

## **Toxicology 4<sup>th</sup> stage**

### **Skin toxicity**

The skin protects the body against external insults to maintain internal homeostasis. It participates directly in thermal, electrolyte, hormonal, metabolic, and immune regulation. If an insult is severe or intense enough to overwhelm the protective function of the skin, acute or chronic injury becomes readily manifest. The specific presentation depends on a variety of intrinsic and extrinsic factors, including body site, duration of exposure, and other environmental conditions

### **Factors Influencing Cutaneous Responses**

#### **1-Body site**

##### **Palms/soles**

Thick stratum corneum—good physical barrier, Common site of contact with chemicals, Occlusion with protective clothing

##### **Intertriginous areas (axillae, groin, neck, finger webs, umbilicus, genitalia)**

Moist, occluded areas, Chemical trapping, Enhanced percutaneous absorption

##### **Face**

Exposed frequently, Chemicals frequently transferred from hands

##### **Eyelids**

Poor barrier function—thin epidermis, Sensitive to irritants.

##### **Postauricular region**

Chemical trapping and occlusion

##### **Scalp**

Occlusion, Chemical trapping, Hair follicles susceptible to metabolic damage

#### **2-Genetic factors**

Predisposition to skin disorders, Variation in sensitivity to irritants, Susceptibility to contact sensitization

#### **3-Temperature**

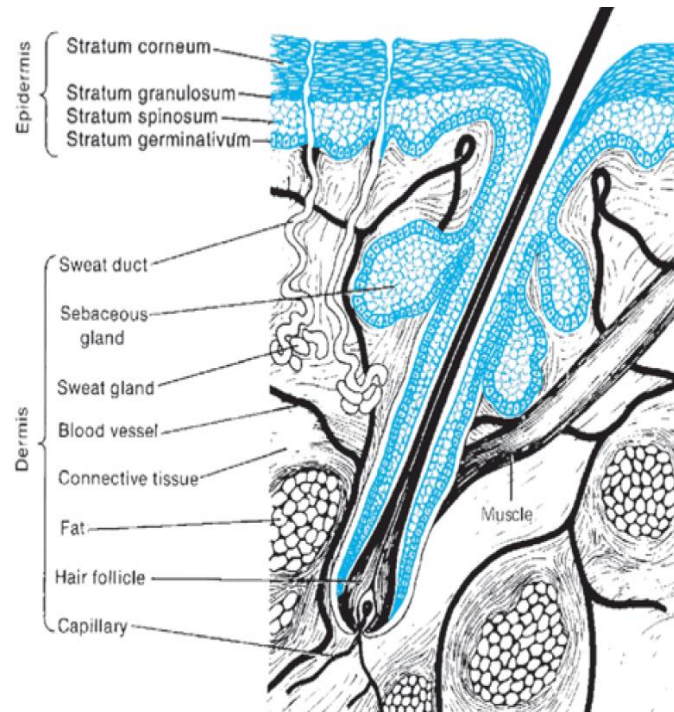
Vasodilation—improved percutaneous absorption, Increased sweating—trapping

## 4-Humidity

Increased sweating—trapping

The skin consists of two major components the outer epidermis and the underlying dermis .epidermal appendages (hair follicles, sebaceous glands, and eccrine glands) span the epidermis and are embedded in the dermis.

In regard to thickness, the dermis makes up approximately 90 percent of the skin and has largely a supportive function. Separating the dermis from underlying tissues is a layer of adipocytes whose accumulation of fat has a cushioning action.



The blood supply to the epidermis originates in the capillaries located in the rete ridges at the dermal-epidermal junction. Capillaries also supply the bulbs of the hair follicles and the secretory cells of the eccrine (sweat) glands. The ducts from these glands carry a dilute salt solution to the surface of the skin, where its evaporation provides cooling

Melanocytes are interspersed among the basal cells and distributed in the papilla of hair follicles. In the epidermis, these cells are stimulated by ultraviolet light to produce melanin granules. The granules are extruded and taken up by the surrounding keratinocytes, which there by become pigmented. Migrating through the epidermis are numerous Langerhans cells, which are important participants in the immune response of skin to foreign agents.

### **Percutaneous Absorption**

The stratum corneum is the primary barrier to percutaneous absorption. Diseases (e.g., psoriasis) and other conditions (e.g., abrasion, wounding) that compromise this barrier can permit greatly increased uptake of poorly permeable substances. The viable layer of epidermis provides a much less effective barrier, because hydrophilic agents diffuse readily into the intercellular water, whereas hydrophobic agents can

partition into cell membranes, and each can diffuse readily to the blood supply in the rete ridges of the dermis.

