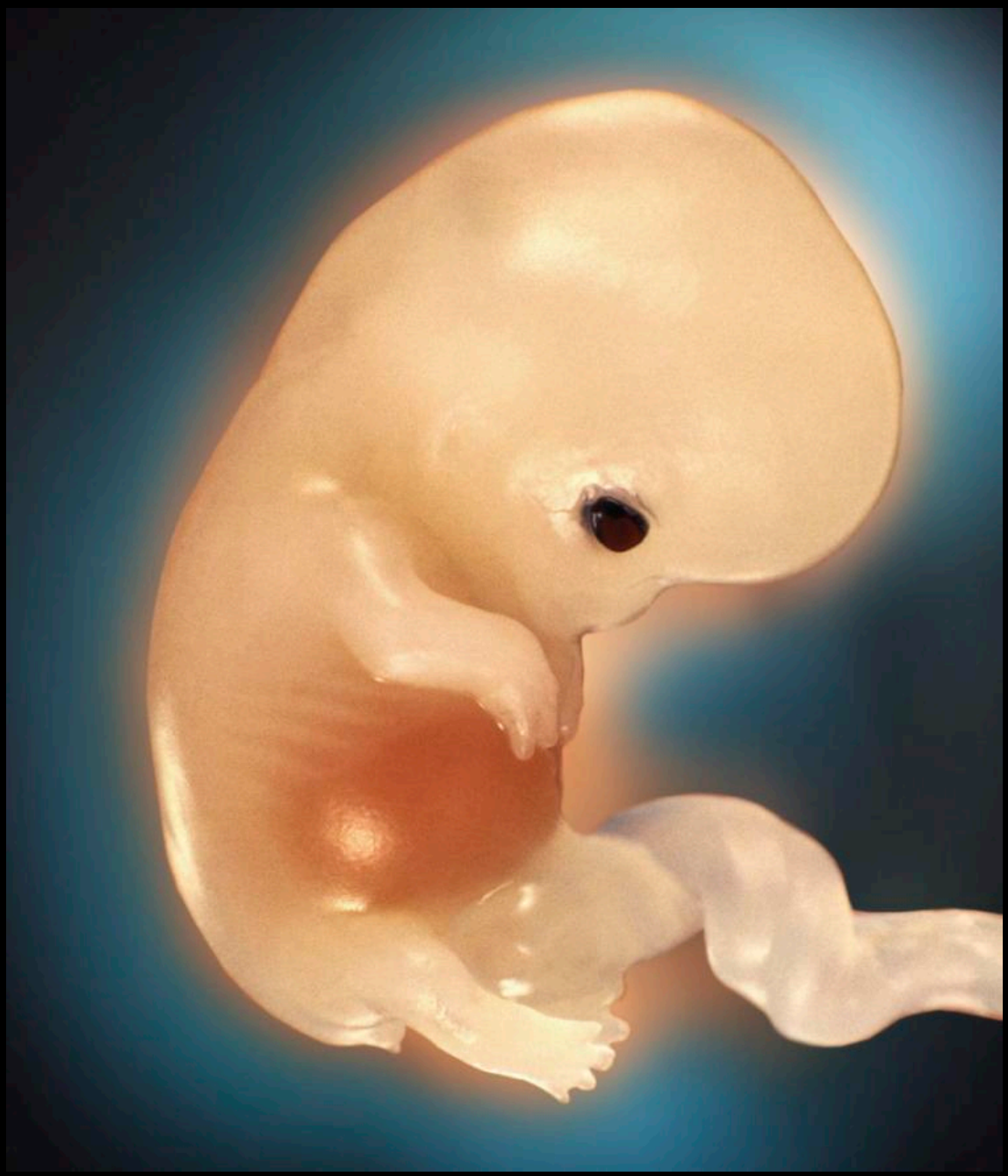


Table 1: Human embryonic Development in weeks 1–8

Age (days)	
1	oocyte fertilization
2–3	morula (4–16 cells)
4	free blastocyst
5–6	attachment of blastocyst to endometrium
7–12	implantation • bilaminar embryo with primary yolk sac
13–15	trilaminar embryo with primitive streak • chorionic villi
16	gastrulation • formation of notochordal process
18	Hensen's node and primitive pit • notochord and neurenteric canal • appearance of neural plate, neural folds and blood islands

