4 Integumentary System Development

Summary
Anatomically, the integumentary system consists of skin, integumentary glands (sweat glands, sebaceous glands, mammary glands), hairs and arrector pili, and teeth. The tissues that compose the integumentary system arise from ectoderm, mesoderm, and neural crest cells.

Keywords: sweat glands, arrector pili, enamel, keratinocytes, mammary ridges, melanin, melanocytes, nail folds, nail plate, stratum basale

4.1 Key Principles

- Skin is derived from only two of the three germ layers—the ectoderm and mesoderm—resulting in a two-layered structure. The outer epidermis arises from surface ectoderm and the underlying dermis arises from mesenchyme.
- Additional skin features such as glands and hair follicles generally arise as a downgrowth of epithelium into the underlying tissue.
- Mammary glands develop along mammary ridges, which are transient developmental structures.
- Nails are keratinized structures that emerge from nail matrix and advance toward the distal aspect of the digits—fingernails slightly ahead of toenails.
- Development of two sets of teeth begins prenatally, and tooth eruption occurs in sequence in childhood.

4.2 Skin Development

Skin is composed of a double-layered membrane, with layers arising from different embryonic sources:
- **Epidermis**, the outer layer of skin, is derived from ectoderm.
- **Dermis**, the inner layer of skin, is derived from mesenchyme (embryonic connective tissue derived from mesoderm).

4.2.1 Epidermis

In the adult, the epidermis is a layered epithelial structure that undergoes renewal process with an epithelial cell turnover time of approximately 6 to 8 weeks.
- Most cells of the epidermis undergo a process called **keratinization**, where the cytoplasm is replaced by a protein called keratin. Skin cells that undergo this process are called **keratinocytes**, composing approximately 90% of the epidermal layer.
- The function of keratinocytes is to provide a protective skin barrier.
- Atypical keratinization in development can lead to scaling of the skin (Correlation 4.1).

Embryonic surface ectoderm gives rise to the layered epidermis.[1] The developmental stages of the epidermis are the following (▶ Fig. 4.1):
- Initially the epidermis is composed of one single layer of ectoderm-derived cells.
- By week 5, the epidermis is composed of two cell layers:
  - The inner layer is composed of simple epithelium (basal layer or stratum germanitivum). The basal layer will produce the outer layers of epidermis.
  - The outer layer, called **periderm,** functions as a transient protective outer layer of the epidermis. Periderm cells continually undergo keratinization and are shed into the amniotic fluid. As shedding occurs new cells are generated by the basal layer. The periderm is ultimately sloughed into the amniotic fluid when the differentiation of the epidermis is complete.
- In week 11, the basal layer produces an **intermediate layer** deep to the periderm.
- By 18 weeks, several intermediate layers are formed.
- By 23 weeks, keratinization is well developed. Most of the periderm layer has been shed.

The histologically distinct layers of the developing epidermis are as follows:
- **Stratum basale (stratum germinativum)**: Mitotically active layer that generates cells of the epidermis. Cells produced by this layer migrate out and become keratinized, forming the

