Basics of Dermatology

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Introduction

It is a great pleasure for me to be able to introduce the text by Professor Tammaro and her collaborators.

This beautiful and highly useful work can be a point of reference for all colleagues in search of a text which is comprehensive and which can also be consulted quickly in order to be able to refer the patient to a specialist dermatologist with a diagnosis that is as close as possible to reality.

I am thinking specifically of aesthetic medicine. In common with dermatology, it studies the skin, a complex and fascinating structure upon whose characteristics a significant part of our appearance often depends. Obviously, aesthetic medicine deals exclusively with investigating physiology. Inevitably, though, in order to identify the physiological state, we must know the pathological conditions; we do not necessarily need to know how to treat them, but we definitely need to be able to diagnose them.

This text allows us to tackle our patients' skin with confidence, helping us to understand and recognise all those conditions that require a dermatological consultation.

Moreover, Antonella Tammaro is a professional who had the foresight and humility — key features of intelligent people — to enroll as a dermatologist and attend the International School of Aesthetic Medicine at the Fatebenefratelli Foundation for Research and Training in Health and Social Care from 2003 to 2007. Professor Tammaro was a keen and active participant in the four–year course. This show of humility allowed her to gain a thorough knowledge of this medical discipline, which has much in common with dermatology, but which differs profoundly from it in terms of the diagnostic/clinical aims and the kind of treatments that are recommended.

The educational pathway taken by Professor Tammaro, in addition to making her a rounded professional who is highly competent in the two disciplines, has also led to the creation of this text, which is ex-

tremely useful on a practical level for all those who, regardless of their specialism, work with the skin either directly or indirectly, putting them in a position to be of great help to specialist dermatologists.

Thanks, therefore, go to Professor Tammaro and to all her collaborators who have contributed to putting together this very useful text.

Figure 1. Prof. Antonella Tammaro.

Skin Anatomy and Cutaneous Lesions

M. Persichetti, A. Tammaro

1. Skin Anatomy

The skin (cutis or integument) forms the external covering of the body and is its largest organ; in the average adult human body, the skin has a surface area of 1.5–2m² and weighs about 15 kg. Its thickness varies across the body, lowest over the eyelids (0.5 mm) and maximal on palmar–plantar and dorsal surfaces (4 mm). Skin color varies with age, race, sun exposure, but most importantly with blood oxygenation, melanin production and light absorption.

On examination with a magnifying glass, we can distinguish:

— **Punctiform depressions**, the orifices of the pilosebaceous units;
— **Superficial sulci**, found in those areas of skin that have hair. These sulci delimit rhomboid areas of skin, and hairs emerge from their points of intersection;
— **Deep sulci** found in hairless skin, arranged in parallel. These sulci border ridges, at the apices of which sweat glands open. These deep sulci and ridges give rise to dermatoglyphics;
— **Folds** can be observed in adults in proximity of joints (articular folds) or certain muscles, especially facial muscles (muscular folds). With aging there is a reduction of adipose tissue and a decrease in elasticity that accentuates these folds.

Skin consists of two layers: the **epidermis**, which is a keratinized stratified squamous epithelium derived from the ectoderm, and the **dermis**, a dense connective tissue deriving from the mesoderm. Deep to the dermis lies the **hypodermis**, containing variable amounts of adipose tissue arranged in lobules. Hair follicles, sebaceous glands,

and sweat glands are **skin appendages** derived from down growth of the epidermal epithelium during development.

1.1. *Epidermis*

The epidermis is a **keratinized stratified squamous epithelium** composed of five layers of keratinocytes. From a morphological and functional point of view four sectors can be distinguished; these represent sequential stages of differentiation, starting from the stratum basale.In other words, cells from the stratum basale progressively differentiate and move outwards to form the other sectors. Differentiation of epithelial cells is a form of apoptosis in which the cell doesn't fragment, but becomes filled with keratin and is then sloughed from the surface; it takes about 30 days for a cell in the stratum basale to reach the skin surface.