Embryological Development OF THE Musculoskeletal System

Bob Caruthers, CST, PhD

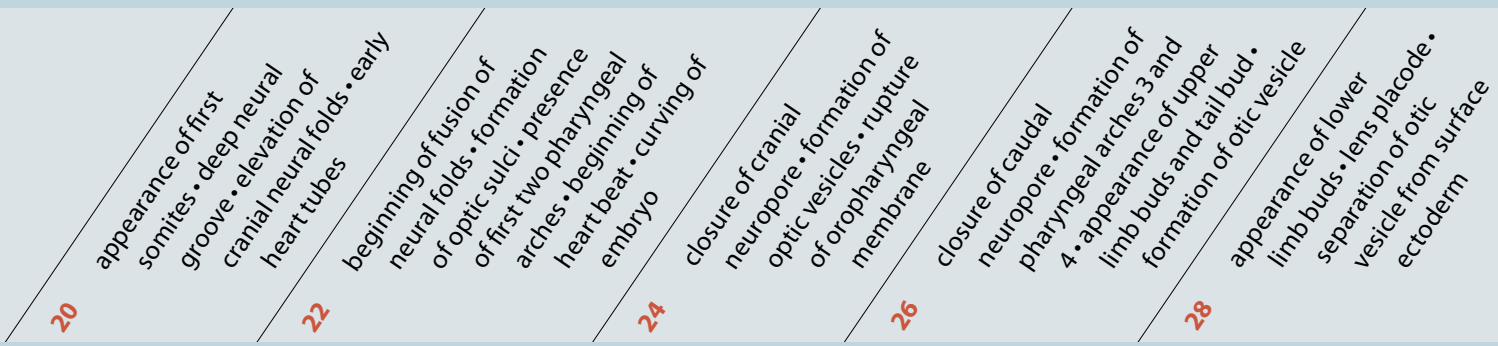
In the first eight weeks of development, incredible changes take place that define the structure of the human embryo (Table 1). This article will provide an overview of the development of the musculoskeletal system.

Skeletal tissue derives from mesenchymal cells, originating in different regions of the body, and may form connective tissue, blood, bone and cartilage. One of the common features of mesenchymal cells, precursors of skeletal formation, is their tendency to be displaced some distance from their point of origin. Mesenchymal cells differentiate into osteoblasts and chondroblasts. Osteoblasts and chondroblasts produce different extracellular macromolecules. The end result of this process is bone and cartilage, two types of connective tissue that are related but significantly different.[1,2,3,6]

Intraembryonic mesoderm

The vast majority of the musculoskeletal system derives from intraembryonic mesoderm, which forms from the epiblast during the process of gastrulation. Gastrulation is the process by which the germ layers are formed through cell movement. The three primary germ layers are the ectoderm (outer layer), mesoderm (middle layer), and endoderm (inner layer).[6] Shortly after formation, the mesenchymal cells spread laterally as a continuous layer between the ectoderm and endoderm, dividing into three regions:

- Paraxial mesoderm (somites)—paired segments (somitomeres) lying along the primitive node. At approximately 20 days, somitomeres begin to transform into somites (solid masses of paraxial mesoderm). These will further develop into the vertebral column and muscles.[6]



- Intermediate mesoderm—a small cord of cells lateral to the somites which forms about day 22. These cells develop into the urogenital system and its related structures.
- Lateral mesoderm—differentiates into somatic (dorsal layer) and splanchnic (ventral layer) mesoderm. The somatic mesoderm contributes to the musculature of the body wall and the limbs. The splanchnic mesoderm develops into the mesentery and walls of the digestive tract.[1,3,6]

Somites develop through a transformation process in which blocks of segmented cells with mesenchymal morphology are changed into a sphere of epithelial cells. This sphere of epithelial cells remains within the paraxial mesoderm. This process is initiated by a signal from the overlying ectoderm. The epithelial somites divide into two structures. The ventral half becomes the sclerotome and the dorsal half, the dermomyotome. The sclerotome forms the vertebral bodies and their associated connective tissue elements. The dermomyotome further splits into two layers, the myotome and the dermatome, which form the dermis, connective tissues and skeletal muscles. A majority of the axial musculoskeletal system arises from the sclerotomes, and the rest of the musculoskeletal system develops from the limb bud mesenchymal cells and lateral somatic mesoderm.[6]

Chondrogenesis and osteogenesis

Chondrogenesis refers to the development of cartilage, and osteogenesis to the development of bone. Cartilage formation begins with the appearance of centers of chondrification of the axial skeleton and limb buds. The initial change appears as an area of mesenchymal condensation but chondroblasts in the centers of chondrification quickly begin to secrete an extracellular matrix that is characteristic of cartilage. The chondroblasts themselves are trapped in the matrix they secrete. Once ensnared, they are called chondrocytes and begin to form cartilage.[6]