### **Transdermal Drug Delivery**

Specially designed patches are currently in use to deliver clonidine, estradiol, testosterone, nitroglycerin, scopolamine, fentanyl, and nicotine for therapeutic purposes, and others are under development. The advantages of this approach over oral dosing include providing a steady infusion for extended periods (typically 1 to 7 days), thus avoiding large variations in plasma concentration; preventing exposure to the acidic pH of the stomach; and avoiding first-pass removal by the gastrointestinal tract or liver.

### **Biotransformation**

The ability of the skin to metabolize agents that diffuse through it contributes to its barrier function. This influences the potential biological activity of xenobiotics and topically applied drugs, leading to their degradation or their activation as skin sensitizers or carcinogens. The epidermis and pilosebaceous units are the major sites of such activity in the skin. Enzymes participating in biotransformation that are expressed in skin include multiple forms of cytochrome P450, epoxide hydrolase, UDP-glucuronosyltransferase, quinone reductase, and glutathione transferases. Other metabolic enzyme activities that are detected in human epidermal cells include sulfatases,  $\beta$ -glucuronidase, *N*-acetyltransferases, esterases, and reductases. The intercellular region of the stratum corneum has catabolic activities (e.g., proteases, lipases, glycosidases, phosphatase).

### **Contact Dermatitis**

two distinct inflammatory processes caused by adverse exposure of the skin: irritant and allergic contact dermatitis. These syndromes have indistinguishable clinical characteristics. Classically, erythema (redness), induration (thickening and firmness), scaling (flaking), and vesiculation (blistering) are present on areas in direct contact with the chemical agent

#### **1-Irritant Dermatitis**

Irritant dermatitis is a non-immune-related response caused by the direct action of an agent on the skin. Extrinsic variables such as concentration, pH, temperature, duration, repetitiveness of contact, and occlusion have a significant impact on the appearance of the eruption. Strong acids, bases, solvents, and unstable or reactive chemicals among human irritants. Direct corrosives, solvents, oxidizing and reducing agents, and dehydrating agents act as irritants by disrupting the keratin ultrastructure or directly injuring critical cellular macromolecules or organelles. Marginal irritants (detergents, soaps, household cleaners) require multifactorial variables to create disease and may not be capable of producing reactions under all

circumstances. The varying time courses necessary to produce dermatitis by different known irritants result from differing rates of percutaneous absorption and also depend on the specific agent selected

### **Chemical Burns**

Extremely corrosive and reactive chemicals may produce immediate coagulative necrosis that results in substantial tissue damage, with ulceration and sloughing. This is distinct from irritant dermatitis, since the lesion is a direct result of the chemical insult and does not rely heavily on secondary inflammation to manifest the cutaneous signs of injury. In addition to the direct effects of the chemical, necrotic tissue can act as a chemical reservoir, resulting in either continued cutaneous damage or percutaneous absorption and systemic injury after exposure.

### **2-Allergic Contact Dermatitis**

Allergic contact dermatitis represents a delayed (type IV) hypersensitivity reaction. Only minute quantities of material are necessary to elicit overt reactions. This is distinct from irritant contact dermatitis, in which the intensity of the reaction is proportional to the dose applied. An estimated 20 percent of all cases of contact dermatitis are allergic in nature, or allergic contact dermatitis to occur, one first must be sensitized to the potential allergen. Subsequent contact elicits the classic clinical and pathologic findings. To mount an immune reaction to a sensitizer, one must be genetically prepared to become sensitized, have sufficient contact with a sensitizing chemical, and then have repeated contact later, Common Contact Allergens ,Bacitracin, Neomycin, Aminoglycosides, Sulfonamides, Benzalkonium chloride, Chlorhexidine, Chloroxylenol, Chromium, Cobalt

### **Phototoxicology**

In the course of a lifetime, the skin is exposed to radiation that spans the electromagnetic spectrum, including ultraviolet (UV), visible, and infrared radiation from the sun, artificial light sources, and heat sources. In general, the solar radiation reaching the earth that is most capable of inducing skin changes extends from 290 to 700 nm, the ultraviolet and visible spectra. For any form of electromagnetic radiation to produce a biological change, it first must be absorbed. The absorption of light in deeper, more vital structures of the skin is dependent on chromophores, epidermal thickness, and water content that differ from region to region on the body. The chromophores melanin and amino acids are capable of absorbing UV-B (290 to 320 nm) radiation

