5	23	56				21–24	2–3.5	4–12	59,71	1.5d		30, 86
Yolk sac; exocolem	9.5	1.5	1–4	1–4,6, 9,12							7		42				12		46	11–13	0.15		9,72	2d		87
Head process/ notochord					7		36				7.5		44	11–18		55	16–18		33	18			36	19–22h		86

Amniotic cavity	9.5	1.5	1–4	1–4,6, 9,12	7.75		5,7–9				6.5–7.5		12,42, 44	9		51,58	10		46,178	8			41	2d		87
Start of somite phase	9.5–10	1.5	1–4	11,12	7.75–8		5,7–9, 34,37	7.75–8.25	1–4	27	7.5		42	14.5		59	20–21		46,60	19–21	1.5–2	1–4	37,64, 67,70, 73	2d	1–4	87
Allantois arises	10	2	1–4	1–4,6, 9, 12	7.25–7.75		5,7–9, 35	8–10		99	7.75	5	42,44	11.75 –13		15,55, 56				16.5–19			35,41	2–3d	30–36	86, 87
Oral membrane perforates	10	2	5–12	1,2,9, 12,18, 22–26	9–9d 2h	19±	5,7,26, 38	10		10	8.5		44				27–28		10,33	26–30	3.3–4	17	12,26, 39,74, 75,76, 77,78	2.2–3d	29–32	26, 88
Ten somites	10.5		10	10	8.5	10	10	8.5	10	10	8	10	10,42	15	10	10	23	10	10	25		10	10	1.5d	10	10, 12
Fusion of neural folds (early)	10.5–10.75			11,27				8.5–9	10–14	27, 99	8.25	12–13	42,44	14–15		15,55	21–23		33	22–24	2–3.5	4–12	66–68, 71,73, 74, 79–82	26–29h	3–4	28
Anterior neuropore closed	10.5–10.75	2.4	17	1,2,4, 9,10, 11,18, 23,27	9d 1h	18±	5,7,8, 39	4	9–9.5	10, 27	8.5	17–20	10,44	15.25		10	25		10	24–26	2.5–4.9	13–20	10,39, 71,73, 83	2.3d		10
Both neuropores closed	10.5–11.5			10,11	9–9.5		10	9.5–10.5		10, 99	8.5–9		10	15.25 –15.5		10	28–31		10,33	25–28			10			
Dorsal flexure disappears; embryo curves ventrally	10.5–11.5	2.4	13–20	1–4, 6,9, 12,27	8.5–9		5,7–9, 39				8.5–8.75	17–20	42,44				25–27		33	26±			39			
Anterior limb bud appears	11	3.3	21–25	1–4, 6,9,12	9.5–9.75	23±	5,7–9, 39	10.5–11		27, 57, 99	8.75	17–20	42,44, 46,47	16.5	23	56	25–28		33,46	26	3–5	21–29	39,73	51–56h	26–28	30, 86
Tail bud	11–11.5	3.3	21–25	1–4,6, 9,12	9.5		5,7–9	9.5		12	8–8.5	7–9	12,44				26		12	29	3.8		12	ca. 50–52h	20–21	86
Hind limb bud appears[d]	11.5–12	3.8	26–28	1–4,6, 9,10, 12	10–10.3		5,7–10	11–12		10, 27, 57, 99	9		44	17.5–18.5	29	10,56	28–30		10,33, 60	28–32	4–6	30–32	9,10, 60,71, 73,84, 85	2.2–3d	29–32	10, 86
Hand (forepaw) rays	13.5–14			3,4, 10–12, 27, 30–32	12.3		7,10, 29,40	14.5		10, 27, 29	10.25–11		10,42, 44,48	22–23.75		10,56	34–35		10,46	35–37	8–11		10	4.75d		30, 86

[a] Age is measured in hours and days from the time of evidence of intromission. For rats, mice, hamsters, and guinea pigs age is counted from 9:00 am on the morning of discovery of either sperm in the vaginal lavage or a copulatory plug. In rabbits, it is measured from time of observation of mating. For primates, age is measured from the midpoint of the cycle (14 d after onset of last menses). In chickens age is generally given as "incubation age" or time after laying. The actual age of the chicken embryo is approximately 24 to 25 h older than the incubation age.
[b] Crown-rump length.
[c] Preincubation age.
[d] Hindlimb bud forms earlier in rodents than in primates.

Table 6.4 Comparative gestational milestones in circulatory system development

Description	Rat				Mouse			Rabbit			Hamster			Guinea Pig			Rhesus Monkey			Human				Chicken		
	Age[a] (d)	Size (mm)	Somites	Ref.	Age (d)	Somites	Ref.	Age (d)	Somites	Ref.	Age (d)	Somites	Ref.	Age (d)	Somites	Ref.	Age (d)	Somites	Ref.	Age (d)	Size (mm)[a]	Somites	Ref.	Age (d/h)	Somites	Ref.
Vascularization of yolk sac											7.5		44	13.5		56	16–18		33	19–20	1.5		74,84, 96–103	20–29h	4	12, 86
Bilateral heart primordia in ventral wall of coelom; two dorsal aortae	7.25–8.5	0.6		1,2,9, 13–22	ca 8d 8h	4	5,7,8, 90	8.25		10	7.75	5	42,44	14.5		15,56						2–6	90			
Fusing heart tubes	9–9.5	1	6	1,2,7–10,12, 13–22, 24	7		5,7,8, 10	8.5–9	12	10, 24	8–8.25	12–13	10, 42–44	15		10,15	22		10,33	21	2		10,24	1.2d		10
First myocardial contractions	9.5	1.5	1–4	1,2,8, 9,13, 14,24, 54	8		5,7,8, 24	8.5	9	24	8–8.25	12–13	42–44	16.5	23	15,56				21–24	2–3.5	4–12	59,71	1.5d		30, 86
Dorsal mesocardium disappears					8d 21h	15	90				8.75–9.25		44									16–17	90			
Aortic arch arteries forming	10–12			10,24	8.5–11		10,24	9–11		10, 24	8–9.5		10	15.5–21.5		10	22–30		10	22–32	2–4		10,12, 24	1.5–4.5d		10, 24
Aortic arch I	10	2	5–12	2,8,9, 13,14, 18,24	8d 13h	9	7,81, 24	9.25		24	8		44				21–23		33	22	2	7	7,12, 81,24	33–38h	9–10	88
Sinus venosus; umbilical vessels; cardinal veins; endocardium	10.5	2.4	16–20	2,8,9, 13,14, 18							8.5		44	17.5	29	56	24–26	13–20	33	24–27	2.5–4.5	13–20	12,71			
S–shaped heart	10	2	10–12	2,8,9, 13,14, 18,24	8.5		10,24	9.5	21	10, 24	8.5		10,44	16		10	25		10,33, 44	25–27	3.3		10,12, 24	48–54h	24–27	10, 24
Anterior cardinals	10.5	2.5	16–20	2,8,9, 13,14, 18	8d 14h	9–10	91				8		44	15.5	13	56						14	91	40h	13	12
Aortic arches I & II	10.5–11	2–2.4	11–20	2,8,9, 13,14, 18,89	9d 4h	20±	92,24	9.5		24	8.5		44	15.5	13	56	21–23		33	30	4	28	12,92, 24	50–55h	20–26	88, 24
Dorsal aortae fuse					9d 4h	20±	92,24				9		44	16.5	23	56				27	3.3	20	92,24	56h	24–27	24