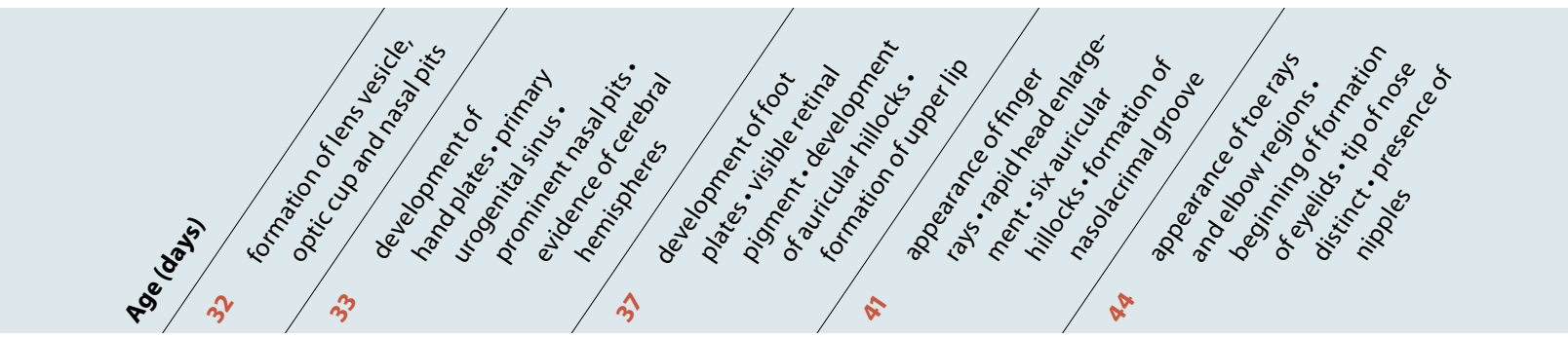
Mature cartilage growth occurs by two means: cell division within the cartilage and the addition of newly differentiated cells onto the outer surface. The first type of growth is called interstitial growth, and it is essential to the growth in length and width of bones. The second type is called appositional growth.

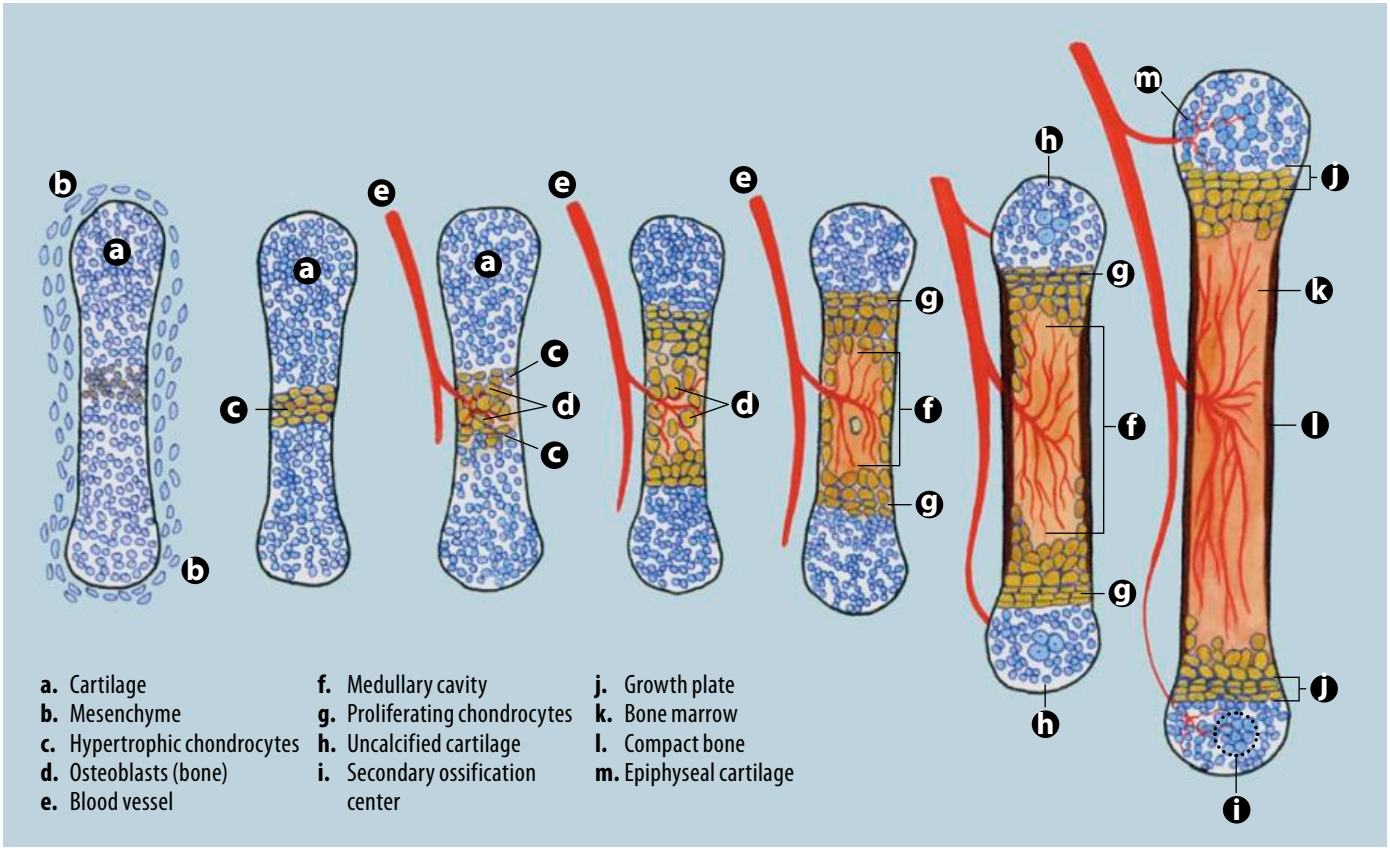
Osteogenesis occurs through a different process. Mesenchymal cells differentiate into osteoblasts. Osteoblasts secrete an extracellular organic matrix, called osteoid, that is later mineralized into bone. Osteoblasts, like chondroblasts, become entrapped in the secretion products and are called osteocytes.[6]

