The axial skeleton

The axial skeleton includes the skull, vertebral column, ribs, and sternum. In general, the skeletal system develops from **paraxial** and **lateral plate (parietal layer) mesoderm** and from **neural crest**. Paraxial mesoderm forms a **segmented** series of tissue blocks on each side of the neural tube, known as **somitomeres** in the head region and **somites** from the occipital region caudally. Somites differentiate into a ventromedial part, the **sclerotome**, and a dorsolateral part, the **dermomyotome**. At the end of the fourth week, sclerotome cells become polymorphous and form loosely organized tissue, called **mesenchyme**, or embryonic connective tissue. It is characteristic for mesenchymal cells to migrate and to differentiate in many ways. They may become fibroblasts, chondroblasts, or **osteoblasts (boneforming cells)**.

The bone-forming capacity of mesenchyme is not restricted to cells of the sclerotome, but occurs also in the parietal layer of the lateral plate mesoderm of the body wall. This layer of mesoderm forms bones of the pelvic and shoulder girdles, limbs, and sternum. Neural crest cells in the head region also differentiate into mesenchyme and participate in formation of bones of the face and skull. The remainder of the skull is derived from occipital somites and somitomeres. In some bones, such as the flat bones of the skull, mesenchyme in the dermis differentiates directly into bone, a process known as **intramembranous ossification**.

In most bones, however, including the base of the skull and the limbs, mesenchymal cells first give rise to **hyaline cartilage models**, which in turn become ossified by **endochondral ossification**.

SKULL

The skull can be divided into two parts: the **neurocranium**, which forms a protective case around the brain, and the **viscerocranium**, which forms the skeleton of the face.

Neurocranium

The neurocranium is most conveniently divided into two portions:

(1) the membranous part, consisting of **flat bones**, which surround the brain as a vault, and

(2) the **cartilaginous part**, or **chondrocranium**, which forms bones of the base of the skull.

Membranous Neurocranium

The membranous portion of the skull is derived from neural crest cells and paraxial mesoderm. Mesenchyme from these two sources invests the brain and undergoes **intramembranous ossification**. The result is formation of a number of flat, membranous bones that are characterized by the presence of needle-like **bone spicules**. These spicules progressively radiate from primary ossification centers toward the periphery. With further growth during fetal and postnatal life, membranous bones enlarge by apposition of new layers on the outer surface and by simultaneous osteoclastic resorption from the inside.

Newborn Skull

At birth, the flat bones of the skull are separated from each other by narrow seams of connective tissue, the **sutures**, which are also derived from two sources: neural crest cells (sagittal suture) and paraxial mesoderm (coronal suture). At points where more than two bones meet, sutures are wide and are called **fontanelles**. The most prominent of these is the **anterior fontanelle**, which is found where the two parietal and two frontal bones meet. Sutures and fontanelles allow the bones of the skull to overlap **(molding)** during birth. Soon after birth, membranous bones move back to their original positions, and the skull appears large and round. In fact, the size of the vault is large compared with the small facial region.

Several sutures and fontanelles remain membranous for a considerable time after birth. The bones of the vault continue to grow after birth, mainly because the brain grows. Although a 5- to 7-year-old child has nearly all of his or her cranial capacity, some sutures remain open until adulthood. In the first few years after birth, palpation of the anterior fontanelle may give valuable information as to whether ossification of the skull is proceeding normally and whether intracranial pressure is normal. In most cases, the anterior fontanelle closes by 18 months of age, and the posterior fontanelle closes by 1 to 2 months of age.

Cartilaginous Neurocranium or Chondrocranium

The cartilaginous neurocranium or chondrocranium of the skull initially consists of a number of separate cartilages. Those that lie in front of the rostral limit of the notochord, which ends at the level of the pituitary gland in the center of the sella turcica, are derived from neural crest cells. They form the **prechordal chondrocranium**. Those that lie posterior to this limit arise from occipital sclerotomes formed by paraxial mesoderm and form the **chordal chondrocranium**.

The base of the skull is formed when these cartilages fuse and ossify by endochondral ossification.