Posterior cardinal veins established	10.5	2.5	16–20	2,9,13, 14,18	9d 4h	20±	7,39				8		44	16.5	23	56				26±			7,39			
Ten-somite stage	10.5		10	10	8.5–8.75	7,10	10	8.5	10	10	8	10	10	15	10	10	23	10	10	23–25		7,10	10	1.5d	10	10, 12
First circulation	10–10.5	2.4	16–20	2,9,13, 14,18, 176	8.5		5,7,24													26	3		71	2d	18	24
Duct of Cuvier (common cardinal vein)	12.5	6.2		12							8.5		44	16.5	23	56				24		14	83	ca. 45h	15	88
Aortic arch III	11	3.3	21–25	2,9,13, 14,18	10	27±	7,93	9.75		24, 27	9		44	16.5	23	56	27–28		33	28–31	4		7,24, 93,	50–55h	26	88, 24
Posterior cardinal; branches of anterior cardinal on mesencepha-lon	13.5	8.5		12							9		44	88,24 17.5	29	56				24		14	83	ca 45h	15	88
Septation occurring	11.5–12.5			10,12, 24	10.5–11.5		10,40, 24	13	34	10, 24	9.25		10	19.5		10	28		10	28–37	3.5–6		10,24, 74,90, 99, 104–111	2.3d	26	10, 24
Four aortic arches; I regressing, IV still small	11.75–13	4.2	29–31	2,9,13, 14,18, 24	10		24	11.75		24	9.25		44	17.5	29	56	28–29		33	31–34	4–4.6		12,24, 83	3d	36	88
Atrioventricular canal	12	5.1	34–35	2,9,13, 14,18																25		16	83	3–4d	ca. 30–44	88
Endocardial cushions appear	12–12.375	5.1–6	35–40	2,9,13, 14,18, 24	9d 18h	26±	39,24	11		24										26–28			39,71	3–4d	ca 30–34	88, 24
Aortic arches III, IV, & VI	12.125	5.2	36	2,9,13, 14,18	10.5		7,24, 93	11		24	9.5		44	19	35	56	29–30		33	32–35	6		24,93	4d		88, 24
Beginning interventricular septum	12.125 –13	5.2	36	2,9,13, 14,18, 24	9–10.5		76,24	12		24	8.5	29	44							29–35	6		24,76	4d		88, 24
Vitelline veins anastomose with liver plexus	12.5	6.2		12	10.5		39				9.25		44									26	39			

Table 6.4 Comparative gestational milestones in circulatory system development (continued)

Description	Rat				Mouse			Rabbit			Hamster			Guinea Pig			Rhesus Monkey			Human				Chicken		
	Age[a] (d)	Size (mm)	Somites	Ref.	Age (d)	Somites	Ref.	Age (d)	Somites	Ref.	Age (d)	Somites	Ref.	Age (d)	Somites	Ref.	Age (d)	Somites	Ref.	Age (d)	Size (mm)[a]	Somites	Ref.	Age (d/h)	Somites	Ref.
Intersegmental artery supplying anterior limb bud											9.25		44	19	35	56					5		83	4d		88
Primordium of atrioventricular valve														23.75		56				31–35	4.3–5.4		74,84, 95,104 –111			
Septum primum	12–12.5	5.1	34–35	2,9,13, 14,18, 24	11–11.5		7,24, 90		34	24	9.25		44	18.5	31	56				28–37	3.5–6		7,24, 71,74, 84,90, 95,104 –111	50–55h	26	88, 24
Pulmonary vein enters left atrium	12.375	6	39–40	2,9,13, 14,18	11.5		7,90							20.75	39	56				35–40	8–10		7,74, 84,90, 95,104 –111	ca 50h	20	88
Endocardial cushions fused	12.5	6.2	41–42	2,9,13, 14,18	11		77,24	14		24										35–40	6–8		24,74, 77,84, 96–98, 100–103	5.5–6d		24
Subcardinal veins formed					11.5		94				9.5		44							28	4		94	70h	30–36	88
Initiation of aortic – pulmonary septum					11.5		77,24				10		44							32–35	7–8		24,71, 77	4d		24
Ostium secundum	13.25			24	11		24	12.75		24										40	8–10		24	5d		24
Septum secundum	14			24				13		24	13		44							40	8–10		24			
Foramen ovale present	13–14	8	46–48	2,9,13, 14,18, 24	11–12		10,24	14		10, 24	10–13		10,44	19.25 –21	38	10,56	34		10	41–44	8–10		10,24	5d		10, 24
Subcardinal anastomosis					12.5		7,94				11.5		44								11		7,94			
Inferior vena cava enters heart					12.5		7,24, 94				9.75		44							45–51	15–20		7,24, 94	6–6.5d		24

Posterior cardinal degeneration					12.5		94				11		44								15		94			
Right dorsal aorta between arches III and IV disappears	15			24	13		7,24, 93	14		24	11		44							41–42	12–14		7,24, 93	7–7.5d		24
Interventricular septum complete	15[c]	12		2,9,13, 14,18, 24	13		7,24, 95	16.5		24	11		44							43–46	13–17		7,24, 71,95	8d		24
Bursa of Fabricius; posterodorsal wall of cloaca (chick only)																							5–6d		88
Truncal septation complete	15.5			10	13–14		10,77	16.5		10	15		10	22		10	36		10	35–46	11–14		10,71, 77	5–7d		10, 88
Initiation of aortic and pulmonary semilunar values					13.5		77,24													35–38			77,24	5.5–6d		24
Fetal circulatory system is established[b]	15.5	14.2	64	2,9,13, 14,18																					

[a] Crown-rump length.
[b] Differs from that in humans mainly by persistence of a capacious vitelline circuit in addition to allantoic (umbilical) circuit.
[c] Completion of rat membranous interventricular septum may occur as late as postnatal day 7 (179, 180).