- **Stratum basale** or stratum **germinativum**: it consists of a single layer of keratinocytes with cuboidal morphology. It is the proliferative sector and contains two cell types:
  - Stem cells (or progenitor cells), which can replicate indefinitely and give rise to transit amplifying cells;
  - Transit amplifying cells, which can divide a finite number of times and then undergo terminal differentiation as they move towards the most superficial layers.
- **Stratum spinosum**: it is composed of several layers of polygonal cells (four to ten) with spinous processes and represents the maturation sector.
- **Stratum granulosum**: it is the preterminal differentiation sector and is made up of two to three layers of flattened epithelial cells. Their cytoplasm contains large keratohyalin granules and lamellar bodies of Odland. Odland bodies contain precursors of lipids important for the barrier function of skin that will be released in the intercellular space of the stratum corneum.
- **Stratum lucidum**: it can only be found in the skin of the palms of the hands and soles of the feet. Cells in this layer contain eleidin.

— **Stratum corneum**: made up of 10–20 layers of anucleate, keratinized cells that have lost all organelles and are filled with keratin, this is the final differentiation area and is normally not found in mucosal areas. Cells are furthermore surrounded by a cornified cell envelope of insoluble proteins and a lipid envelope, composed mainly of ceramides, derived from the exocytosis of Odland bodies.
  – The cornified cell envelope and the lipid envelope form the water barrier of the epidermis.

The **epidermal keratinization unit** is the portion of epidermis deriving from a single basal stem cell and its related transient amplifying cells.

Intraepidermal cell junctions

— **Maculae adhaerentes** or **desmosomes** are the main adhesion complex of keratinocytes. They anchor keratin filaments to the membrane on one side, and bind to desmosomes of adjacent keratinocytes on the other, enabling cells to withstand trauma;
— **Zonulae adhaerentes** or **intermediate/adherens junctions** bind to the actin cytoskeleton. They play an important role in the maintenance of epidermal stratification;
— **Zonulae occludentes** or **tight/occluding junctions**: Constituting the permeability barrier, these can selectively leaky to different molecules;
— **Maculae comunicantes** or **gap junctions** allow the exchange of ions and low molecular weight substances. They are important for the regulation of keratinocyte differentiation and maturation.

Dermal–epidermal junction

When studied with light microscopy, the dermal–epidermal junction can be seen in PAS–stained histological sections. It is characterized by a wavy profile due to the presence of dermal papillae (dermal protrusions that project into the epidermis) and corresponding epidermal ridges (epidermal protrusions projecting into the dermis).

Electron microscopy allows identification of four components:

- **Basal cell plasma membrane,** which contains hemidesmosomes (junctions similar to desmosomes, linking the cytoskeletal intermediate filaments to the underlying connective tissue) and focal adhesions (anchor actin filaments into the basement membrane);
- **Lamina lucida**, an electron lucent area between the basal lamina and the cell membrane. It is traversed by anchoring filaments (laminin 5), which connect hemidesmosomes to the lamina densa. Some studies suggest that it may actually be an artifact of fixation;
- **Basal lamina** or **lamina densa**, an electron dense layer mainly composed of type IV collagen, and also laminins, proteoglycans and glycoproteins.
  - On the epidermal side, the basal lamina is connected to hemidesmosomes by anchoring filaments (formed by laminin 5), whereas on the dermal side, it is connected to the reticular lamina through anchoring fibrils (formed by type VII collagen).
- **Fibro–reticular lamina**, merges with the dermis and is traversed by anchoring fibrils. Type III collagen (reticular fibers) are a product of the dermis (not of the epithelium).