Intramembranous versus endochondral ossification

Bones are formed through two processes: Intramembranous ossification and endochondral ossification. Intramembranous ossification is the process by which most of the flat bones of the jaw and skull (excluding the base) are formed. Intramembranous ossification requires no preexisting cartilage. These bones form from and replace an embryonic membrane of connective tissue. A periosteum develops in the surface of this bone, forming osteoblasts which continue the ossification process. There is a close association with blood vessels in this process.[3,6,7,8]

While these bones are not commonly of concern in orthopedic surgery, a brief outline of the process follows:

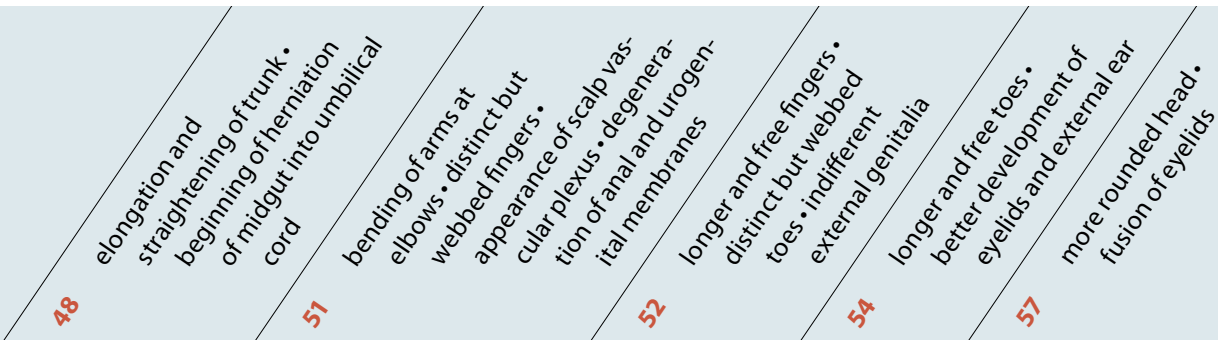




- Condensation of mesenchymal cells occur in close association with blood cells. Osteoprogenitor cells differentiate into osteoblasts, and the osteoblasts secrete osteoid.
- The osteoid is rapidly mineralized, and spicules of bone begin to grow around the blood vessels.
- The growing spicules merge creating large spongy networks of trabeculae which contain bone lamellae and entrapped osteocytes.
- The trabeculae thicken with the addition of new layers of bone on the outer surface.
- Osteoprogenitor cells on the outer surface continue this cycle until the bone reaches its final size, at which time the osteoblasts revert to osteoprogenitor cells.[3,6,7,8]

Endochondral ossification requires the presence of preexisting cartilage which is utilized as a temporary structure. The cartilage is partially degraded prior to bone formation. This type of ossification accounts for the formation of the long bones of the extremities, vertebral column, bones of the pelvis and the bones forming the base of the skull. These bones are sometimes referred to as cartilage bones, because cartilaginous models appear in the embryo. The process of endochondral ossification will be presented in

FIGURE 1: During endochrondal ossification, existing cartilage provides a framework for developing bone.