Viscerocranium

The viscerocranium, which consists of the bones of the face, is formed mainly from the first two pharyngeal arches. The first arch gives rise to a dorsal portion, the **maxillary process**, which extends forward beneath the region of the eye and gives rise to the **maxilla**, the **zygomatic bone**, and **part of the temporal bone**. The ventral portion, the **mandibular process**, contains the **Meckel cartilage**. Mesenchyme around the Meckel cartilage condenses and ossifies by intramembranous ossification to give rise to the **mandible**. The Meckel cartilage disappears except in the **sphenomandibular** ligament. The dorsal tip of the mandibular process, along with that of the second pharyngeal arch, later gives rise to the incus, the malleus, and the stapes. Ossification of the three ossicles begins in the fourth month, making these the first bones to become fully ossified. Mesenchyme for formation of the bones of the face is derived from neural crest cells, including the nasal and lacrimal bones.

At first the face is small in comparison with the neurocranium. This appearance is caused by
(a) virtual absence of the paranasal air sinuses and
(b) the small size of the bones, particularly the jaws. With the appearance of teeth and development of the air sinuses, the face loses its babyish characteristics.

VERTEBRAE AND THE VERTEBRAL COLUMN

Vertebrae form from the sclerotome portions of the somites, which are derived from paraxial mesoderm. A typical vertebra consists of a **vertebral arch** and **foramen** (through which the spinal cord passes), a **body**, **transverse processes**, and usually a **spinous process**. During the fourth week, sclerotome cells migrate around the spinal cord and notochord to merge with cells from the opposing somite on the other side of the neural tube. As development continues, the sclerotome portion of each somite also undergoes a process called **resegmentation**.

Resegmentation occurs when the caudal half of each sclerotome grows into and fuses with the cephalic half of each subjacent sclerotome. Thus, each vertebra is formed from the combination of the caudal half of one somite and the cranial half of its neighbor.

Mesenchymal cells between cephalic and caudal parts of the original sclerotome segment do not proliferate but fill the space between two precartilaginous vertebral bodies. In this way, they contribute to formation of the **intervertebral disc**. Although the notochord regresses entirely in the region of the vertebral bodies, it persists and enlarges in the region of the intervertebral disc. Here it contributes to the nucleus pulposus, which is later surrounded by circular fibers of the annulus fibrosus. Combined, these two structures form the intervertebral disc. Rearrangement of sclerotomes into definitive vertebrae causes the myotomes to bridge the intervertebral discs, and this alteration gives them the capacity to move the spine. For the same reason, intersegmental arteries, at first lying between the sclerotomes, now pass midway over the vertebral bodies. Spinal nerves, however, come to lie near the intervertebral discs and leave the vertebral column through the intervertebral foramina.

Ribs and Sternum

Ribs form from costal processes of thoracic vertebrae and thus are derived from the sclerotome portion of paraxial mesoderm. The sternum develops independently in somatic mesoderm in the ventral body wall. Two sternal bands are formed on either side of the midline, and these later fuse to form cartilaginous models of the manubrium, sternebrae, and xiphoid process.

Muscular System

With the exception of some smooth muscle tissue, the muscular system develops from the mesodermal germ layer and consists of **skeletal, smooth,** and **cardiac muscle.** Skeletal muscle is derived from **paraxial mesoderm,** which forms somites from the occipital to the sacral regions and somitomeres in the head. Smooth muscle differentiates from visceral **splanchnic mesoderm** surrounding the gut and its derivatives and from ectoderm (pupillary, mammary gland, and sweat gland muscles). Cardiac muscle is derived from visceral **splanchnic mesoderm** surrounding the heart tube.