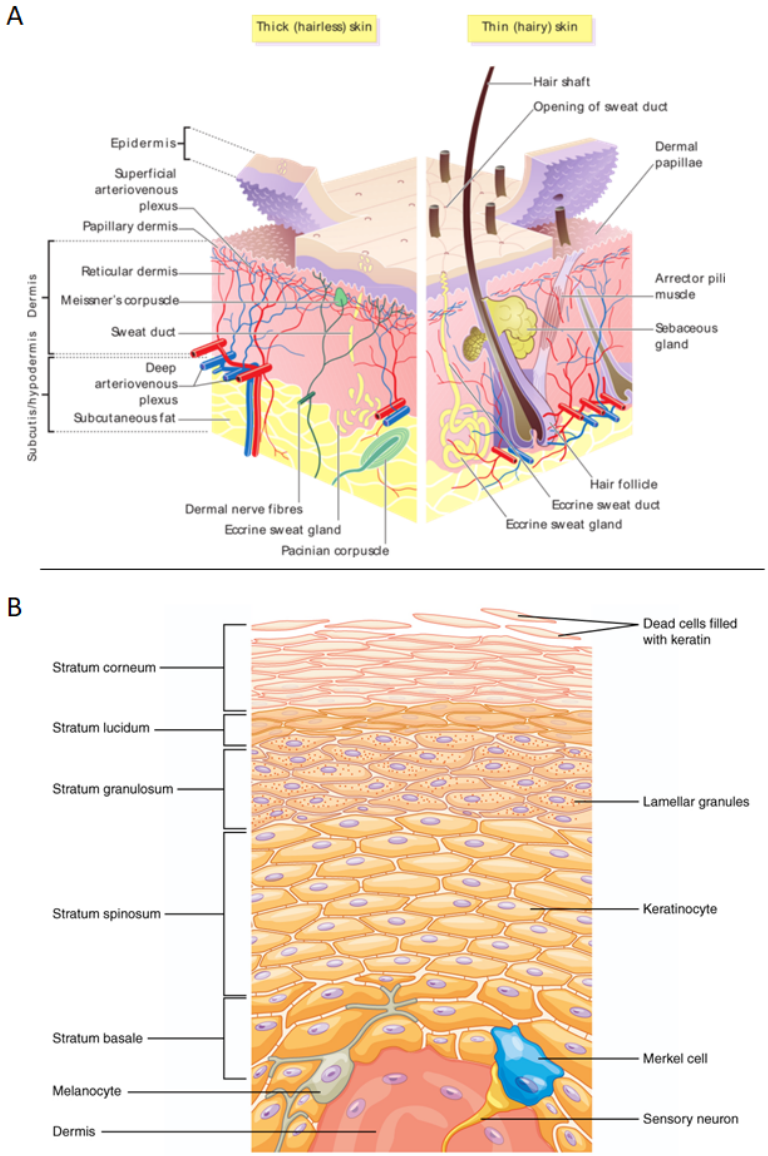

Figure 1. A: Anatomic structures within the skin; B: Epidermal layers (adapted from: Wikimedia Commons).

Cells of the epidermis

In addition to keratinocytes, we can find four additional cell types in the epidermis, which are melanocytes, Langerhans' cells, Merkel cells and T–lymphocytes.

— **Melanocytes** derived from the neural crest:

  – They are found in the stratum basale, where there are an average of ten basal cells for every melanocyte. Melanocytes are dendritic cells because of their long processes that bridge numerous cells of the epidermis;
  – They are not connected to epidermal cells;
  – They synthesize melanin in melanosomes, which then mature into melanin pigment granules that are transferred to basal cells and to the shaft of hair follicles;
  – Melanin granules can either be eliminated with corneal cells or be destroyed by lysosomes in keratinocytes of the stratum spinosum.

— **Langerhans' cells**: originate from the common lymphoid progenitor:

  – Found in the stratum spinosum;
  – Langerhans' cells are antigen presenting dendritic cells;
  – They can be identified by the fact that their cytoplasm contains Birbeck granules, and they are ATPase and S–100 positive.

— **Merkel cells**:

  – They are found in the stratum basale;
  – They have a sensory function, and each Merkel cell is associated with a sensory nerve ending. They are most numerous in areas of high tactile acuity.

— **T–lymphocytes**: can move into the epidermis and reside there (*dermatotropism*) or move out of there (*exocytosis*).

1.2. *Dermis*

The dermis is the connective tissue beneath the epidermis that gives the skin mechanical support and strength. It can be divided in three layers: superficial, middle and deep.

— The **superficial** or **papillary layer** is a thin layer of loose connective tissue, characterized by the presence of dermal papillae. The connective tissue fibers are loosely organized and thin, and consist mainly of reticular fibers (type III collagen), type I collagen and elastic fibers. It contains small blood vessels that supply, but do not enter the epidermis, and sensory nerve endings;
— In the **middle layer**, collagen fibers are thicker and more organized, forming a more compact and dense tissue. There are fewer reticular fibers. Arterioles and venules are found in this layer;
— The **deep layer** is characterized by thick bundles of type I collagen and coarser elastic fibers that are arranged in regular lines of tension that form Langer's lines. Vessels are of even greater caliber in this layer.

