The First Clinical Manifestation of Atopy

Among the skin allergy diseases, we distinguish atopic dermatitis (AD) and urticaria-angioedema, characterized by IgE-mediated reactions, as well as allergic contact dermatitis (ACD), with prevalent delayed-type hypersensitivity (DTH) cell-mediated reactions, where the allergens reach the skin directly (unlike AD). Urticaria, the most immediate, also occurs in the first phase of AD. Depending on its onset, AD is the first atopic disease in an absolute sense: the dendritic cells (DCs) appear first in the skin and then in the lungs (Fig. 2.24), and CLA (cutaneous lymphocyte-associated antigen) [195] is expressed by 45% of skin T cells [24], but not by lung T cells [196].

The first description of AD could go back two millennia as, according to the historian Svetonius, Emperor Augustus suffered from an extremely itchy skin disease, in addition to chest tightness and seasonal rhinitis. In 1891, Brocq and Jacquet classified AD as neurodermatitis [27], a term that often occurs in the German literature, but this is confusing because one might deduce that AD could be caused by a nervous system instability. The following year, Besnier separated AD from the diseases with itching and described it with the term “prurigo diathèse,” underlining its hereditary nature, the frequent association with asthma and pollinosis in the same patient, as well as its typical skin lesions [16]. In 1933, Wise and Sulzberger coined the term “atopic dermatitis,” indicating that it could be considered as the “skin analogous of asthma and allergic rhinitis” (AR) [314]. The term “eczema,” although widely employed, is merely descriptive, being a simple transliteration of the Greek word ἐκζέμα, meaning “boiling out,” and is misleading, since it fails to imply both the serum exudation in infants and the dry and scaling lesions in older children. This is why we cannot comply with the term “atopic eczema/dermatitis syndrome” proposed by the European Academy of Allergy and Clinical Immunology (EAACI).

Several factors are implied by AD appearance and subsequent evolution. Recent evidence suggests intriguing aspects of the Th1-Th2 contraposition [269]: aeroallergens such as Der p (also as a contact allergen) and pollens can contribute to AD outbreaks and the study of some staphylococcal enterotoxins (SEs) has attracted growing interest, since they are able to act as microbial superantigens (Table 1.29), in addition to the possible keratinocyte pathogenic role capable of producing a veritable arsenal of inflammatory interleukins (ILs). Since AD is an IgE-mediated disease, blood and tissue eosinophils express CD137 [100]. In high-risk (HR) neonates, it is hypothesized that a drop in IFN-γ secretion is predictive of AD development, and a specific response to bovine proteins predicts the association with food allergy (FA) [302]. Table 7.1 outlines the main characteristics of AD [147].

Definition

AD is a disease with a poorly understood etiology, exceedingly complex and multifactorial, with a chronic recurring course. Due to its complexity, AD is a disease that defies attempts at definition, with no clear-cut marker such as one type of basic lesion, specific histological patterns and typical laboratory data, but with a chronic and inflammatory state accompanied by intensely pruritic lesions, erythematous, exuding or papulovesicular eruption, where phases of upsurge alternate with periods of remissions, and skin hyperreactivity. Particularly in its severe, chronic form, AD is a distressing and even disabling disease, due to the irritation, dryness, sweating, and itching. The itching with nocturnal exacerbations disrupts nocturnal sleep of both infants and parents, while skin lesions can socially marginalize the affected child/adolescent. Persistence into adulthood is possible, even if some features may be absent [36, 96].

Epidemiology

AD is a disease common in atopic infants (Table 5.6), never observed at birth and rarely in the first 6 weeks of life, the mean age of onset generally being around the 3rd month, thus earlier than that of asthma [48]. In genetically at-risk babies, the onset in 48%–65% of cases was in the first 6 months of life, but even before 4 months of life in 66 babies (57%) [48], in 75%–80% of cases within the 1st year, with a male prevalence higher than females: 1.3–1.5:1 (Table 5.5). Table 5.8 stresses the increasing frequency of AD in the last 25 years.
AD pathogenesis is complex. Therefore it is necessary to focus, beyond the immunological abnormalities, on the particular stigmata characterizing the skin such as xerosis or constitutional dryness associated with alterations of surface lipids and transepidermal water loss and with anomalies of both microvasculature and skin surface barrier function.

### The Role of Skin Surface Barrier

The anatomo-functional unit called skin protects the organism from injurious external influences, either passively by means of its basal properties, integrity and impermeability, or actively by developing inflammatory reactions [104]. The main skin constituents are, from the external to the internal layer, epidermis, dermis, and hypodermis. The transitional zone between epidermis and dermis is the dermoepidermal junction. The *epidermis*, a stratified squamous epithelium, as seen in sections perpendicular to the surface, is formed by four main layers, disposed from the skin to the dermoepidermal junction: the corneum, granular, lucidum and basal layers. The last three layers form the *stratum Malpighi*, where 95% of the cells are keratinocytes [10], Langerhans cells (LCs), melanocytes, and less immunocompetent CDs (but IL-producing), disposed in the stratum above the basement membrane, which has no immunological functions being devoid of cells. It is distinctly lamina lucida rich in laminine, lamina densa and sub-lamina densa, consisting of fibronectin, elastin, collagen and myofibrils anchoring to the underlying dermis. Keratinocytes progress through a program of differentiation as they move up through the skin to become corneocytes, dead bundles of precipitated keratin proteins wrapped in remnants of plasma membrane. These proteins form the cutaneous barrier called the *stratum corneum*. The *dermis*, placed immediately beneath the epidermis, consists of fibrous bundles (collagenous and elastic fibers) and connective cells, in addition to a cementing substance formed by ialuronic acid, fibronectin and proteoglicans. The dermis plays an active role in thermoregulatory phenomena, metabolic and nutritive exchanges and immunopathological events. The *hypodermis* consists of adipose and loose connective tissue and performs functions of mechanical support, thermal protection and energy store [70, 104].

The epithelial integrity is maintained by several mechanisms, including the molecular forces which ensure the cohesion between the cells and their peculiar disposition: the adjacent cells are kept together by cytoplasmic processes, forming intercellular bridges, called desmosomes (*macula adherens*), effectively ensuring the connections between epithelial cells, also through keratin filaments formerly known as tonofilaments, which from one side penetrate inside the cells and from the other converge toward the dense plaque of desmosomes [104]. Epithelial integrity is thus ensured by desmosomes disposed among the keratinocytes; the connection systems between columnar and basal cells are completed and strengthened by hemidesmosomes, which promote the adhesion between cell basal facies and basal membrane by tight junctions (*zonula occludens*), and by *zonula adherens*, with no keratin filaments, located just below the junctions [59]. To understand some typical aspects of AD, especially the significance of dry skin and easy aggressiveness of irritants [70], it is necessary to contend with problems related to defective water retention, increased skin permeability and the resulting transepidermal water loss, a characteristic feature [277]. The *stratum corneum* plays a fundamental role in ensuring the skin barrier function, since