Table 6.5 Comparative gestational milestones in digestive system development

Description	Rat				Mouse			Rabbit			Hamster			Guinea Pig			Rhesus Monkey			Human				Chicken		
	Age[a] (d)	Size (mm)	Somites	Ref.	Age (d)	Somites	Ref.	Age (d)	Somites	Ref.	Age (d)	Somites	Ref.	Age (d)	Somites	Ref.	Age (d)	Somites	Ref.	Age (d)	Size (mm)[a]	Somites	Ref.	Age (d/h)	Somites	Ref.
Foregut and oral plate	9.5	1.5	1–4	1,2,9, 10,18, 22–26	7.8	0	10,26	8.5		10	7.75–8	5	10,44	14–14.5		10,56	20.5		10	20.5–22	2.1	2	10,26, 71,115	23h–1.1d		10, 26,88
Pharyngeal pouches appear; stomodeum	10	2	5–12	2,9,18, 25,26	8.3–8.8	4	26				8		44				24–26		33	24–27	3.3	7	26,39, 76,77, 81,96, 116	36–39h	12	26,88
Oral membrane perforates	10	2	5–12	1,2,9, 18, 22–26	9–9d 2h	19±	26	10		10	8.5		44				27–28	21–29	10,33	26–30	3.3–4	17	12,26, 39,76–78,96, 116	2.2–3d	29–32	26,88
Liver primordium	10.5–11	2.4	13–20	1,2,9, 10,18, 22–26	8.8	14–15	10,26	9.5		10	8.5		10,44	16		10	24–26	13–20	10,33	21–27	2–3.3		10,26, 39,78, 116–118	50–56h	22	10, 12, 26,88
Hindgut	11	3.3	21–25	1,2,9, 18, 22–26	8–8.5	6–7	10,26	9		10	8		10,44	15.5		10,56	21		33	21.5		7	10,26, 81	50–53h	21	10, 12, 26,88
Second pharyngeal pouch	11	3.3	21–25	2,9,18, 25	8d 19h	14	26	9.5		57	8.5		44	15.5		56	25–26		33			14	91			
Gallbladder[b]	NA				9.625–9.7	25±	10,26	11.5		10	8.7		10	19		10	28–29		10,33	26–30	3.3–4		10,26, 39,71, 78	2.8–3.5d		10, 26,88
Pancreas, ventral	11			26	9.7–11		7,26										29–30		33	31–35	4.3–7.5		26,39, 71,96, 117, 119, 120	3d		26
Pancreas, dorsal	11			26	9.7		26										28–29		33	26	3.5		26,71	4	35	26,88
Vitelline duct closes	11	3.3	21–25	1–4,6, 9,18, 22–25	9.5		5,7–9																			
Cloaca	11	3.3	21–25	1,2,9, 18, 22–25																27	3.3		39,76, 77,96, 116			
Liver epithelial cords	11.5			10,26	9.5–9.625	25±	10,26	10.5		10	8.75–9		10,44	16.5		10				26		25	10,26, 39	3		10

Stomach appears	11.5			10,26	11.5		10,26	10.5		10	8.5		10	16.5		10	28–29		10,33	28–32	3.5–4		10,26, 39,76, 77,84, 96,116	3d		10,26
Third pharyngeal pouch; laryngotracheal groove	11.5	3.8	26–28	2,9,18, 25							8.75		44	19	35	57	27–28	21–24	33	28	4.5		71	50–55h	23–24	12
First and third pharyngeal pouches touch ectoderm, second ruptured into visceral groove	12.125	5.2	36	1,2,9, 18,22–25							8.75		44							25		14	83			
Umbilical hernia begins	12.25–14			9	11–12.3		10,26	12.5–14.5		10	9.3–11		10	22–23		10	33–35		10	36–45	8		10,26, 84,121	4.75–6d		10
Urorectal septum appears	12.375–17	6	39–40	2,9,10, 26, 112, 113				15		10	9.5		10,44							28–48	4.3–6		10,39, 76,77, 84,96, 114, 116			
Trachea separates from esophagus	12.5			1,2,9, 18, 22–26	11		26				9.75		44							29–31			26,71	4–4.5d		12
Primordium of bile duct											9.5		44							31–37	4.3–6		96,122	68h	35	88
Anal plate posterior to genital tubercle	12.5	6.2		12							10		44	20.75	40	57										
Tongue primordium; tuberculum impar	12.5	6.2	41–42	1,2,9, 18, 22–25							9.75		44	20.75	40	57				36–40	6–10		39,76, 77,84, 123	4		88
Fusion of dorsal and ventral pancreas	13	8	46–48	1,2,9, 18, 22–25	11.5		7,26				11.5		44				35–36		33	35–44	8–14		7,26, 71,77, 96,124			
Tip of tongue free	14.5	10.5	56–60	1,2,9, 18, 22–25							10.5		44	23.75		57										
Dental lamina; upper and lower incisor buds forming	14.5	10.5	26–60	1,2,9, 18, 22–25							11.5		44	20.75	40	57				40–48	8–15.6		125–128	6[d]		88

Table 6.5 Comparative gestational milestones in digestive system development (continued)

Description	Rat				Mouse			Rabbit			Hamster			Guinea Pig			Rhesus Monkey			Human				Chicken		
	Age[a] (d)	Size (mm)	Somites	Ref.	Age (d)	Somites	Ref.	Age (d)	Somites	Ref.	Age (d)	Somites	Ref.	Age (d)	Somites	Ref.	Age (d)	Somites	Ref.	Age (d)	Size (mm)[a]	Somites	Ref.	Age (d/h)	Somites	Ref.
Fusion of mandibular and lower jaw elements completed														19.75	38	57	37–38		33	38	8		39,76, 77,84, 123			
Mandibular glands; mucosa near mandibular symphysis to base of tongue	14.5–15	10.5–12	56–63	1,2, 9,18, 22–25																40–50	8–17		96, 116, 124	8		88
Anal membrane perforates	15	12		10,12, 26	14		10	10		10	13		10				39–40		33	45–50	16.5		10,26, 39,76, 77,84, 96,116	6		10,26
Maximal size of umbilical hernia	15.5	14.2	64	9	14.5		5,7–9				12.5		44							9wk		167				
Palatal folds uniting (not all at the same stage of union)[c]	17			10,11	15		10	19.5		10	12		10	26		10	45–46		10,33	56–63			10,12, 83, 116, 167	N/A		
Umbilical hernia reduced	17–18.5	16–20		1–4, 6,9, 10–12, 27	16–16.5		5,7–10	20		10	13		10				45–48		10,33	8.5–10wk	26–45		9,10, 39,66, 76,77, 84,96, 116, 121	18		10

[a] Crown-rump length
[b] Rats do not have gallbladders.
[c] In the chick palatal folds do not fuse.
[d] Transient structure; teeth do not form.