### **Adverse Responses to Electromagnetic Radiation**

After exposure, the most evident acute feature of UV radiation exposure is erythema (redness or sunburn). The minimal erythema dose (MED), the smallest

dose of UV light needed to induce an erythematous response, varies greatly from person to person. The vasodilation responsible for the color change is accompanied by significant alterations in inflammatory mediators such as prostaglandins D<sub>2</sub>, E<sub>2</sub>, and F<sub>2</sub>; leukotriene B<sub>4</sub>; and prostacyclin I<sub>2</sub>. Also, interleukin-1 (IL-1), released from local inflammatory cells as well as from injured keratinocytes, may be responsible for several of the systemic symptoms associated with sunburn, such as fever, chills, and malaise.

UV-B (290 to 320 nm) is the most effective solar band in causing erythema in human skin. Environmental conditions that affect UV-induced injury include duration of exposure, season, altitude, body site, skin pigmentation, and previous exposure. A substantially greater dosage of UV-A (320 to 400 nm) reaches the earth compared with UV-B (up to 100-fold); however, its efficiency in generating erythema in humans is about 1000-fold less than that of UV-B. Overt pigment darkening is another typical response to UV exposure. This may be accomplished by enhanced melanin production by melanocytes or by the photooxidation of melanin. Tanning or increased pigmentation usually occurs within 3 days of exposure to UV light, whereas photooxidation is evident immediately. The tanning response is produced most readily by exposure in the UV-B band. The tanning response serves to augment the protective effects of melanin in the skin. However, the immediate pigment-darkening characteristic of UV-A and visible light exposure does not confer improved photoprotection

### **Photosensitivity**

An abnormal sensitivity to UV and visible light, photosensitivity may result from endogenous or exogenous factors. Various genetic diseases and the autoimmune disease lupus erythematosus impair a cell's ability to repair UV light-induced damage. In hereditary or chemically induced porphyrias, enzyme abnormalities disrupt the biosynthetic pathways that produce heme, leading to the accumulation of porphyrin precursors or derivatives throughout the body. These compounds in general fluoresce when exposed to light of 400 to 410 nm (Soret band) and in this excited state interact with cellular macromolecules or with molecular oxygen to generate toxic free radicals. Chlorinated aromatic hydrocarbons induce this syndrome

### **Phototoxicity**

Phototoxic reactions from exogenous chemicals may be produced by systemic or topical administration or exposure. In acute reactions, the skin may appear red and blister within minutes to hours after ultraviolet light exposure and resemble a bad sunburn. Chronic phototoxic responses may result in hyperpigmentation and thickening of the affected areas. UV-A (320 to 400 nm) is most commonly responsible; UV-B (290 to 320 nm) occasionally may be involved

## Photoallergy

In contrast to phototoxicity, photoallergy represents a true type IV delayed hypersensitivity reaction. Hence, while phototoxic reactions can occur with the first exposure to the offending chemical, photoallergy requires prior sensitization. Induction and subsequent elicitation of reactions may result from topical or systemic exposure to the agent. If the exposures are topical, the reactions are termed *photocontact dermatitis*, whereas systemic exposures are termed *systemic photoallergy*

## Acne

Acne is a pleomorphic disease with a multifactorial etiology. The influence of sebum, hormones, bacteria, genetics, and environmental factors is well known. In many situations, one of these factors has an overwhelmingly greater influence in the genesis of lesions than do the others

Chemicals that are termed *comedogenic* induce comedone lesions, which may be open or closed (blackhead or whitehead, respectively, in the vernacular). Additionally, papules, pustules, cysts, and scars may complicate the process. Hair follicles and associated sebaceous glands become clogged with compacted keratinocytes that are bathed in sebum. The pigmentary change most evident in open comedones comes from melanin.