Adapted from Carlson BM. Human Embryology and Developmental Biology, 2nd ed. St Louis: Mosby; 1999.

steps, but many of the steps temporarily coexist with other steps.[3,6,7,8]

The formation of a cartilage model initiates the process of endochondral ossification. This cartilage model provides a type of framework for the developing bone. (Figure 1)

An area of cartilage, called the perichondrium, is surrounded by a dense connective tissue capsule. The inner layer of the perichondrium contains a layer of chondroblasts that secretes cartilage matrix, entraps and become chondrocytes.

In the diaphyseal region of the cartilage model, the perichondrium differentiates into a layer of osteoprogenitor cells which become osteoblasts and secrete osteoid around the cartilage model. The osteoid calcifies quickly forming a kind of collar around the cartilage model. The cells in the center of the cartilage model hypertrophy and then degenerate. This action leaves a cavity in the center of the developing bone.[6,7,8]

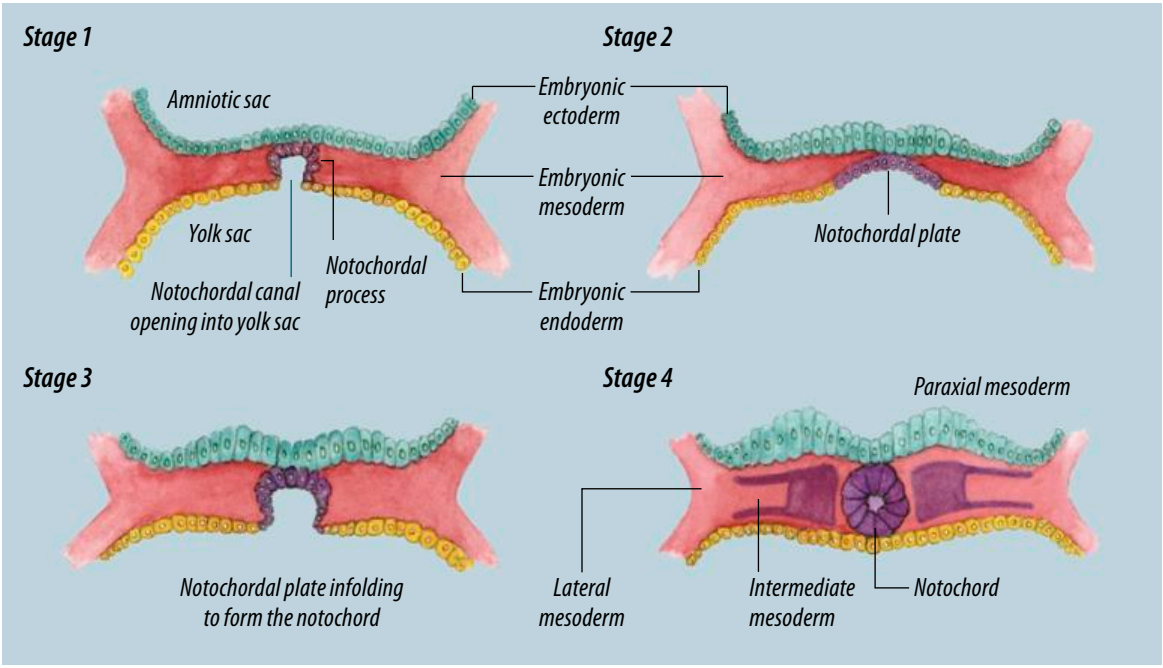
A vascular bud, assisted by osteoclasts, makes a hole in the bony collar and invades the cavity formed by the degeneration of the central cells of the cartilage model. The cavity is rapidly filled by hematopoietic stem and osteoprogenitor cells, both of which are derived from mesenchymal cells. This action establishes a marrow cavity inside the growing bone. The blood vessels proliferate toward the ends of the bone, enlarging the marrow cavity. The bony collar increases by the process of appositional growth.

At the ends of the bones, the cartilage continues to proliferate, hypertrophy, and degenerate resulting in calcified cartilage. This cartilage changes into bony spicules, leading to the formation of spongy (cancellous) bone. New vascular buds may secondarily invade the epiphyses, thereby reinitiating the cycle of cartilage degeneration, ossification and spongy bone formation.[3,6,7,8]

It is important to remember that cartilage remains at the epiphyseal plate in children with growing bones. The cycle of proliferation, hypertrophy, degeneration and cartilage calcification continues in children and adolescents. (The epiphyseal plate becomes inactive and ossifies when adult stature has been reached.) Cartilage remains on the articular surfaces of bones throughout life.

An inactive and closed epiphyseal place does not preclude all bone growth, however. Growth in length is prohibited but growth in diameter can continue through the process of appositional growth. Surface bone can be modified by new bone formation, spongy bone can change in response to several factors, and bones can respond to fractures.[3,6,]

FIGURE 2: Development of the notochord.