STRIATED SKELETAL MUSCULATURE

Head musculature is derived from seven **somitomeres**, which are partially segmented whorls of mesenchymal cells derived from paraxial mesoderm. Musculature of the axial skeleton, body wall, and limbs is derived from **somites**, which initially form as somitomeres and extend from the occipital region to the tail bud. Immediately after segmentation, these somitomeres undergo a process of **epithelization** and form a “ball” of epithelial cells with a small cavity in the center. The ventral region of each somite then becomes mesenchymal again and forms the **sclerotome**, the bone-forming cells for the vertebrae and ribs. Cells in the upper region of the somite form the dermatome and two muscle-forming areas at the ventrolateral (VLL) and dorsomedial (DML) lips (or edges), respectively. Cells from these two areas migrate and proliferate to form progenitor muscle cells ventral to the **dermatome**, thereby forming the **dermomyotome**. Some cells from the VLL region also migrate into the adjacent parietal layer of the lateral plate mesoderm. Here they form **infrahyoid, abdominal wall** (rectus abdominus, internal and external oblique, and transversus abdominus), and **limb muscles**. The remaining cells in the myotome form **muscles of the back, shoulder girdle**, and **intercostal muscles**. Initially, there is a well-defined border between each somite and the parietal layer of lateral plate mesoderm called the **lateral somatic frontier**. This frontier separates two mesodermal domains in the embryo:

1 The **primaxial domain** that comprises the region around the neural tube and contains only somite-derived (paraxial mesoderm) cells.

2 The **abaxial domain** that consists of the parietal layer of lateral plate mesoderm together with somite cells that have migrated across the lateral somitic frontier.

Muscle cells that cross this frontier (those from the VLL edge of the myotome) and enter the lateral plate mesoderm comprise the **abaxial** muscle cell precursors and receive many of their signals for differentiation from lateral plate mesoderm; those that remain in the paraxial mesoderm and do not cross the frontier (the remaining VLL cells and all of the DML cells) comprise the **primaxial** muscle cell precursors and receive many of their developmental signals from the neural tube and notochord.

Regardless of their domain, **each myotome receives its innervation from spinal nerves derived from the same segment as the muscle cells**.

The lateral somitic frontier also defines the border between dermis derived from dermatomes in the back and dermis derived from lateral plate mesoderm in the body wall. It also defi nes a border for rib development, such that the bony components of each rib are derived from primaxial sclerotome cells and the cartilaginous parts of those ribs that attach to the sternum are derived from sclerotome cells that migrate across the lateral somitic frontier (abaxial cells).

SKELETAL MUSCLE AND TENDONS

During differentiation, precursor cells, the **myoblasts**, fuse and form long, multinucleated muscle fibers. Myofi brils soon appear in the cytoplasm, and by the end of the third month, cross-striations, typical of skeletal muscle, appear. A similar process occurs in the seven somitomeres in the head region rostral to the occipital somites. However, somitomeres never segregate into recognizable regions of sclerotome and dermomyotome segments prior to differentiation. **Tendons** for the attachment of muscles to bones are derived from sclerotome cells lying adjacent to myotomes at the anterior and posterior borders of somites. The transcription factor ***SCLERAXIS*** regulates development of tendons.

PATTERNING OF MUSCLES

Patterns of muscle formation are controlled by connective tissue into which myoblasts migrate. In the head region, these connective tissues are derived from **neural crest cells**; in cervical and occipital regions, they differentiate from **somatic mesoderm**; and in the body wall and limbs, they originate from the **parietal layer of lateral plate mesoderm**.

HEAD MUSCULATURE

All voluntary muscles of the head region are derived from paraxial mesoderm (somitomeres and somites), including musculature of the tongue, eye (except that of the iris, which is derived from optic cup ectoderm), and that associated with the pharyngeal (visceral) arches. Patterns of muscle formation in the head are directed by connective tissue elements derived from neural crest cells.

LIMB MUSCULATURE

The first indication of limb musculature is observed in the seventh week of development as a condensation of mesenchyme near the base of the limb buds. The mesenchyme is derived from dorsolateral cells of the somites that migrate into the limb bud to form the muscles. As in other regions, connective tissue dictates the pattern of muscle formation, and this tissue is derived from the parietal layer of lateral plate mesoderm, which also gives rise to the bones of the limb.