Table 6.6 Comparative gestational milestones in endocrine system development

Description	Rat				Mouse			Rabbit			Hamster			Guinea Pig			Rhesus Monkey			Human				Chicken		
	Age (d)	Size (mm)	Somites	Ref.	Age (d)	Somites	Ref.	Age (d)	Somites	Ref.	Age (d)	Somites	Ref.	Age (d)	Somites	Ref.	Age (d)	Somites	Ref.	Age (d)	Size (mm)[a]	Somites	Ref.	Age (d/h)	Somites	Ref.
Pharyngeal Pouches																										
Two pharyngeal pouches	11	3.3	21–25	2,9,18,25	8.5–8.8	6–14	91,115										24–26		33	27	3.3	12–14	91,115			
Three pharyngeal pouches	11.5	3.8	26–28	2,9,18,25	9d 15h	25±	135										27–28	21–29	33	28	3.5	22	135			
Four to six pharyngeal pouches (ultimobranchial complex)	12.125	5.2	36	2,9,18,25							11.5		44				28–29		33		13.5		83	68h		12,88
Epiphysis — Pineal Gland																										
Pineal; epiphyseal evagination	14–14.5	9.5–10.5	52–60	1,2,4,9,18,23,25,129–134	11.5		77				11		44				32–38		60	33–48	13–17		60,77	52–64h	30–35	88
Adrenal Gland																										
Adrenal gland, cortical component; coelomic epithelium	12.5			10	11		10	18		10	10		10	23		10				34			10	3.25d	37–40	10,88
Adrenal gland, medullary component; migratory cells of neural crest and sympathetic ganglia	13.5	8.5	49–51	2,9,18,25,129–134							11–12.5		44							44	16		83	4–7d		88
Pancreas																										
Pancreas — dorsal	11–12.125	5.2	36	2,9,10,18,25,129–134	9.5		10	10		10	9.5		10	17.5		10	28–29		10,33	28			10	3d	35	10,88

Table 6.6 Comparative gestational milestones in endocrine system development (continued)

	Rat				Mouse			Rabbit			Hamster			Guinea Pig			Rhesus Monkey			Human				Chicken		
Description	**Age (d)**	**Size (mm)**	**Somites**	**Ref.**	**Age (d)**	**Somites**	**Ref.**	**Age (d)**	**Somites**	**Ref.**	**Age (d)**	**Somites**	**Ref.**	**Age (d)**	**Somites**	**Ref.**	**Age (d)**	**Somites**	**Ref.**	**Age (d)**	**Size (mm)[a]**	**Somites**	**Ref.**	**Age (d/h)**	**Somites**	**Ref.**
Pancreas — ventral	11.5–12.125	5.2	36	2,9,10, 18,25, 129–134	9.7		10	11.5		10	9.5		10				29–30		10,33	31–32			10	4d		10,88
Islets of Langerhans within pancreatic diverticula	13	8	46–48	2,9,18, 25,129 –134																8–9 wk	40–50		96, 117, 137	8–9d		88
Pancreas fused	13	8	46–48	2,9,10, 18,25, 129–134	11.5		10	14		10	11.5		10				35–36		10	40–44			10	6d		10
Thymus																										
Thymus	12.375 –12.5	6	39–40	2,9,10, 18,25, 129–134	12		10	12.5		10	8.75–9		10,44				*			30–40			10	6–8d		10,88
Thymus and parathyroid detaching from 3rd pouch	13	8	46–48	2,9,18, 25,129 –134							11.5		44								23		83			
Thyroid																										
Thyroid	10.5–12	2.4	13–20	2,9,10, 18,25, 129–134	8.5		10	9.5		10	8.5		10	16.5	23	10,57	28–29		10,33	24–27			10	40h	12	10,88
Thyroid shows open diverticulum from floor of mouth	11.75	4.2	29–31	2,9,18, 25,129 –134										17.5	29	57										
Vesicular ultimobranchial body (lateral thyroid) detaching	13	8	46–48	2,9,18, 25,129 –134	9.5	24±	136				12		44									20	136			
Ultimobranchial vesicles detached from pharynx	13.5	8.5	49–51	2,9,18, 25,129 –134																						

Parathyroid																									
Parathyroids	12.5	6.2	41–42	2,9,10, 18,25, 129	11		5,7,10				8.75–9		10,44							35–38			10	6–8		10,88
Parathyroids attached to left and right wings of thyroid	17–18	16–20		2,9,18, 25,129			5,7, 132																		
Hypophysis — Pituitary Gland																									
Rathke's pouch appears	10.5			10	8.5–9	23+	10,39	9.5		10	8.5		10	15.5	13	10,57	28–32		10,60	28–34			10,39, 60	50–52h	20	10,88
Neural hypophyseal evagination	11.5–11.75	4.2		10,12, 60	11.5		10,77	12		10	10		10	18.5		10	30–34		10,60	30–42	8–11		10,60, 77	3		10
Rathke's pouch closed off, connected to oral ectoderm	13.5–14	8.5	49–51	2,9,11, 18,25, 129	12		60				9		44	19.75	38	57					14		83			
Stalk of Rathke's pouch detached from stomodeal epithelium	15.5	14.3	64	2,9,11, 18,25,	12.5		138				12		44				36–42		60		19		138			
Pars intermedia thin-walled; pars distalis — trabecular and secondary vesicles					14		60										40–44		60	53–54	22–24		60			

[a] Crown-rump length.

Table 6.7 Comparative gestational milestones in respiratory system

	Rat				Mouse			Rabbit			Hamster			Guinea Pig			Rhesus Monkey			Human				Chicken		
Description	Age (d)	Size (mm)	Somites	Ref.	Age (d)	Somites	Ref.	Age (d)	Somites	Ref.	Age (d)	Somites	Ref.	Age (d)	Somites	Ref.	Age (d)	Somites	Ref.	Age (d)	Size (mm)[a]	Somites	Ref.	Age (d/h)	Somites	Ref.
Laryngotracheal groove	11	3.3	21–25	1,2, 9,18, 22–25										18–18.5		56						25	83	ca. 50–54h	23	88
2nd pharyngeal pouch	11	3.3	21–25	2,9,18, 25	8.75		7				8.5		44				24–26		33							
Primary lung diverticulum	11.5–12	3.8	26–28	2,9,10, 18,25	9.5–9.75	25±	7,10, 76	10.5		10	9		10	16		10	27		10	26–28	3.3		10,71, 76,84, 140–142	3d		10
Primary bronchi											9		44	18.5		56	29–30		33	29	4.5		71	96h		88
Trachea separated from esophagus	11.75–12.5	4.2	29–31	2,9,18, 25	11		76				9		44	16.5		56				29–32	6		71,76	96h		88
Secondary bronchi	12.75	7	43–45	2,9,18, 25	12		7,77							18.5		10				35–38	9		71,77			
Asymmetric lung buds; 3 bronchial areas in right lung bud	12.75–13	7	43–45	2,9,10, 18,25	10.5–11.5		10,76	12		10	9.5–10		10,44	18.5–21.5		10,56	29		10	32			10	NA[b]		10
Bucconasal membrane ruptured					13		60				15–15.25		60				36–42		60	48–51	16–18		60			
Major bronchial divisions	15.5			10	13		10	15		10	10.5–11		10,44	21.5		10,56	36		10	46			10	NA[b]		10
Palatal shelves uniting (Not all at the same stage of union)	17			10	15		10	19.5		10	12–12.5		10,44	26		10	45–46		10,33	57			10	NA[c]		10
Developing alveoli					16.5		139														85		139			

[a] Crown-rump length
[b] Pattern of avian lung development is different from that of mammals.
[c] In the chick, palatal shelves do not fuse.