The acellular components are collagen fibers, elastic fibers and ground substance.

Cells of this layer include fibroblasts, mast cells, dendritic cells, and non–resident cells from blood (lymphocytes, plasma cells, etc.).

1.3. *Subcutaneous tissue / Hypodermis*

It is a connective tissue specialized in fat production and thus contains variable amounts of adipose tissue arranged in lobules separated by connective tissue septa. The characteristic cellular element of this tissue is the adipocyte. About 80% of body fat is subcutaneous.

1.4. *Skin Appendages*

They include hair, nails, and glands.

— **Hairs** are composed of keratinized cells developing from follicles (an invagination of the epidermis), at the base of which is

the dermal papilla. The epithelial cells around this area make up the matrix, which is the proliferative layer of the follicle and also contains melanocytes (responsible for melanin production and thus coloration of the hair). Hair is absent from palms, soles, lips and urogenital orifices only. A sebaceous gland secretes its product into the follicle and an arrector pili muscle inserts on it. The hair follicle, hair, arrector pili muscle and sebaceous gland make up the **pilosebaceous unit**;

— Glands in the skin are of three types:
  - **eccrine sweat glands**,present along the entire cutaneous surface, except the labia minora, the internal surface of the prepuce, the glans and the inner surface of the pinna. They are most numerous in the palms of the hand, the soles of the feet and on the forehead. They produce sweat and are responsible for thermoregulatory sweating;
  - **apocrine sweat glands** are found only in certain areas of the body: armpits, mammary areola, the area of the abdomen below the umbilicus, inguinal folds, mons pubis, labia majora, scrotum and perineum. Their excretory ducts end in the pilosebaceous follicle. They do not serve a thermoregulatory purpose, but produce lipid and protein rich secretions that may function as pheromones;
  - **sebaceous glands** are part of the pilosebaceous unit, meaning they are present in areas with hair. They are branched acinous glands producing a holocrine secretion called sebum (an oily substance that coats hair and skin).

— Nails are composed of a nail plate, nail bed, matrix, hyponychium, the proximal nail fold, eponychium (cuticle), and paronychium (lateral nail folds):
  - The **nail plate** is a rigid structure, rich in sulfur, consisting of keratinized cells that do not desquamate, containing hard keratin (like that of hair) as opposed to soft keratin of the epidermis;
  - The nail plate emerges from beneath the **proximal nail fold**,which has a dorsal (superficial) and a ventral surface; at the junction between the two surfaces is the **eponychium,** or cuticle. The nail plate is bordered on its sides

by **lateral nail folds**. The **hyponychium** is a thickened epidermal layer between the skin of the fingertip and the free edge of the nail plate, which secures the nail plate;
- The nail plate lies on the **nail bed**, consisting of a thin epidermal layer and a dermal layer (which contains blood vessels imparting the typical pink color of nails);
- The **matrix** is the germinative zone and is beneath the proximal nail fold. It contains stem cells that divide, migrate and differentiate into keratinized cells that become integrated in the nail plate as onychocytes;
- There may be a white crescent shaped area near the root, called the **lunula**, which is the visible portion of the distal matrix. The nail plate becomes transparent as it becomes fully keratinized.

1.5. *Cutaneous Circulation*

The cutaneous circulation is formed by a continuous artero–capillary–venous network.

The skin has two vascular plexuses that run parallel to the cutaneous surface: a deep cutaneous vascular plexus, found between the hypodermis and the dermis, and the superficial subpapillary plexus. Vessels originating from the deep cutaneous plexus reach the dermis and form the subpapillary plexus, from which capillary loops extend into the dermal papillae (note that vessels do not enter the epidermis). Blood is then drained by venules forming intermediate plexuses.

The main function of the cutaneous circulation is to provide nutrient and oxygen supply, but also plays an important role in thermoregulation. This is achieved by controlling blood flow to the superficial layers of the dermis through the arteriovenous anastomoses that act like shunts. Vasodilation and opening of blood vessels increase blood flow to the skin allowing heat dissipation, whereas vasoconstriction permits conservation of body heat.