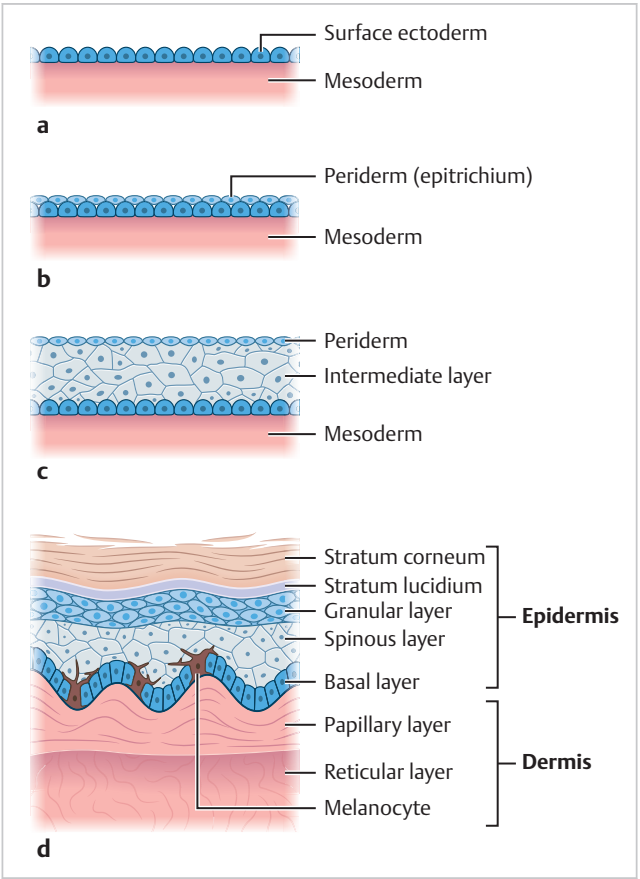


Fig. 4.1 (**a**) The skin is composed of tissues derived from the surface ectoderm and underlying mesoderm. (**b**, **c**) The ectoderm acquires additional layers over time during development. (**d**) The mesoderm gives rise to the layers of the dermis, as seen in mature skin.

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more superficial layers of the epidermis. This layer is responsible for the continual renewal of skin that occurs after birth, replacing outer skin layers that are sloughed off.
- **Stratum spinosum:** It is 5 to 10 cells thick and overlies the basal layer.
- **Stratum granulosum:** Cells in this layer contain granules that bind keratin filaments together.
- **Stratum corneum** (also called horny layer): Cells in this layer lack nuclei (are not living cells). This layer provides protection and moisture barrier.
- An additional layer called the **stratum lucidum** is found on the palms of the hands and soles of the feet.

The epidermis contains additional scattered cell types:
- **Melanocytes** (dendritic pigment-producing cells) are derived from neural crest cells.[2] They develop in a cranial-to-caudal manner within the skin beginning around month 3. In adult skin, melanocytes are found in the deepest layer, the **stratum basale**. Pigment (**melanin**) is transferred from melanocytes to surrounding basal keratinocytes. Melanin accounts for variations in human skin color. Melanin is a protective substance, blocking skin damage caused by ultraviolet radiation emanating from the sun. Developmental differences can result in variations in skin pigmentation (Correlation 4.2).
- **Langerhans cells** (dendritic antigen-presenting immune cells) are migratory and arise in bone marrow, appearing in the skin around 7 weeks gestation. These cells are found in all layers of the epidermis except the outermost layer, the **stratum corneum**.
- **Merkel cells** (pressure-sensitive mechanoreceptors) arise between 8 and 12 weeks of gestational age from epidermis and are found near the epidermal–dermal border. These cells associate with small nerves to transmit information regarding light touch sensations.

4.2.2 Dermis

Dermis consists of dense connective tissue, composed primarily of fibroblasts, dermal dendritic cells, macrophages, and mast cells. Dermis contains nervous system components (free nerve endings, thermoreceptors, mechanoreceptors), blood capillaries, and other components of the integumentary system such as hair follicles and sweat glands.
- Dermis is derived from mesenchyme from the following embryonic sources:
  - **Lateral plate mesoderm** which gives rise to mesenchyme of the limbs and majority of the body wall.
  - **Paraxial mesoderm** which gives rise to somites. The dermatome region of somites becomes mesenchyme of the dorsal body wall.
  - **Neural crest cells** which give rise to mesenchyme of the head and neck.
- In month 3, the dermis forms two layers: the outer **papillary layer** and the inner **reticular layer**.
  - At this stage, proliferation of the dermis forms ridges in the papillary layer called **dermal papillae**, structures that project into and interdigitate with downward projections of the epidermis, called **rete ridges**. The unique pattern of ridges created by dermal papillae results in the formation of fingerprints.
- Angiogenesis occurs in the dermis, forming a capillary network that nourishes both dermal and epidermal skin layers. For more on vascular development, see Chapter 5, Vascular System Development.

4.3 Gland Development

Glands that are part of the integumentary system have epidermal origin, and include the following types: sebaceous glands, sweat glands, and mammary glands.

4.3.1 Sweat Glands

Primordial sweat glands appear at about 12 weeks of development (▶ Fig. 4.2). Two main types of sweat glands are formed:
- **Eccrine sweat glands** are numerous, are distributed across the body, and begin functioning shortly after birth. Secretions from these glands are released onto the surface of the skin.
  - The development of eccrine sweat glands begins with proliferation and downgrowth of the epidermis, forming structures called **cellular buds**. The buds elongate and the deep portion coils. Degeneration of cells in the central portion of the duct forms the lumen of the duct.
  - The primary function of eccrine sweat glands is thermoregulation. Release of eccrine gland secretions (sweat) on the surface of the skin leads to evaporative cooling.
- **Apocrine sweat glands** are found in limited regions of the body such as the axillae and anogenital region. These glands begin functioning around puberty and are closely associated with hair follicles.
  - Apocrine sweat glands develop from outgrowths of the epidermis that gives rise to hair follicles. Development is similar to eccrine sweat glands, with the exception that the gland releases secretions into the hair follicles instead of directly on the skin surface.
  - The primary function of apocrine sweat glands is debated. It has been suggested that they represent scent glands.