Table 6.8 Comparative gestational milestones in nervous system development

	Rat				Mouse			Rabbit			Hamster			Guinea Pig			Rhesus Monkey			Human				Chicken		
Description	Age (d)	Size (mm)	Som-ites	Ref.	Age (d)	Som-ites	Ref.	Age (d)	Som-ites	Ref.	Age (d)	Som-ites	Ref.	Age (d)	Som-ites	Ref.	Age (d)	Som-ites	Ref.	Age (d)	Size (mm)[a]	Som-ites	Ref.	Age (d/h)	Som-ites	Ref.
Primitive streak	9			10	8		10	7.25		10	7		10	13		10	17		10	17			10	12h		10
Neural plate	9–9.5	1		1,2,4, 9,10, 18,23	7		5,7–10	8		10	7.5		10	13.5		10	20		10	18–19	1–1.5		10,39	1d		10
Elevated brain plate, neural folds	9.5	1.5	1–4	1,2,4, 9,11, 18,23				7.75–8.25	1–4	27				14.5	2	56				ca 19–20	1–2		115	23–26h	4	88
Neural crest for ganglia of IX and X; spinal flexure sometimes present	10	2	5–12	1,2,4, 9,18, 23																24±1	3–5		92,144	ca 45–49h	17	88
Trigeminal, neural crest component; neural crest at level of metencephalon	10	2	5–12	1,2,4, 9,18, 23							8.5	17–20	44											ca. 40–45h	13–14	88
Ganglia of VII and VIII; neural crest and posterodorsal epibranchial placode of first pharyngeal groove	10	2	5–12	1,2,4, 9,18, 23							8.5	17–20	44											ca 45h	15	88
Fusion of neural folds (early)	10.5—10.75			11,27				8.5–9	10–14	27	8.25	12–13	44	14–15		15,55				22–24	2–3.5	4–12	66–68, 71,73, 74, 79–82	26–28h	3–4	28
Anterior neuropore completely closed	10.5–10.75	2.4	17	1,2,4, 10,11, 18,23, 27	9d 1h	18±	5,7–9, 39	9–9.5		10, 27	8.5	17–20	10,44	15.25		10	25		10	24–26	2.5–4.9	13–20	10,39, 71,73, 83	2.3d		10
Otic pits; optic vesicles, and auditory pits appear	10.5–10.75			11,27	8d 22h	16	39	8.5–9	10–14	27	8.25	12–13	44									20	39			
Both neuropores closed — anterior first	10.5–11.5			10,11	9–9.5		10	9.5–10.5		10	8.5–9		10	15.25 –15.5		10	25–31		10	25–28			10			

Table 6.8 Comparative gestational milestones in nervous system development (continued)

	Rat				Mouse			Rabbit			Hamster			Guinea Pig			Rhesus Monkey			Human				Chicken		
Description	Age (d)	Size (mm)	Somites	Ref.	Age (d)	Somites	Ref.	Age (d)	Somites	Ref.	Age (d)	Somites	Ref.	Age (d)	Somites	Ref.	Age (d)	Somites	Ref.	Age (d)	Size (mm)[a]	Somites	Ref.	Age (d/h)	Somites	Ref.
Optic vesicle; optic pits	10.5–11	2	4–13	27,89				8.5–9	10–14	27, 99	8.5	17–20	44	15–16		56	21–23		33	24±	2.5–5	13–20	71,73, 92,144	29–33	7	86
Neural tube differentiates into the three primary brain vesicles; anterior neuropore closed	10.5–12	2.4	13–20	1,2,4, 9,10, 18,23	8		5,7–10	8.25–8.5		27	8.5	17–20	10,44	15–15.3		10,15	25–30		10,60	26±1	3.8–4.9		10,39	33–38	10	10,88
Five brain vesicles	11.5	3.8	26–28	1,2,4, 9,18, 23							8.75		44	17.5	29	56	30–33		60	33±	7–11		77, 144, 145			
Otic cyst and otic pit closed; endolymphatic appendage; deep cervical flexure	11.5–12			27	9.1–10	19±	39,60	10		99				16.75		56	28–30		60	28–32	4–6		39,60, 146			
Posterior neuropore closing	11			11	9.5	24±	76	9+		99							27		60	26±			76			
Thickened lens disc; lens placode					9.625	25±	76	11		99							28–29		33	28–35	5.4	38	76,84, 85			
Endolymphatic evagination					10		60				9		44	19		56	28–30		60							
Shallow olfactory pits					10		60	11–12		27, 99	9		44				28–30		33,60							
Posterior neuropore closes[b]	11.5–12			11,27	10.5		60	10		99	9		44				28–30		60	26–27	3–6	21–29	71,73, 76			
Cerebral hemispheres (early)	12–12.125	5.2	36	1,2,4, 9,10, 18,23	10	27±	5,7–9, 77	11		10, 99	9		10	17		10	29		10	29–33	5.5–9		10,73, 76,77, 144	3d		10,88
Pontine flexure	13.5	8.5	49–51	1,2,4, 9,18, 23	10.5		5,7–9, 60	10		99							30–33		60	35–38	7–9		60			
Vomeronasal organ					11.5		77													37±			77			

Formation of choroid plexus of lateral and fourth ventricles	13.5	8.5	49–51	1,2,4, 9,18, 23	12.5–13		5,7–9, 60,143				11		44				36–42		60	48–51	16–18		60,143			
Cerebellum	14			10	12		10	15		10	11		10	19		10	30–36		10,60	37			10	4.5d		10
Lens cavity crescentic; primitive lens fibers present; primordial semicircular ducts; primordial cochlear duct; nasal fin					12		60										34–36		60	42–44	11–14		60			
Superior and inferior colliculi separate					12.5		77													37±			77			
Earliest reflex responses observed																				41±1	18–23		144, 147, 148			
Neostriatum; telencephalic cortex																					~17		83	8–12d		88

[a] Crown-rump length.
[b] Posterior neuropore closes earlier in primates than in rodents.