Axial skeleton

The term axial skeleton refers to the skeletal elements that develop along the long axis of the embryo. These elements are the vertebral column, ribs, sternum and skull. The notochord, the first component of the axial skeleton to form (about 3.5 weeks), extends cephalad to the prochordal plate (Figure 2).[6] The notochord represents those components that will develop into the vertebral column and base of the skull.[1]

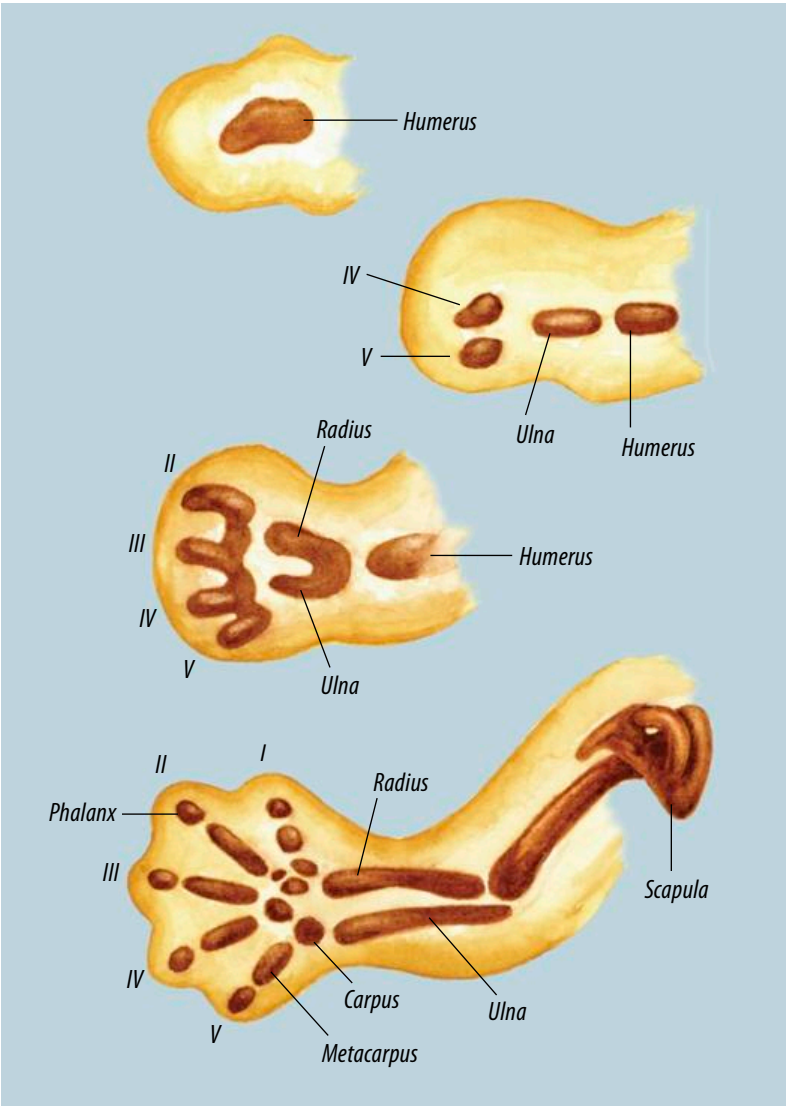
As stated, most of the skull and facial bones develop by intramembraneous ossification. Somites soon appear followed by rapid cell division. Each somite forms a cavity known as a myocoele. Cells in the sclerotomal portion of the somite migrate away from the myocoele and disperse around the notochord and neural tube. The vertebral bodies develop from the somite sclerotome. Cells migrate cephalad and caudad to form a specific vertebral body. The notochord degenerates where the vertebral bodies form but remains in the gaps between the vertebrae.[1,6]

Mesenchymal cells migrate dorsally and laterally away from the vertebral bodies to form rudimentary vertebral arches and costal processes. Both the vertebral processes and the motor nerves retain a segmented arrangement. Sensory nerves passing to the skin are also segmented and produce the characteristic dermatomes used in neurological evaluation.[1]

Somites contribute to the intercostal muscles and the muscles that flex and extend the vertebral column. Intervertebral disks derive from the rostral half of the sclerotome in the somites. The spaces between vertebral bodies are packed with mesenchymal cells that differentiate into fibroblasts and chondrocytes. These cells ultimately form the annulus fibrosus, while notochordal cells become the nucleus pulposus.[1,6]

Four developmental variations occur in the vertebrae that are important functionally and, at times, clinically:

- The first cervical vertebra has an unusually large central foramen to accommodate the spinal cord emerging from the foramen magnum.
- Thoracic vertebrae have large costal processes that form the ribs.
- Lumbar vertebrae form large vertebral bodies in order to withstand the forces of weight bearing.
- The costal processes of the sacral vertebrae fuse.[1,3]



Adapted from Carlson BM. Human Embryology and Developmental Biology. 3rd ed. Philadelphia: Mosby; 2004: 223.