4.3.2 Sebaceous Glands

Sebaceous glands produce **sebum**, an oily/waxy protective substance of the skin and hair. Sebaceous glands are associated with hair follicles, and are most numerous in the scalp, face, upper neck, and back. Sebum also contributes to the formation of **vernix caseosa**, a waxy protective substance that encases the fetus and is shed prior to birth. Sebaceous glands arise as tissue buds from the epidermal root sheaths of hair follicles, beginning about month 4 of development. New sebaceous glands do not typically develop after birth, but the size and function are regulated by hormone exposure.

The steps of sebaceous gland development are as follows:
- Epithelial tissue buds grow into the tissue adjacent to the hair follicle, forming the primordial structure of the gland.
- The cells in the central portion of the gland break down and form sebum. This process results in hollow **glandular alveoli** (sacs) and **ducts**.
- Sebaceous glands are well-developed and enlarged in the newborn stimulated by exposure to hormones in utero. Shortly after birth the glands atrophy as hormone levels drop off. Sebaceous glands enlarge again at puberty, stimulated by gonadal androgens.

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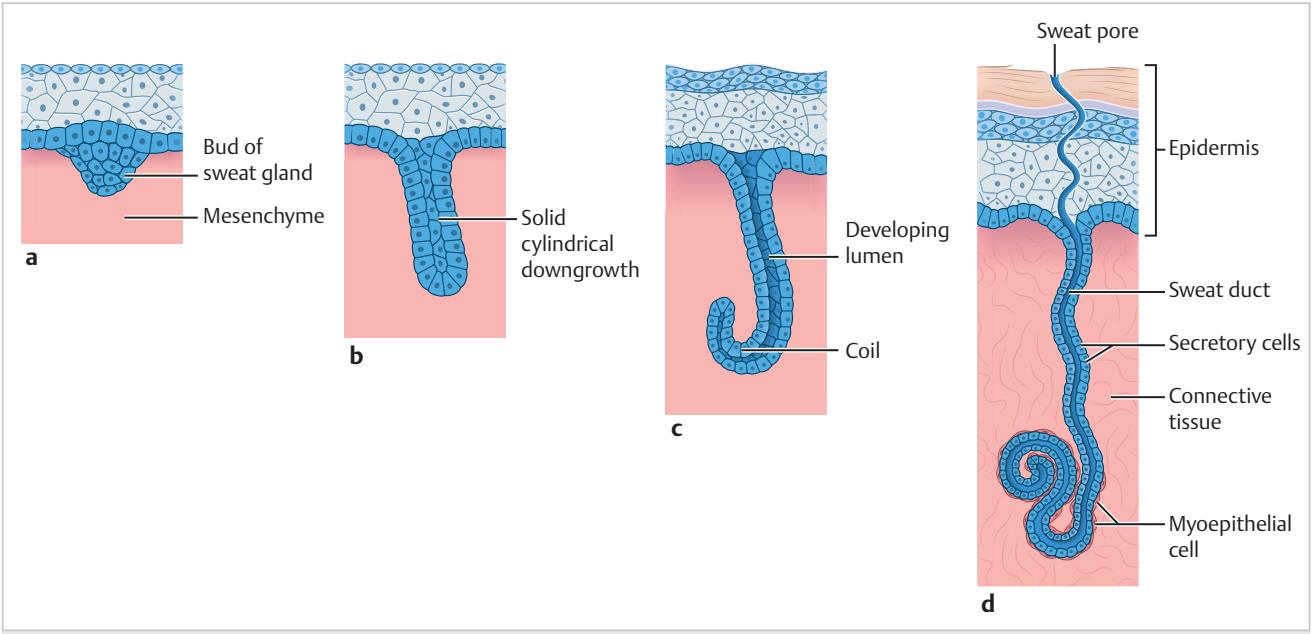


Fig. 4.2 Sweat glands in the skin initially develop from a downgrowth of a solid cord of epithelium into the underlying dermis (**a, b**). A lumen develops (**c, d**), creating a passageway for the release of glandular secretions onto the surface of the skin.