Cardiac Muscle

Cardiac muscle develops from splanchnic mesoderm surrounding the endothelial heart tube. Myoblasts adhere to one another by special attachments that later develop into intercalated discs. Myofibrils develop as in skeletal muscle, but myoblasts do not fuse. During later development, a few special bundles of muscle cells with irregularly distributed myofibrils become visible. These bundles, the Purkinje fibers, form the conducting system of the heart.

Smooth Muscle

Smooth muscle in the wall of the gut and gut derivatives is derived from mesoderm surrounding the endoderm of these structures. Vascular smooth muscle differentiates from mesoderm adjacent to vascular endothelium. Sphincter and dilator muscles of the pupil and muscle tissue in the mammary gland and sweat glands originate from ectoderm.

Limbs

LIMB GROWTH AND DEVELOPMENT

The limbs, including the shoulder and pelvic girdles, comprise the appendicular skeleton. At the end of the fourth week of development, limb buds become visible as outpocketings from the ventrolateral body wall. The forelimb appears first followed by the hindlimb 1 to 2 days later. Initially, the limb buds consist of a mesenchymal core derived from the parietal (somatic) layer of lateral plate mesoderm that will form the bones and connective tissues of the limb, covered by a layer of cuboidal ectoderm. Ectoderm at the distal border of the limb thickens and forms the **apical ectodermal ridge (AER)**. This ridge exerts an inductive influence on adjacent mesenchyme, causing it to remain as a population of undifferentiated, rapidly proliferating cells, the **progress zone**. As the limb grows, cells farther from the influence of the AER begin to differentiate into cartilage and muscle. In this manner, development of the limb proceeds proximodistally.

In 6-week-old embryos, the terminal portion of the limb buds becomes flattened to form the **hand-** and **footplates** and is separated from the proximal segment by a circular constriction. Later, a second constriction divides the proximal portion into two segments, and the main parts of the extremities can be recognized. Fingers and toes are formed when **cell death** in the AER separates this ridge into five parts. Further formation of the digits depends on their continued outgrowth under the influence of the five segments of ridge ectoderm, condensation of the mesenchyme to form cartilaginous digital rays, and the death of intervening tissue between the rays.

Development of the upper and lower limbs is similar except that morphogenesis of the lower limb is approximately 1 to 2 days behind that of the upper limb. Also, during the seventh week of gestation, the limbs rotate in opposite directions.

The upper limb rotates 90° laterally, so that the extensor muscles lie on the lateral and posterior surface, and the thumbs lie laterally, whereas the lower limb rotates approximately 90 degrees medially, placing the extensor muscles on the anterior surface and the big toe medially.

While the external shape is being established, mesenchyme in the buds begins to condense, and these cells differentiate into chondrocytes. By the sixth week of development, the first **hyaline cartilage models**, foreshadowing the bones of the extremities, are formed by these chondrocytes. Joints are formed in the cartilaginous condensations when chondrogenesis is arrested, and a joint **interzone** is induced. Cells in this region increase in number and density, and then a joint cavity is formed by cell death. Surrounding cells differentiate into a joint capsule. Factors regulating the positioning of joints are not clear, but the secreted molecule WNT14 appears to be the inductive signal. Ossification of the bones of the extremities, **endochondral ossifi cation**, begins by the end of the embryonic period. Primary **ossification centers** are present in all long bones of the limbs by the 12th week of development. From the primary center in the shaft or **diaphysis** of the bone, endochondral ossifi cation gradually progresses toward the ends of the cartilaginous model.

At birth, the diaphysis of the bone is usually completely ossified, but the two ends, the **epiphyses**, are still cartilaginous. Shortly thereafter, however, ossification centers arise in the epiphyses. Temporarily, a cartilage plate remains between the diaphyseal and epiphyseal ossification centers. This plate, the **epiphyseal plate**, plays an important role in growth in the length of the bones. Endochondral ossification proceeds on both sides of the plate. When the bone has acquired its full length, the epiphyseal plates disappear, and the epiphyses unite with the shaft of the bone. In long bones, an epiphyseal plate is found on each extremity; in smaller bones, such as the phalanges, it is found only at one extremity; and in irregular bones, such as the vertebrae, one or more primary centers of ossification and usually several secondary centers are present. **Synovial joints** between bones begin to form at the same time that mesenchymal condensations initiate the process of forming cartilage.