Parallel to the blood network is a lymphatic network.

1.6. *Cutaneous Innervation*

The cutaneous innervation is made up by a nervous network that branches in the dermis and surrounds the skin appendages. The skin is endowed with sensory receptors (sensory nerve termini) as well as motor autonomic nerve endings to blood vessels, arrector pili muscles and sweat glands.

Sensory nerve termini can be categorized into free and encapsulated nerve endings:

- Free nerve endings are unmyelinated fibers transmitting mainly pain sensation;
- Encapsulated nerve endings (enclosed in a connective tissue capsule) transmit information about touch and temperature, and include:
  - Pacinian corpuscles (rapid vibrations around 200–300 Hz and pressure);
  - Golgi–Mazzoni corpuscles (similar to Pacinian, but found only in fingertips);
  - Meissner's corpuscles (changes in texture and slow vibrations around 50 Hz);
  - Ruffini's corpuscles (tension deep in the skin and tendons; sliding over skin; temperature);
  - Krause's corpuscles (in mucosa of lips and tongue and penis and clitoris, cold temperature receptors);
  - Free nerve endings (temperature, pain, touch, pressure, stretching).

1.7. *Skin Functions*

The skin performs six major functions:

a) **Protection** from physical (trauma and electromagnetic radiation), chemical and biological agents, acting as a **barrier**. In particular, protection from UV light damage is provided by melanin, a pigment that absorbs UV light;
b) **Regulation of body temperature** through sweating and vascular reflexes;

c) **Regulation of water homeostasis** through perspiratio insensibilis and transpiration;
d) **Sensory activity**, transmitting information about the external environment to the central nervous system;
e) **Metabolic functions** (UV light converts 7–dehydrocholesterol to cholecalciferol, an essential step for vitamin D3 activation);
f) **Immunological activity**, thanks to epithelial cells themselves, which participate in innate immunity, and the other cells of the immune system present in this tissue.

2. Skin Lesions

For an appropriate differential diagnosis of any skin disorder, detecting and correctly describing and classifying any skin lesion a patient may have is key. In particular, one must determine the color, shape, distribution, pattern and arrangement of skin lesions, as well as their size and composition. It is also important to determine whether they are primary or secondary skin lesions. Primary lesions are features of skin disease that are unmodified by external forces, whereas secondary lesions are modifications of primary lesions by an external influence.

2.1. *Primary Skin Lesions*

Primary skin lesions include macules, papules, nodules, wheals, vesicles, bullae and pustules. **Macules** are flat, circumscribed, non–palpable lesions of any shape that differ in color from the surrounding skin. They can be of various types:

— *Erythematous* macules are pink–red in color and fade when pressure is applied. They are typical of measles, rubella, and drug–induced rashes;
— *Vascular* macules also disappear with pressure and are the result of vasodilation in the superficial derma. We can distinguish acquired vascular macules (telangiectasia) and congenital vascular macules (flat hemangiomas);
— *Purpuric* macules, instead, do not disappear with pressure. They are the result of extravasation of blood in the dermis;

— *Pigmented* macules can vary in color, and include café au lait spots, ephelids, fixed drug eruptions, Mongolian spots, and tattoos;
— *Achromic* macules are areas of discoloration due to a reduction of melanin content of the epidermis. Examples include vitiligo and epiloia.

Papules are elevated, solid, palpable lesions less than 1cm in diameter.

— *Epidermal* papules are the result of a thickening of the epidermis and can be follicular (follicular hyperkeratosis), or non follicular (warts);
— *Dermal* papules are due to thickening of the dermis. Examples include papular amyloidosis, papular mucinosis, and secondary syphilis;
— *Dermo–epidermal* papules are due to thickening of both dermis and epidermis, for example lichen ruber planus.

Nodules are elevated, solid, palpable lesion that are distinguished from papules by their diameter of more than 1 cm. Nodules may consist of fluid, extracellular material, inflammatory infiltration or neoplastic cells. Examples include fibromas, basaliomas, melanomas, and lymphomas. The image depicts a rheumatoid nodule.
Wheals are short–lived elevations of the skin due to dermal edema, and are often pale centrally with an erythematous rim. They have variable dimensions, elastic consistency and are itchy. They are seen in urticaria and insect bites.
Vesicles are circumscribed, elevated, fluid–filled lesions $\leq$ 1cm in diameter. They can be clear, serous or hemorrhagic.