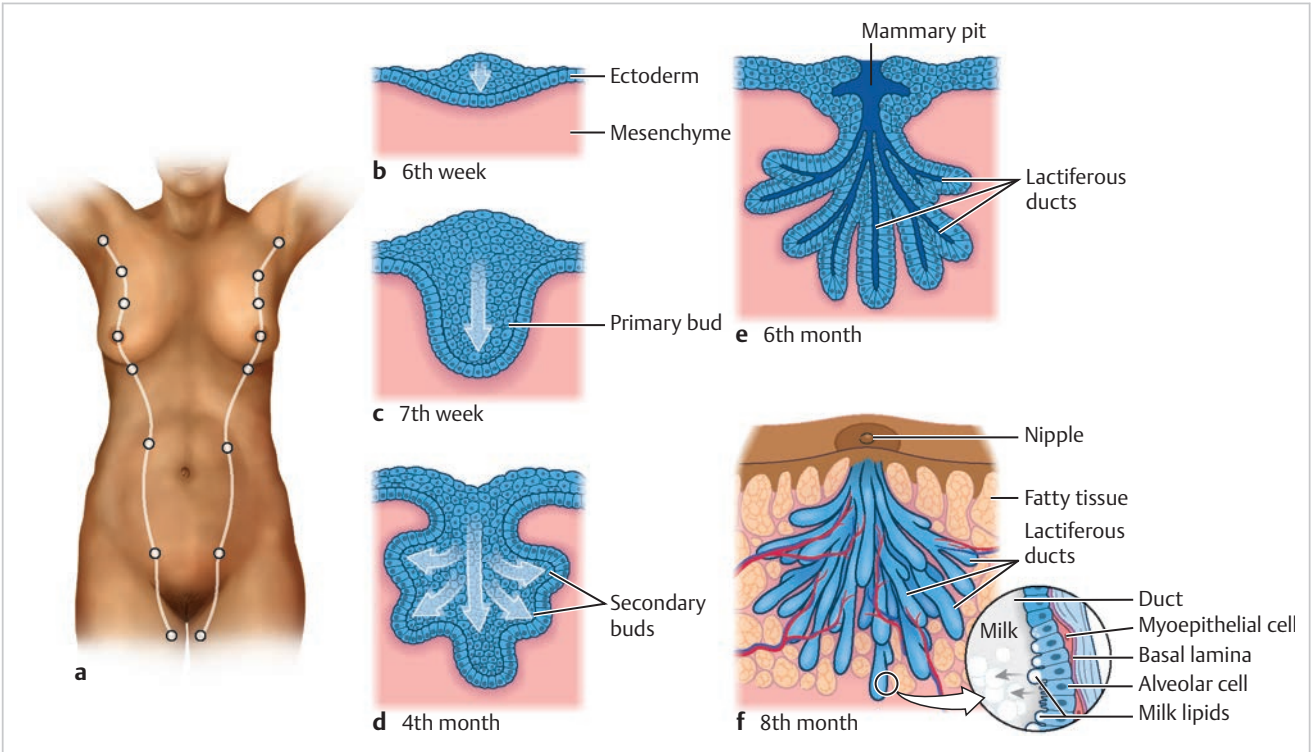


Fig. 4.3 Mammary tissue develops from mammary ridges (equivalent adult location denoted by *white lines* in part **a**). Lactiferous ducts develop from an ingrowth of branching epithelial tissue that extends into underlying dermis (**b–f**).

4.3.3 Mammary Glands

Mammary glands are paired glands located in breast tissue (▶ Fig. 4.3).

- Key steps of mammary gland development are the following:
  - In week 4, thickened epithelial ridges called **mammary ridges** appear on the ventral aspect of the embryo. They extend from the future axilla (armpit region) to the upper medial thigh and regress except for the location of the mammary glands.
  - In week 5, the **mammary** ridge epithelium proliferates, forming mammary buds that grow into the underlying dermis.
  - The primary mammary bud branches into secondary mammary buds, developing into a more complex structure.

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Lactiferous ducts are formed by coalescing passageways formed within the developing mammary gland.
- Mammary gland development is similar across all sexes. However, at puberty, hormones influence further growth and development of the mammary glands of the female sex.
- Rarely, supernumerary mammary glands may arise (Correlation 4.3).