Table 6.9 Comparative gestational milestones in the development of sense organs

Description	Rat				Mouse			Rabbit			Hamster			Guinea Pig			Rhesus Monkey			Human				Chicken		
	Age (d)	Size (mm)	Somites	Ref.	Age (d)	Somites	Ref.	Age (d)	Somites	Ref.	Age (d)	Somites	Ref.	Age (d)	Somites	Ref.	Age (d)	Somites	Ref.	Age (d)	Size (mm)[a]	Somites	Ref.	Age (d/h)	Somites	Ref.
Eye																										
Optic sulci	10	2		2	8.54	23±	39															14	39			
Optic vesicle forming	10.5		10	10	9.5	20±	10,39	9		10	8	10	10	15.5	13	10,56	23–25	10	10,33	21–24	2–2.8		10,74	26–33h		10,88
Optic bulbs	10.5	2.4		2		23±	39,60																			
Lens placode	11.5	3.8		2	10	24±	39,60				9.5		44				28–30		33,60	27–35	3.3–5.4		84, 149, 151		20–21	176
Invagination of lens placodes begins	11.75	4.2		2	10–10.5		60,76				9.25		44	17.5	29	56	28–32		60	27–32	4–7	30+	71,73, 76	48h		88
Extrinsic premuscle masses appear																				31–44	4.3–14		152			
Lens vesicle forming; choroid fissure	12.125 – 12.375	5.2–6		2							10		44	16.5		56	35–38		60					48h		88
Lens separated	12.5	6.2		2,10	11.5		10	11.5		10	10		10,44	18		10	32		10	35–37	6		10,84, 149, 151, 153, 154	2.5d		10
Primordium of hyaloid artery	12.5	6.2		2							10		44							35–37	6		84, 149, 151, 153, 154			
Lens vesicle closed	13–14	6.2		2,11, 27	11–11.5		60							19.75		56	32–34		60	34.5	7–9		71			
Definite retinal pigmentation					11–12	25±	39,60	14–15		27, 57							30–36		60	33–44	7–14	25	39,60, 73,77, 84	3–3.5d	40–43	86,88
Differentiation of retina																				42–44	12–14		84, 149, 151	100h		88
Choroid fissure fusing; hyaloid canal	13.5	8.5		2	12		149				15–15.25		60				34–36		60	42–44	14.5		60,149			

Optic nerve fibers present	14	9.5		2,10	13		10	15		10	11		10	21.5		10	39		10	46–48	14.6–15.6		10,84, 149, 151	4d		10
Differentiation of cornea					13		60				15–15.25		60				36–42		60	48–51	16–18		60,84, 149, 151			
Anterior chamber differentiating	15	12		2	14		9										40–44		9	53–54	22–24		60	6d		88
Ciliary body differentiation; primordium of choroidea sclera																				56–70	26–45		84, 149, 151	8d		88
Ear																										
Otic placodes	10	2		2	8.54	23±	39													27		14	39			
Otic cups	10.5	2.4		2,11		23±	39																			
Otic vesicle forming	11.5			10	8.5–8.75	13	10,39	9		10	8.5		10	15.5	13	10,56	25		10	21–29	2–6		10,73, 146	2.3d		10
Otocyst (closure)	11–11.5	3.3–3.8		2,11		24±	39				9		44				29		33	30	4	17	39,146	11d	12	88
Otic vesicles with short endolymphatic duct	11.75	4.2		2	10.5		76													29–32	5–7	29±	73,76			
Endolymphatic sac appears pinched off from otic vesicle	12–13			11,27	11		77										30		33	33–37	6.5		77, 146, 155			
Thickened, hollow epithelial primodia of semicircular canals					11.5		77													38–44	8–13	35±	77, 155, 156			
Cochlear and vestibular regions	12–13	6.2		2,27	11–11.5		60										30–34		60	35–42	7–9		60			
Separation of utricular and saccular regions	12.5	6.2		2	14.5		150														33		150	6–7d		88
Cochlea appearing	13.5			10	12		10	13		10	10		10	20.5		10	37		10	44			10	7d		10

Table 6.9 Comparative gestational milestones in the development of sense organs (continued)

Description	Rat				Mouse			Rabbit			Hamster			Guinea Pig			Rhesus Monkey			Human				Chicken		
	Age (d)	Size (mm)	Somites	Ref.	Age (d)	Somites	Ref.	Age (d)	Somites	Ref.	Age (d)	Somites	Ref.	Age (d)	Somites	Ref.	Age (d)	Somites	Ref.	Age (d)	Size (mm)[a]	Somites	Ref.	Age (d/h)	Somites	Ref.
One or more semicircular canals formed	14	9.5		2	12		77										34–36		60	44–48	13.5–15	37±	77,84, 146, 149, 151, 155, 156	5–6d		88
Condensations of ocular muscles	14	9.5		2																						
Otic capsule cartilaginous	15			10	14.5		10	20		10	11		10	22		10	42		10	56			10	8d		10
Ocular muscles innervated	15	12		2																				6d		88
Ossification of anterior process of malleus																				56–70	28		160, 161			
Olfactory																										
Olfactory placodes	11–11.5	2–3.8	4–13	2,89	10	24–27	39,76				8.75		44				28–29		33	28–31	7–9	17–25	39,76, 77, 157, 158		28	88
Olfactory pit	12.125	5.2–5.6		2	10.5–11		60,76							18.5		56	30–33		60	33–38	7–8	29±	73,76, 84, 141, 159	52–64h	29–32	88
Olfactory nerve; olfactory epithelium	12.5	6.2		2		27±	39																	4–6d		88
Olfactory bulbs	13.5			10	11		10	14		10	11		10	23		10	38		10	37			10	7d		10
Partly cartilaginous nasal septum and capsule	15	12		2																				6d		88

[a] Crown-rump length.

Table 6.10 Comparative gestational milestones in muscular, skeletal, and integumentary system development

Description	Rat				Mouse			Rabbit			Hamster			Guinea Pig			Rhesus Monkey			Human				Chicken		
	Age (d)	Size (mm)	Somites	Ref.	Age (d)	Somites	Ref.	Age (d)	Somites	Ref.	Age (d)	Somites	Ref.	Age (d)	Somites	Ref.	Age (d)	Somites	Ref.	Age (d)	Size (mm)[a]	Somites	Ref.	Age (d/h)	Somites	Ref.
Muscular System																										
Primitive streak	9			10	8		10	7.25		10	7		10	13		10	17		10	17			10	0.5d		10
First pharyngeal arch	10	2	5–12	1–4,6, 9	8–8.5		5,7–9	9.5		27										23	10		83			
Ten-somite stage	10.5		10	10	8.5		10	8.5	10	10	8	10	10	15	10	10	23	10	10	25		10	10	1.5d	10	10
Pharyngeal arches I and II, clefts I and II								9.5–9.75		27	8.5	17–20	44							24–27	3.3	13–20	9,71, 83–85, 91	2–3d	22	86,87
Anterior limb bud	11	3.3	21–25	1–4,6, 9	9.5–9.75	23±	5,7–9, 39	10.5–11		27, 57	8.75	17–20	42,44, 46,47	16.5	23	56	25–26		46	26	3–5	21–29	39,73	51–56h	26–28	30,86
Three pharyngeal arches	11.5	3.8	26–28	1–4,6, 9	10		5,7–9, 60	9.75		27	8.75		44	16.5	23	56	28–30		60	28–32	4–6	21–24	60,84, 92,166	53–55h	24–27	86,87
Hind limb bud[b]	11.5–12	3.8	26–28	1–4,6, 9,10	10–10.3		5,7–9, 10	11–12		10, 27, 57	9		44	17.5–18.5	29	10,56	28–30		10,60	28–32	4–6	30–32	9,10, 60,71, 73,84, 85	2.2–3d	29–32	10,86
Appearance of 4th pharyngeal arches	11.75	4.2	29–31	1–4,6, 9	10.25		5,7–9	9.75–10.5		27	9		44	16.5	23	56	28–29		33	32	4.6–5	33–34	83,84	3.5d	43–44	86
Maxillary processes meet nasolateral and medial processes	12–13	7	43–45	1–4,6, 9,27				9	12–13	27	9.25		44				37–38		33	42–45	12–13		83	23–26h	4–5	88
Subdivision of forelimb bud	12.75–14	7	43–45	1–4,6, 9,27	10.5		60	12–13		27	10.5		44	20.75	39	56	30–32		60	31–35	5–7		60			
Cervical sinus obliterated	13–13.5	8–8.5	46–51	1–4,6, 9,18, 25	12		5,7–9	13–14		27	10		44	23.75		56	33–34		33	40–44	8–15		83,84			
Digital rays (forepaw)	13.5–14			3,4,10, 27, 29–32	12.3		7,10, 29,40	14.5		10, 27, 29	10.25–11		10,42, 44,48	22–23.75		10,56	34–35		10,46	35–37	8–11		10	4.75d		30,86
Pleuroperitoneal canal closed; complete diaphragm	15	12	61–63	1–4,6, 9										26		56					20		83			