— *Epidermal* vesicles are seen in herpes simplex, varicella, herpes zoster and eczema;
— *Sub–epidermal* vesicles are seen in herpetic dermatitis.

A **bulla**, a circumscribed, fluid–filled lesion of >1cm in diameter that contains liquid (clear, serous or hemorrhagic) differs from vesicles by its diameter.

— **Intraepidermal** bullae are seen in pemphigus vulgaris and pemphigus erythematosus;
— **Subepidermal** bullae are seen in bullous pemphigoid.

Pustules are circumscribed, elevated lesions containing pus. They may appear as primary skin lesions, but also may develop from vesicles or bullae. We can distinguish **follicular** pustules, such as acne and folliculitis, and **non–follicular** pustules, such as pustular psoriasis or subcorneal pustular dermatosis.

2.2. *Secondary Skin Lesions*

Secondary skin lesions include scales, crusts, excoriations, fissures, exulcerations, ulcers and scars.
Scales are visible accumulations of keratin, forming a flat plate or flake. It is the product of exfoliation of the stratum corneum. Based on size and thickness we can distinguish, from smallest to largest, furfuraceous, pityriasiform, lamellar and laminar scales.
Crusts are formed when organic liquids, which can be physiological or pathological (serum, blood, pus, etc.), dry out. Crusts appear in areas corresponding to former skin lesions, and their color and size varies depending on the skin lesion that preceded the crust.
Excoriation is a loss of epidermis and a portion of the dermis due to scratching or an exogenous injury. They may be covered by crusts.
Fissures are linear ulcers that break through the superficial layer of the dermis. They are painful and determined by a loss of skin elasticity. An example is athlete's foot.
An **erosion** or **exulceration** is a circumscribed loss of substance of variable extension, involving the epidermis and superficial layer of the dermis, determined by a pathological process.
An **ulcer** is a loss of substance that involves epidermis, dermis and hypodermis. Spontaneous resolution is difficult to achieve. It is almost always painful.
Scars are the result of repair of a cutaneous loss of substance (due to trauma or disease) by replacement with newly formed connective tissue and epidermis. Scars result only if the loss of substance extends beyond the dermal–epidermal junction.

2.3. *Pathognomonic Lesions*

Scutula are characteristic of favus (tinea favosa). A scutulum is a yellow, cup–shaped crust (1–2 mm) that develops around a hair that is then lost. Combined with secondary bacterial infection, it has an odor that has been compared to that of mouse urine.
Burrows are pathognomonic lesions of scabies. They consist of the intraepidermal tunnel created by the mite. They are small (2–3 mm) elevations with a cephalic extremity, which is the point of entry of the mite, and a caudal extremity, marked by a pearly vesicle containing the mite.

Figures

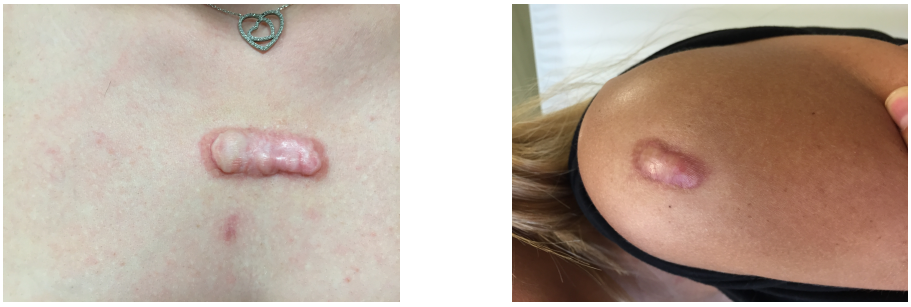

Figure 2. Keolid.

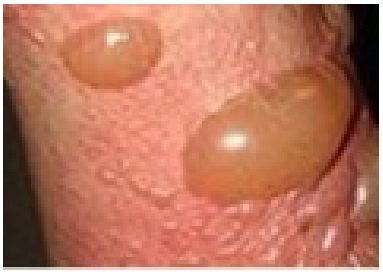

Figure 3. Bulla.