4.4 Nail Development

Fingernails and toenails are specialized keratinized structures located on the dorsal aspect of the digits. Components of nails include the keratinized nail plate, nail bed (tissues under the nail plate), nail matrix (produces nail plate), nail folds, and cuticle.
- The steps of nail development include the following (▶ Fig. 4.4):
  - The first sign of nail development is the appearance of epidermal thickenings called **primary nail fields** on the dorsal aspect of the digits.
  - The lateral and proximal borders of the nail field are demarcated by grooves called **nail folds**. The proximal nail fold overlies matrix cells that will produce the **nail plate**, a hardened structure composed of compressed keratinocytes. The crescent-shaped **lunula** near the nail base marks the location of the nail matrix.
  - The nail plate advances from the proximal nail fold and grows toward the distal tip of the digit.
- Fingernails develop ahead of toenails, consistent with the cranial-to-caudal development pattern of the fetus:
  - Fingernail epidermal thickenings appear around week 10 and reach the distal fingertips around week 32.
  - Toenail epidermal thickenings appear around week 14 and reach the distal tip of the toes around week 36.

4.4.1 Hair Development

Hair follicles are the epithelial structures that surround and produce hairs. The first sign of hair development is the appearance of hair germs at the end of month 2 in the region of eyebrows and scalp. Hair follicle development proceeds in a cranial-to-caudal manner. Steps of hair follicle development include the following (▶ Fig. 4.5):
- In the region where a hair follicle will develop, the stratum basale forms in a crowded region of epidermal cells known as a **hair germ**. Cells from these structures grow downward into the dermis, forming a solid epithelial cord (**hair bud**).
- The distal aspect of the hair bud enlarges to become a hair bulb. Adjacent mesenchyme from the dermis condenses and grows into the hair bulb, forming the **dermal papilla**.
- The hair bulb cells immediately adjacent to the dermal papilla are called the germinal matrix. These cells proliferate and give rise to keratinocytes that advance toward the skin surface and compose the hair shaft. The periphery of the hair follicle surrounding the hair shaft is composed of an inner **epidermal root sheath** and a surrounding **dermal root sheath**.
- Hair pigment (**melanin**) is provided to the hair shaft cells (**keratinocytes**) by **melanocytes** that arise from migratory neural crest–derived precursor cells that colonize the hair bulb.
- **Arrector pili** muscles are tiny smooth muscle bundles that are autonomically innervated and cause hair to stand "on end" when they contract. The smooth muscle arises from dermal mesenchyme adjacent to the developing hairs, attaching the dermal root sheath of the follicle to the papillary layer of the dermis.