Table 6.10 Comparative gestational milestones in muscular, skeletal, and integumentary system development (continued)

Description	Rat				Mouse			Rabbit			Hamster			Guinea Pig			Rhesus Monkey			Human				Chicken		
	Age (d)	Size (mm)	Somites	Ref.	Age (d)	Somites	Ref.	Age (d)	Somites	Ref.	Age (d)	Somites	Ref.	Age (d)	Somites	Ref.	Age (d)	Somites	Ref.	Age (d)	Size (mm)[a]	Somites	Ref.	Age (d/h)	Somites	Ref.
Skeletal System																										
Subdivision of forelimb bud	12.75–14	7	43–45	1–4,6,9,27	10.5		60	12–13		27	10.5		44	20.75	39	56	30–32		60	31–35	5–7		60			
Subdivision of hindlimb bud					11		60										30–33		60	37	8–11		73			
Mesenchymal condensation for ribs					12		162				10.5		44							31–33			162	5d		88
Auditory ossicles; mesoderm above dorsal extremity of tubotympanic cavity											11		44											5–6d		88
Digital rays (forepaw)	13–14.5	8.5	19–51	1–4,6,9,10,11,27	12–12.5		5,7–9,10,60	14.5		10	11–14		10,44,60	22		10	34–38		10,60	37–48	11–17		10,60,73,84,121	4.75d		10
Anlagen of centra and neural arches	14	9.5	52–55	1,2,9,13–15,17–22							9.5		44	18.5	31	56				28			167			
First sign of elbow					13		60										36–42		60	48–51	16–18		60	4.5–5d		86
Distinct finger rays; rim of hand plate crenated; primitive palatine processes					13		60				14		60				35–38		60	44–48	13–17		60			
Chondrification centers in ribs					13		162				11		44	23.75		56					15		162			
Primordial Meckel's cartilages					13		60				14		60				35–38		60	44–48	13–17		60			
Interdigital notches in hand plate	15–15.5			27	13.5		77	16–17		27							36–42		60	37±			77			
First sign of wrists					14		60										40–44		60	53–54	22–24		60			

Distal phalanges of fingers separated	16.5–17			11	14		60										40–44		60	53–54	22–24		60			
First seven ribs chondrified and in contact with sternum					14.5		162														30–35		162			
Digital separation of hindpaws	15.5–16.5			27													40–44		60	45	16–18		60			
Complete separation of digits of forelimb	16.5–17			11,27				17–17.5		27							46–50		60	56–60	27–31		60			
Palatal folds uniting (not all at the same stage of union)	17–18			1–4,6, 9,10, 11	15–16.5		5,7–9, 10	19.5		10	12		10	26		10	44–48		10,60	54–57	23–28		10,60	NA[c]		
Primary ossification center in humerus with trabeculae					15.5		123										43–44		33		50		123			
Ossification centers present in all ribs					15.5		163														68		163			
Integumentary System																										
Milk line appears	12.125–13	5.2–8	8–36	1–4,6, 9, 13–15, 17–22	12		5,7–9	14–15		27	10		44	21.75		56					7		83			
Nasolacrimal groove	13–14			27	11.5		60										30–34		60	37–42	8–11		60			
Periderm present					12		164														16		164			
Skin differentiated into stratum germinativum and stratum intermedium					13.5		165														22		165			

Table 6.10 Comparative gestational milestones in muscular, skeletal, and integumentary system development (continued)

	Rat				Mouse			Rabbit			Hamster			Guinea Pig			Rhesus Monkey			Human				Chicken		
Description	Age (d)	Size (mm)	Somites	Ref.	Age (d)	Somites	Ref.	Age (d)	Somites	Ref.	Age (d)	Somites	Ref.	Age (d)	Somites	Ref.	Age (d)	Somites	Ref.	Age (d)	Size (mm)[a]	Somites	Ref.	Age (d/h)	Somites	Ref.
Stratum granulosum					15.5		164														60		164			
Vibrissary papillae appear on maxillary process	14–14.5	9.5	52–55	1,2,9,11,13–15,17–22,27				14–15		5,7,8,27	10.5		44	23.75		56								N/A		
Hair follicle primordia appearing											12		44													
Distinct auricular hillocks	14–14.5	9.5	52–55	1–4,6,9,27	11.5		60	14–15		27	14		60				32–34		33,60	37–48	8–17		60,73	N/A		
Eyelids — small ectodermal folds	15	12	61–63	1,2,9,13–15,17–22	13		5,7–9,60,154				15–15.25		60				36–42		60	48–51	16–18		60,154			
Feather germs (chick)																								6.5–7d		86
First trunk hair papillae appear	15.5–16.5			11,27				17.5–18.75		27	12.5		44											NA		

[a] Crown-rump length.
[b] Hindlimb bud forms earlier in the rodents than in primates.
[c] In the chick, palatal folds do not fuse.