Thus, in the region between two chondrifying bone primordia, called the **interzone** (for example between the tibia and femur at the knee joint), the condensed mesenchyme differentiates into dense fibrous tissue. This fibrous tissue then forms **articular cartilage**, covering the ends of the two adjacent bones; the **synovial membranes**; and the **menisci and ligaments within the joint capsule** (e.g., the anterior and posterior cruciate ligaments in the knee). The **joint capsule** itself is derived from mesenchyme cells surrounding the interzone region. **Fibrous joints** (e.g., the sutures in the skull) also form from interzone regions, but in this case the interzone remains as a dense fibrous structure.

LIMB MUSCULATURE

Limb musculature is derived from dorsolateral cells of the somites that migrate into the limb to form muscles and, initially, these muscle components are segmented according to the somites from which they are derived.

However, with elongation of the limb buds, the muscle tissue first splits into flexor and extensor components and then additional splittings and fusions occur, such that a single muscle may be formed from more than one original segment.

The resulting complex pattern of muscles is determined by connective tissue derived from lateral plate mesoderm. Upper limb buds lie opposite the lower five cervical and upper two thoracic segments, and the lower limb buds lie opposite the lower four lumbar and upper two sacral segments. As soon as the buds form, ventral primary rami from the appropriate spinal nerves penetrate into the mesenchyme. At first, each ventral ramus enters with dorsal and ventral branches derived from its specific spinal segment, but soon branches in their respective divisions begin to unite to form large dorsal and ventral nerves. Thus, the **radial nerve**, which supplies the extensor musculature, is formed by a combination of the dorsal segmental branches, whereas the **ulnar** and **median nerves**, which supply the fl exor musculature, are formed by a combination of the ventral branches. Immediately after the nerves have entered the limb buds, they establish an intimate contact with the differentiating mesodermal condensations, and the early contact between the nerve and muscle cells is a prerequisite for their complete functional differentiation.

Spinal nerves not only play an important role in differentiation and motor innervation of the limb musculature, but also provide **sensory innervation** for the **dermatomes**. Although the original dermatomal pattern changes with growth and rotation of the extremities, an orderly sequence can still be recognized in the adult.

Malformations of skull and limbs

***** In some cases the cranial vault fails to form (**cranioschisis**), and brain tissue exposed to amniotic fluid degenerates, resulting in **anencephaly.**

****Craniosynostosis*** Another important category of cranial abnormalities is caused by premature closure of one or more sutures.

*****Premature closure of the coronal suture results in a short, high skull, known as **acrocephaly,** or **tower skull** If the coronal and lambdoid sutures close prematurely on one side only, asymmetric craniosynostosis, known as **plagiocephaly**.

***Achondroplasia**, the most common form of dwarfism, primarily affects the long bones.

***Acromegaly** is caused by congenital hyperpituitarism and excessive production of growth hormone

***Microcephaly** is usually an abnormality in which the brain fails to growand the skull fails to expand.

-Abnormalities of the limbs vary greatly, and they may be represented by partial (***meromelia**) or complete absence (***amelia**) of one or more of the extremities.

-Sometimes the long bones are absent, and rudimentary hands and feet are attached to the trunk by small, irregularly shaped bones (***phocomelia,** a form of meromelia),

-Sometimes all segments of the extremities are present but abnormally short (***micromelia**).

-A different category of limb abnormalities consists of extra fingers or toes (***polydactyly**)

Abnormal fusion is usually restricted to the fingers or toes (***syndactyly**).

-Cleft hand and foot (lobster claw deformity) consists of an abnormal cleft between the second and fourth metacarpal bones and soft tissues.

-Clubfoot usually accompanies syndactyly. The sole of the foot is turned inward, and the foot is adducted and plantar flexed. It is observed mainly in males and in some cases is hereditary.