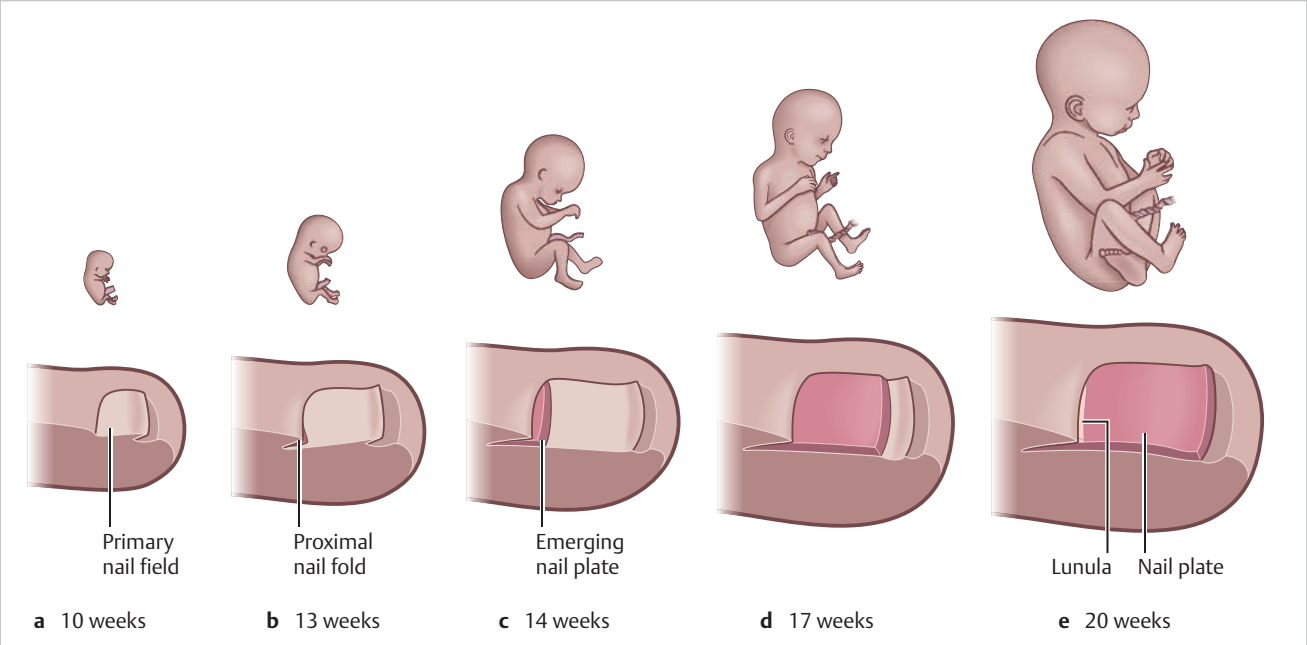


Fig. 4.4 Nails develop beginning in week 10 for fingers (week 14 for toes) with the appearance of primary nail fields (**a**). The nail plate emerges from the matrix located at the proximal nail fold (**b**) and advances toward the distal tip of the digit (**c–e**). The nail plate reaches the distal tip of the fingers at around week 32 (or around week 36 for toes).

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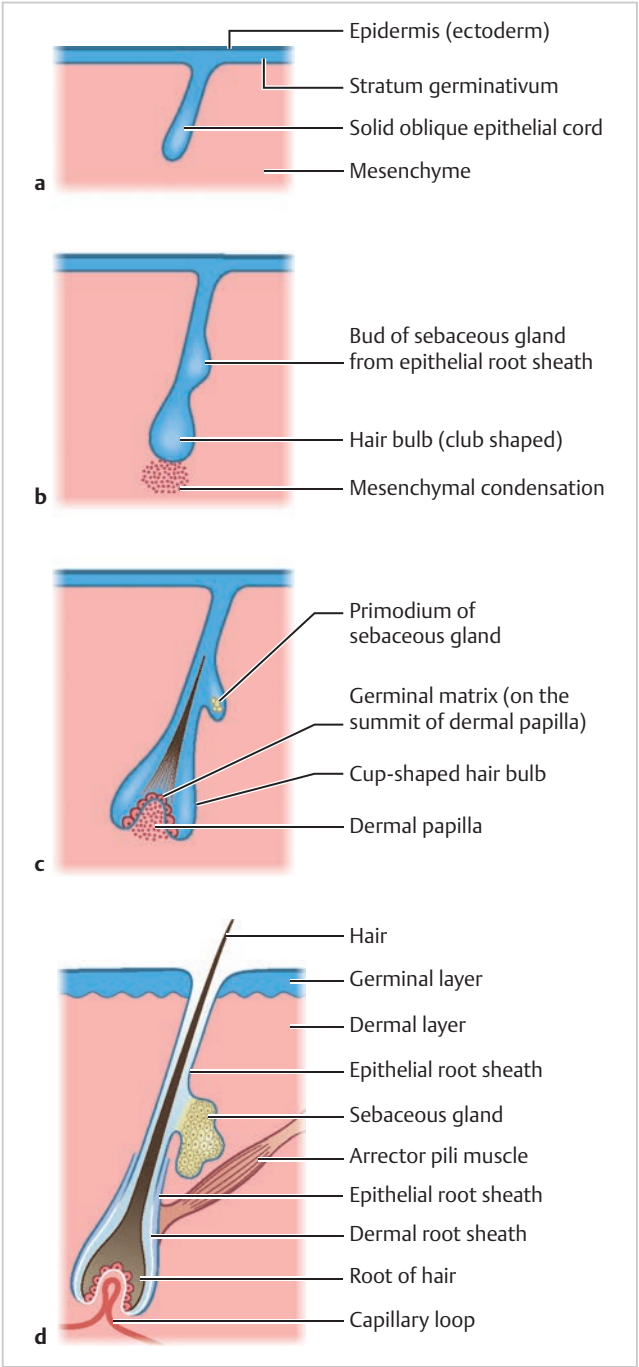


Fig. 4.5 Hair follicle development begins with a downgrowth of epithelium into the underlying dermis (**a**). Sebaceous glands develop in association with hair follicles (visible in **b–d**). The structure of the mature hair follicle is depicted in part **d**.