## Pigmentary Disturbances

Several factors influence the appearance of pigmentation on the skin. Melanin is produced through a

### Selected Phototoxic Chemicals

<b>Furocoumarins</b>
8-Methoxypsoralen
5-Methoxypsoralen
Trimethoxypsoralen
<b>Polycyclic aromatic hydrocarbons</b>
Anthracene
Fluoranthene
Acridine
Phenanthrene
<b>Drugs</b>
Tetracyclines
Sulfonamides
Sulfonylureas
Nalidixic acid
Thiazides
Phenothiazines
Nonsteroidal anti-inflammatories
<b>Dyes</b>
Disperse blue 35
Eosin
Acridine orange
<b>Porphyrin derivatives</b>
Hematoporphyrin

### Selected Causes of Cutaneous Pigmentary Disturbances

<b>I. Hyperpigmentation</b>
Ultraviolet light exposure
Postinflammatory changes (melanin and/or hemosiderin deposition)
Hypoadrenalism
Internal malignancy
Chemical exposures
Coal tar volatiles
Anthracene
Picric acid
Mercury
Lead
Bismuth
Furocoumarins (psoralens)
Hydroquinone (paradoxical)
<b>Drugs</b>
Chloroquine
Amiodarone
Bleomycin
Zidovudine (AZT)
Minocycline
<b>II. Hypopigmentation/depigmentation/leukoderma</b>
Postinflammatory pigmentary loss
Vitiligo
Chemical leukoderma/hypopigmentation
Hydroquinone
Monobenzyl, monoethyl, and monomethyl ethers of hydroquinone
<i>p</i> -( <i>t</i> -Butyl)phenol
Mercaptoamines
Phenolic germicides
<i>p</i> -( <i>t</i> -Butyl)catechols
Butylated hydroxytoluene

series of enzymatic pathways that begin with tyrosine. Errors in this pathway or exposure to tyrosine analogs may result in abnormal pigmentation. Hyperpigmentation results from increased melanin production or deposition of endogenous or exogenous pigment in the upper dermis. Exogenous hyperpigmentation can arise from deposition of metals and drugs in dermal tissue. Conversely, hypopigmentation is a loss of pigmentation resulting from melanin loss, melanocyte damage, or vascular abnormalities.

## **Urticaria**

Urticaria is an immediate type I hypersensitivity reaction driven primarily by histamine and vasoactive peptide release from mast cells. Potential nonimmune releasers of histamine from mast cells include curare, aspirin, azo dyes, benzoates, and toxins from plants and animals. The majority of urticarial responses result either from systemically ingested substances to which a person has a specific allergy or from completely idiopathic mechanisms. Localized urticaria may be elicited by certain substances in the area of epicutaneous contact and is referred to as *contact urticaria*. A syndrome of contact urticaria, rhinitis, conjunctivitis, asthma, and rarely anaphylaxis and death has been associated with latex proteins found in rubber. The allergens in natural latex rubber are incompletely characterized water-soluble proteins that are capable of inducing type I allergic responses in sensitized individuals

## **Toxic Epidermal Necrolysis**

Toxic epidermal necrolysis (TEN) represents one of the most immediately life-threatening dermatologic diseases and often is caused by drugs and chemicals. It is characterized by full-thickness necrosis of the epidermis accompanied by widespread detachment of this necrotic material. After the epidermis has sloughed, only dermis remains, severely compromising heat, fluid, and electrolyte homeostasis. The inflammatory reaction of CD8 lymphocytes and a role of nitric oxide metabolites as mediators of epidermal necrosis in TEN.

## **Carcinogenesis**

### **Radiation**

Skin cancer is the most common neoplasm in humans. At present, the major cause of skin cancer is sunlight, which damages epidermal cell DNA. UV-B (290 to 320 nm) induces pyrimidine dimers, thus eliciting mutations in critical genes. The *p53* tumor suppressor gene has been targeted in nearly all squamous cell carcinomas. Because the *p53* protein arrests cell cycling until DNA damage is repaired and may induce apoptosis, its loss destabilizes the genome of initiated cells and gives them a growth advantage. UV light also has immunosuppressive effects that may help skin tumors survive

## **Polycyclic Aromatic Hydrocarbons**

Substances rich in polycyclic aromatic hydrocarbons (coal tar, creosote, pitch, and soot) are skin carcinogens in humans and animals. Oxidative biotransformation of polycyclic aromatic compounds produces electrophilic epoxides that can form DNA adducts

## **Arsenic**

High exposures from smelting operations and from well water derived from rock strata with a high arsenic content are associated with arsenical keratoses (pre-malignant lesions), blackfoot disease (a circulatory disorder that reflects endothelial cell damage), and squamous cell carcinoma of the skin and several other organs (bladder, lung, liver). Arsenite (+3 oxidation state) avidly binds vicinal thiols and is thought to inhibit DNA repair, whereas arsenate (+5 oxidation state) can replace phosphate in macromolecules such as DNA, but the resulting esters are unstable. Arsenic also alters DNA methylation, suppresses keratinocyte differentiation markers, and enhances growth factor secretion in the epidermis