FIGURE 3: Formation of the skeleton in the mammalian forelimb.

Appendicular skeleton

The bones of the upper and lower limbs are referred to as the appendicular skeleton. The appendicular skeleton develops from mesenchymal elements in the limb buds. Limb buds have three components: a core of mesenchyme, a cover of ectoderm, and a cap called the distal apical ectodermal ridge. The apical ectodermal ridge has the ability to induce differentiation.[1,5]

The limb buds form in a somatic mesoderm at four weeks. Forelimb buds appear first and

develop faster than hindlimb buds. The bones of the appendicular skeleton are formed by the process of endochondral ossification. By the fifth week, the forelimb buds have elongated slightly and soon divide into arm, forearm and hand components (Figure 3). Hands with partially separated fingers are evident by the beginning of the seventh week. Individual fingers and toes are visible by the eighth week. Digital separation occurs through a process of controlled cell death. Long bone development occurs by the process previously described.[1,5,6]

Joints

Joint development must be accounted for in two major categories based on mobility. The joints with limited mobility, called synarthroses, are formed from mesenchymal cells that arise between developing bones and differentiate into connective tissue.[1]

Diarthroses (ie synovial joints with considerable mobility) are typically found in the appendicular skeleton, but occur in the axial skeleton (eg the temporomandibular joint). Cartilage models in the limb bud contain mesenchymal cells that lie between the areas of cartilage. These mesenchymal cells differentiate into joint capsule fibroblasts. Spaces appear between the mesenchymal cells and join to form a cavity in the joint. The cartilage models, themselves, undergo ossification, except at an area on the articular surfaces, where a sheet of hyaline cartilage remains throughout life. The fibroblasts around the joint differentiate into synoviocytes at approximately the same time that the surrounding mesenchymal cells change into blood vessels, ligaments, and layers of synovial cells that line the joint cavity.[1]

Muscle development—skeletal muscle

There are three types of muscle: smooth, cardiac, and skeletal (Table 2). Some mesenchymal cells differentiate into myoblasts, the precursors of muscle cells. Myoblasts aggregate and fuse to form myotubes, which are multinucleated masses of primitive skeletal muscle. As the myoblasts fuse, a complex series of changes occur in the cytoarchitecture, involving the production of

Table 2: Major Types of Muscle - Embryologic Origins

Muscle	Origin	Innervation
Extrinsic eye muscles (most)	Somitomeres 1-3 & prechordal plate	Cranial nerves 3 & 4
Muscles that close the jaw	Somitomere 4	Cranial nerves 5
Lateral rectus of eye	Somitomere 5	Cranial nerves 6
Muscles that open the jaw	Somitomere 6	Cranial nerves 7
Third-arch branchial muscles	Somitomere 7	Cranial nerves 9
Intrinsic laryngeal muscles & pharyngeal muscles	Somites 1 & 2	Cranial nerves 10
Muscles of tongue, larynx & neck	Occipital somites	Cranial nerves 11 & 12; spinal nerves
Trunk, and limb muscles & diaphragm	Trunk somites	Spinal nerves
Cardiac muscles	Splanchnic mesoderm	Autonomic
Smooth muscles of gut & respiratory tract	Splanchnic mesoderm	Autonomic
Other smooth muscles	Local mesenchyme	Autonomic

Adapted from Carlson BM. Patten's foundations of embryology, ed 6. New York: McGraw-Hill; 1996.

tissue-specific proteins and modifications in the structure of the cell.[1] The changes can be summarized as:

- Proteins of the contractile apparatus accumulate and change the cell structure (actin, α-actin, myosin, tropomyosin, and troponin complex). Actin and myosin filaments form sarcomeres, the basic contractile units in striated muscle.
- Sarcomere formation results in structural changes in the cell: nuclei are forced to the periphery; endoplasmic reticulum becomes sarcoplasmic reticulum; and mitochondria are elongated and oriented along the long axis of the sarcomeres.[1]

Congenital abnormalities

Embryonic development is a complicated process. The vast majority of the time the process produces its intended product, a healthy fetus. However, there are many congenital problems that result in negative outcomes in a continuum from very mild to severe to death. Approximately 2%–3% of all newborns are found to have at least one recognizable congenital defect, although the figure rises to 6% when all diagnoses for the first few years of life are totaled.