- There are three different types of hairs:
  - **Lanugo hair** is formed in month 3 of development. It is soft, fine hair that covers most of the body surface. The function of lanugo hair is to bind **vernix**, a waxy protective covering of fetal skin composed of fetal skin cells and sebum. Lanugo hair is shed about 4 weeks prior to birth and is replaced with the other two types of hairs: vellus and terminal.
  - **Vellus hair** is short, thin, contains little pigment, and covers much of the body surface. Vellus hair plays a role in thermoregulation, wicking sweat away from the body to increase efficiency of evaporative cooling.
  - **Terminal hair** is longer, thicker, and more pigmented than vellus hair. At birth it is found in the scalp, eyebrows, and eyelashes. At puberty, sex hormones stimulate terminal hair to replace vellus hair in some locations of the body, such as the face, armpits, and pubic areas.

4.5 Teeth Development

Two sets of teeth, deciduous and permanent teeth, develop and erupt in a predictable sequence in childhood.

- Teeth are primarily composed of tissues derived from two embryonic sources: ectoderm and mesenchyme.
  - The enamel covering of teeth is derived from ectoderm.
  - All other tissues are derived from mesenchyme (cranial neural crest cell origin).
- The process of teeth development depends on reciprocal epithelial–mesenchymal interactions between oral epithelium and mesenchyme. The stages of tooth development include the following (▶ Fig. 4.6**):**
  - **Bud stage**: Early in week 6, ectodermal proliferation results in the formation of tooth buds (tooth precursors).
  - **Cap stage**: Early in the fetal period, there is an ingrowth of mesenchyme into the tooth bud. The mesenchymal ingrowth will give rise to cells and tissues in the center of teeth including **odontoblasts** (dentin-producing cells) and **dental pulp**. The overlying **ectodermal cap** contains **ameloblasts** that will produce the **enamel** covering of the tooth. Mesenchyme adjacent to the tooth will form the **dental sac**, a structure that will become **cementum** (bone-like substance that covers the root) and the **periodontal ligament** (attaches tooth to bony socket).
  - **Bell stage**: Teeth increase in size and become bell-shaped. Tissue differentiation continues, and dentin and enamel are produced. The roots of teeth develop at this stage.
  - **Tooth eruption**: The process of tooth eruption is the emergence of teeth through the bone and overlying mucosa into the mouth.
    - Between 6 and 24 months after birth, 20 **deciduous teeth** erupt gradually and are shed at various times throughout childhood.
    - At about 6 years of age through adulthood, 32 **permanent teeth** replace deciduous teeth. Permanent teeth develop later in a similar manner to deciduous teeth.