Table 6.11 Comparative gestational milestones in excretory system development (continued)

Description	Rat				Mouse			Rabbit			Hamster			Guinea Pig			Rhesus Monkey			Human				Chicken		
	Age[a] (d)	Size (mm)	Somites	Ref.	Age (d)	Somites	Ref.	Age (d)	Somites	Ref.	Age (d)	Somites	Ref.	Age (d)	Somites	Ref.	Age (d)	Somites	Ref.	Age (d)	Size (mm)[a]	Somites	Ref.	Age (d/h)	Somites	Ref.
Intermediate mesoderm thickens nephrogenic cord	10	2	5–12	2,9, 112, 113	8.75		7				7.75		44	15.5	13	56				22	2.1		71			
Pronephros appears	10			10,26																22			10,26	1.4–1.5d		10,26
Ten-somite stage	10.5	10		10	8.5	10	10	8.5	10	10	8	10	10	15	10	10	23	10	10	25		10	10	1.5d	10	10
Nephrogenic cord with mesonephric tubules and duct	11	3.3	21–25	2,9, 112, 113	8d 21h–9.5	15–24	5,7–9, 38,79				8.75		44	16.5		56				25–28	3.5	10	71,79	1.75d		30,86
Mesonephros appears	11.5		10	10,26	9.5		10,26													24–25	3.5	10	26,38	2.3–3d	10	10,26
Kidney: mesonephric duct enters urogenital sinus or cloaca	11.75–12	4.2	29–31	2,9,10, 26, 112, 113	11		5,7–9, 10, 26,76	11.5		10	9–9.5		10,44	17.5–19	29–35	10,56	28–29		10,33	28±	4.5		10,26, 71,76	3d		10
Primitive mesonephric tubules, mostly solid; Wolffian duct discontinuous	11.75–12.125	4.2–5.2	29–36	2,9, 112, 113										17.5–21.75	29–35	56				28	3.5		71	1.75d	19–32	88
Germinal epithelium (testis) appearing	12			10,26	11.5–12.5		10,26	13		10	9		10				33–34		10	38–40			10,26	4d		10,26
Kidney: ureteric bud	12.3			26	11–11.5		76,114	11.5		10	9.25–9.3		44	19–20	35	56	29–30		33	28–29			26,76	4d		114
Urorectal septum dividing cloaca	12.375–17	6–6.2	39–42	1,9,10, 18, 22–25, 112, 113				15		10	9.5		10							28–48			10			
Ureteric bud with metanephric "cap"	12.5			2,9,10, 26, 112, 113				13		10	9.5		44	21		10	31–32		10	32	6		10,26, 71	5d		10

Table 6.11 Comparative gestational milestones in excretory system development (continued)

	Rat				Mouse			Rabbit			Hamster			Guinea Pig			Rhesus Monkey			Human				Chicken		
Description	Age[a] (d)	Size (mm)	Somites	Ref.	Age (d)	Somites	Ref.	Age (d)	Somites	Ref.	Age (d)	Somites	Ref.	Age (d)	Somites	Ref.	Age (d)	Somites	Ref.	Age (d)	Size (mm)[a]	Somites	Ref.	Age (d/h)	Somites	Ref.
Kidney: metanephros	12.5–12.8			10,26	11		10	23		10	10		10	23		10	38–39		10	35–37			10,26	6d		10,26
Paramesonephric duct appears	13.5	8.5	49–51	2,9,10, 26, 112, 113	10		5,7–9, 10,26	15		10	11		10,44	23.75		56	35–36		10	42–44			10,26	4d		10,26
Testes histologically differentiated	13.5			10,26, 114	12		10,26	16.5		10, 26	12		10,26	26		10, 26	36–39		10,26	46–48			10,26	13d		10,26
Paramesonephric duct reaches cloaca	15.5			10,26	14		10	20		10	13		10	26		10	37–38		10	49–56			10,26	7d		10
Rectum and urogenital sinus completely separated	17	16		2,9, 112, 113							15		44							43			59	N/A		

[a] Crown-rump length.

Table 6.12 Comparative gestational milestones in reproductive system development

Description	Rat				Mouse			Rabbit			Hamster			Guinea Pig			Rhesus Monkey			Human				Chicken		
	Age[a] (d)	Size (mm)	Somites	Ref.	Age (d)	Somites	Ref.	Age (d)	Somites	Ref.	Age (d)	Somites	Ref.	Age (d)	Somites	Ref.	Age (d)	Somites	Ref.	Age (d)	Size (mm)[a]	Somites	Ref.	Age (d/h)	Somites	Ref.
Primitive streak	9			10	8		10	7.25		10	7		10	13		10	17		10	17			10	0.5d		10
Germ cells in yolk–sac epithelium	9.5–10	1.5–2	1–12	1–4,6, 9,18, 112, 131, 134, 168–171	8–8.5		5,7–9													27	3.3	13–20	9,84, 85,91			
Pronephros appears	10			114																22			114	1.4–1.5d		10,26
Ten-somite stage	10.5			10	8.5	10	10	8.5	10	10	8	10	10	15	10	10	23	10	10	25			10	1.5d	10	10
Germ cells in mesentery	10.5–11.5	2.4–3.8	13–28	1–4,6, 9,18, 112, 131, 134, 168–171	9.5		5,7–9													29	3.8	25–27	84,85, 116			
Mesonephros appears	11.5			114	9.5		114													24			114	3d		114
Germ cell migration reaches borders of mesonephric ridges	11.75	4.2	29–31	2,9,18, 112, 131, 134, 168–171										20.75	39	56				31	4.3	30–32	9,84, 85			
Germinal epithelium	12			10, 114	11.5–12.5		10,114	13		10	9		10				33–34		10	38–40			8	3–4d	38	10, 88, 114
Mesonephric duct enters urogenital sinus	12			10, 114	11		76,114	11.5		10	9.25–9.3		10,44	19	35	10,56	28–29		10,33	28	4.5		10,26, 71,76, 114			
Indifferent gonadal folds; rapid increase in number of germ cells	12.125	5.2	36	2,9, 112, 113													33–34		33							
Germ cells in genital ridges, end of migration	12.75	7	43–45	2,9,18, 112, 131, 134, 168–171																35–37	6		9,84, 121, 174			

Table 6.12 Comparative gestational milestones in reproductive system development (continued)

Description	Rat				Mouse			Rabbit			Hamster			Guinea Pig			Rhesus Monkey			Human				Chicken		
	Age[a] (d)	Size (mm)	Somites	Ref.	Age (d)	Somites	Ref.	Age (d)	Somites	Ref.	Age (d)	Somites	Ref.	Age (d)	Somites	Ref.	Age (d)	Somites	Ref.	Age (d)	Size (mm)[a]	Somites	Ref.	Age (d/h)	Somites	Ref.
Paramesonephric duct appears	13.5	8.5	49–51	2,9–10, 112–114	10		5,7–9, 10,114	15		10	11		10,44	23.75		56	35–36		10,33	42–44			10,114	4d		10, 88, 114
Gonads begin sexual differentiation	13.5	8.5	49–51	2,9,18, 25, 129–134																	17		83			
Histologic differentiation of testes	13.5–14.5	10.5	56–60	2,9,18, 112, 114, 131, 134, 168–171	12.5		5,7–9, 172				12		11,173				38–39		33	46–48	14–16		85, 114, 16,175	5.5d		114
Gonad, rete cords; in stroma between genital primordium and mesonephros					12.5		172							21.75		56					17		83	5d		88
Oogonia; germ cells in secondary sexual cords of ovarian cortex	14.5	10.5	56–60	2,9,18, 112, 131, 134, 168–171																	17		83	7–8d		88
Paramesonephric ducts reach urogenital sinus	15.5	14.2	64	2,9,18, 112, 114, 131, 134, 168–171																49–56			114	7d		88
Indifferent external genitalia	19			10																37			10			
Differentiation of male and female external genitalia																				56–70	26–45		9,66, 84,121			

[a] Crown-rump length.

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