A paradoxical situation currently exists. With the decline in infant mortality rates secondary to infection and malnutrition, an increase in birth defects is seen. As many as 30% of the infants admitted to neonatology or pediatric units are diagnosed with a disease or problem that is congenital in origin.[1] A basic list of causative factors for congenital malformation is found in Table 3. The developmental process itself can go awry. Problems in the developmental process are summarized in Table 4.[1,4,5]

One cause of congenital problems is the effect of teratogens on embryonic development. Table 5 lists some common teratogens, the critical period of their activity, and common fetal malformations.

About the author

Bob Caruthers, CST, PhD, served as former AST deputy director and director of professional development. He was responsible for leading

Table 3: Causes of Congenital Malformations

Genetic factors	Abnormal chromosome numbers
	Abnormal chromosome structure
	Genetic mutation
Environmental factors	Maternal infections
	Chemical teratogens – folic acid antagonists – androgenic hormones – anticonvulsants – sedatives / tranquilizers – antineoplastic agents – alcohol – vitamin A – antibiotics – other drugs
Physical factors	Ionizing radiation
	Others (data often inconclusive)
Maternal factors	Diabetes
	Smoking

Table 4: Problems in the Developmental Process Resulting in Malformations

Duplication of anatomical structure
Reversal of anatomical structure
Faulty inductive tissue interactions
Absence of normal cell death
Failure of tube formation
Failure of tissue resorption
Failure of migration
Persistence of an earlier stage of development
Failure of fusion
Hypoplasia and Hyperplasia
Other molecular failures or variances

Table 5: Common Teratogens and Resultant Malformations

Teratogen	Critical period (gestational days)	Malformations
Rubella virus	0–60	Cataract; heart malformations
	0–120	Deafness
Thalidomide	21–40	Reduction defects of limbs
Androgenic steroids	< 90	Clitoral hypertrophy; labial fusion
	> 90	Clitoral hypertrophy only
Coumadin type anticoagulants	< 100	Nasal hypoplasia
	> 100	Mental retardation
Radioiodine therapy	> 65	Fetal thyroid deficiency
Tetracycline	> 120	Primary teeth, stained dental enamel
	> 250	Permanent teeth, stained crowns

Adapted from Carlson BM. Human Embryology and Developmental Biology, 2nd ed. St Louis: Mosby; 1999.

many significant educational efforts: becoming executive editor of the first edition of *Surgical Technology for the Surgical Technologist: A Positive Care Approach;* launching a program of educational CD-ROMs; and initiating the development of advance practice forums.

In January 2000, Bob was diagnosed with glioblastoma multiforme and faced his illness with strength and determination. In 2002, he lost the battle and is still missed. This article was excerpted from the beginning of his manuscript related to an orthopedic advanced practice manual.

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1. The process by which germ layers form through cell movement is:
a. osteogenesis
b. gastrulation
c. differentiation
d. chondrogenesis

2. Which region further divides into somatic and splanchnic mesoderm?
a. paraxial mesoderm
b. intermediate mesoderm
c. lateral mesoderm
d. none of the above

3. Which is mismatched?
a. interstitial growth: cell division within cartilage
b. osteoblasts: differentiated from mesenchymal cells
c. appositional growth: addition of cells on the outer surface
d. osteocytes: secrete osteoid

4. Which process requires the prior existence of cartilage?
a. intramembranous ossification
b. osteogenesis
c. endochondral ossification
d. chondrification

5. The vertebral column, ribs, sternum and skull are all elements of the:
a. axial skeleton
b. notochord
c. myocoele
d. appendicular skeleton

6. Which is not a component of a limb bud?
a. core of mesenchyme
b. rod of fibroblasts
c. apical ectodermal ridge
d. cover of ectoderm

7. Controlled cell death begins after____ to separate individual fingers and toes.
a. week 5
b. week 6
c. week 7
d. week 8

8. Joints with limited ability to move are:
a. synovial
b. synarthroses
c. diarthroses
d. axial

9. The embryonic origins of cardiac muscles are:
a. the prechordal plate
b. trunk somites
c. somitomeres 1–3
d. splanchnic mesoderm

10. Myotubes are multinucleated masses of ____ muscle.
a. smooth
b. cardiac
c. skeletal
d. synovial

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Embryological development

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2	❑	❑	❑	❑	7	❑	❑	❑	❑
3	❑	❑	❑	❑	8	❑	❑	❑	❑
4	❑	❑	❑	❑	9	❑	❑	❑	❑
5	❑	❑	❑	❑	10	❑	❑	❑	❑

Mark one box next to each number. Only one correct or best answer can be selected for each question.