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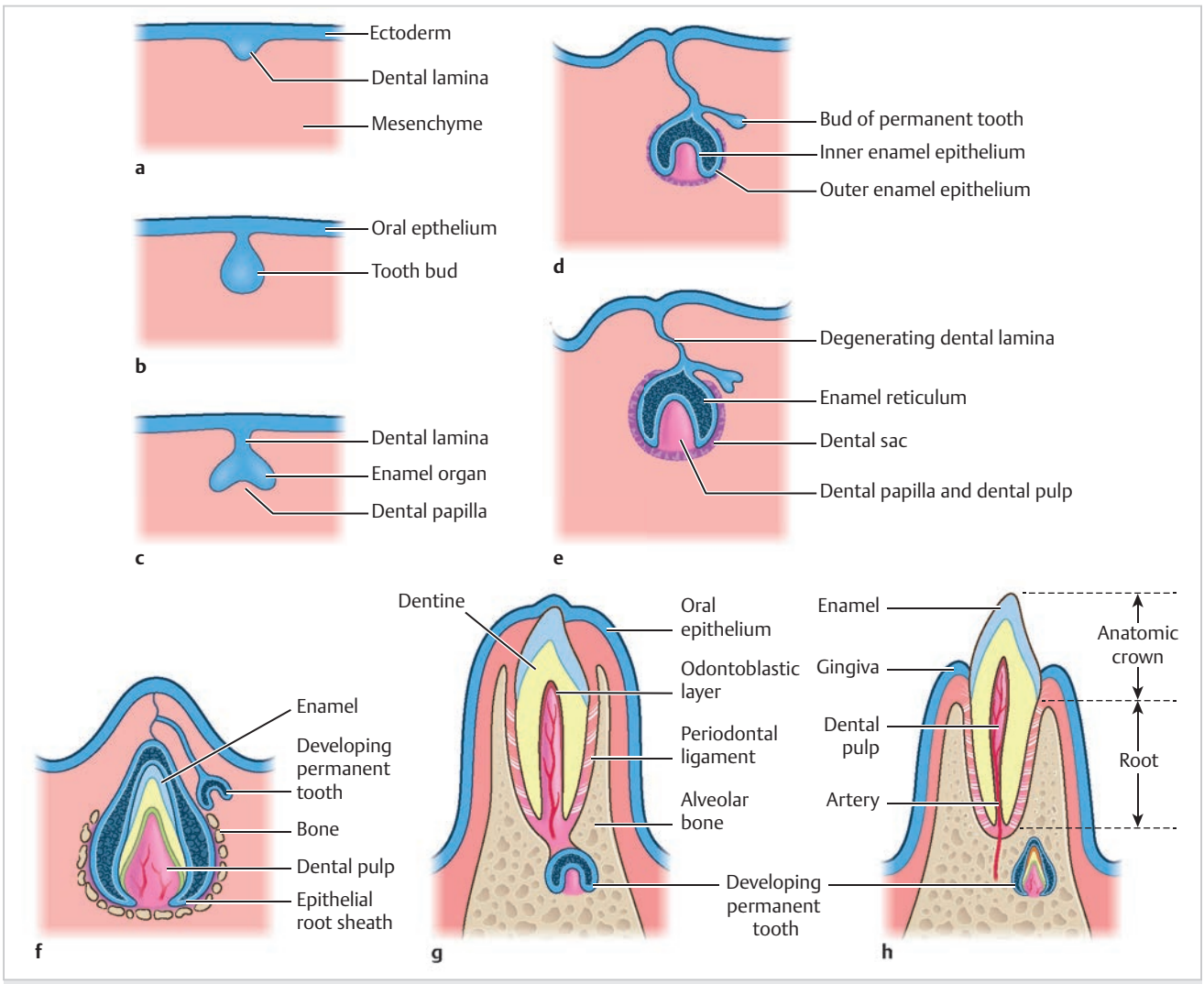


Fig. 4.6 (**a–h**) Tooth development depends on reciprocal interactions between the oral epithelium and underlying mesenchyme. Developmental tooth stages include the bud stage (**b**), cap stage (**c**), and bell stage (**d–e**). The mature tooth (**h**) consists of an enamel covering derived from ectoderm. Other structures composing the tooth are derived from mesenchyme (cranial neural crest cell origin).

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Clinical Correlations

Correlation 4.1: Clinical—Ichthyosis

Ichthyosis is a skin condition characterized by atypical keratinization.[3] Ichthyosis can be present at birth since the process of keratinization begins prior to birth. Characteristics of ichthyosis include scaly or dry skin, and the clinical manifestations range from mild to severe. The most severe form is called harlequin ichthyosis. At birth, the skin of infants with harlequin ichthyosis is "armor-plated" and is marked by deep fissures. Infants with harlequin ichthyosis typically do not survive for long periods after birth due to restricted respiration, poor feeding, and dehydration.

Correlation 4.2: Clinical—Developmental Pigment Variations

Neural crest cell–derived melanocytes produce and secrete melanin, the pigment that is responsible for coloration of skin, hair, and eye structures. There are congenital skin pigment variations that arise from atypical melanocyte development or altered melanin production. Some examples of pigment variations include:

- **Albinism**, which is characterized by absence of pigment in hair, eyes, and skin. A lack of melanin in eye structures may lead to visual deficits. Individuals are more susceptible to harmful effects of ultraviolet radiation from sun exposure. Albinism can result from a variety of underlying genetic variants that impact melanin production.
- **Piebaldism** is a rare congenital skin variation characterized by unpigmented patches of skin. Affected regions of skin have an absence of melanocytes. Piebaldism also has a genetic basis (*KIT* gene mutation).
- **Congenital dermal melanocytosis (Mongolian blue spots)** is a type of skin pigment variation that appears as a slate-blue discolored region, often located over the sacral region. This is thought to arise from incomplete transdermal migration of neural crest cell melanocyte precursors. Incomplete migration results in the presence of melanocytes in the deep reticular layer of dermis instead of the normal epidermal location.

Correlation 4.3: Clinical—Supernumerary Mammary Glands

Accessory mammary tissue can develop along the mammary ridges that normally regress.[4] **Polythelia** is the presence of an additional nipple, and **polymastia** is the presence of additional mammary glands. These congenital variations are classified based on the type of mammary tissue present (nipple, areola, glandular tissue).

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