

Historical Perspectives on Atopic Dermatitis: Eczema Through the Ages

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Abstract: Throughout history, individuals have had a myriad of dermatologic conditions characterized as chronic pruritic dermatoses. The term atopic dermatitis was not coined until the early 20th century. Many diseases typical of this condition were reported using a variety of eponyms and descriptive terms. Even as the incidence of atopic dermatitis rises, it remains poorly understood in the modern era, and viewing the disease from a historical perspective provides useful insight into its nature. This article highlights the evolution of concepts related to the pathogenesis of and recommended treatments for atopic dermatitis.

Pruritic rashes have long been recognized as specifically dermatologic problems even before the disease entity called atopic dermatitis (AD) was first described in 1933 (1). Because nomenclature in dermatology has transformed so dramatically through the ages, delving into the historical beginnings of AD is best accomplished by studying descriptions, drawings, and images in early medical texts. This article highlights some of the concepts and approaches to AD that have changed over time, based on a number of more modern works that translate and reference older, less accessible documents. Some have remained constant, while others have fallen out of favor in the past, only to return in modern times.

ANCIENT HISTORY

One of the earliest known medical documents referencing dermatology is Ebers Papyrus. Compiled in

Egypt in 1500 BCE, it contains remedies to “still” itching of the skin (2,3). Skin conditions similar to AD were also considered in traditional Chinese medicine (TCM). In accordance with the principles of TCM, external factors such as wind-heat and damp-heat, respectively classified under the elements earth and wood, were often implicated in eczema (4). Several Chinese terms have also been identified that describe entities consistent with infantile eczema (*nai hsien* or *tai lien chung*), with corresponding herbal remedies such as *Hsin-san-miao-san*, that have moisturizing and possibly antiinflammatory effects (4).

Around 400 BCE, Hippocrates added much to ancient understanding by explaining skin conditions as cutaneous manifestations of internal humoral imbalances (6). The Romans later alluded to certain conditions similar to AD. Roman physician Celsus described a condition with a “certain degree of hardness of the skin with pustules, some humid and

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some dry” (7), and the poet Suetonius described the atopic syndrome in Emperor Augustus in his writings *The Twelve Caesars* (8).

Avicenna (980–1037 CE), a Persian polymath, was one of the most prominent physicians of the Middle Ages. Praised by the esteemed William Osler as “a medical Bible,” his *Canon of Medicine* assimilated medical knowledge of the ancients into one comprehensive text (9). Avicenna describes several conditions and treatments consistent with modern knowledge of AD and dry skin. In one anecdote, he notes a connection between bathing and skin dryness, stating that longer bathing times result in dryness and shorter bathing times in skin moistness (10). In another anecdote from *Canon*, Avicenna recognized “undue dryness of the skin of the hands” as its own clinical entity, recommending a specialized bathing procedure to treat it. His description is similar to the hand eczema prevalent today, nearly 1,000 years later.

These ancient schools of thought were integral in contributing to our understanding of AD and laid the foundation for premodern interpretations of the disease.

PREMODERN ERA

The Italian physician Girolamo Mercurialis wrote the first dermatology text in 1572, *De morbis cutaneis*. Mercurialis described an oozing and itchy condition (*achores*) occurring on the heads of infants (11). A century and a half later, the author of a first English dermatology text, Daniel Turner, gave an account of a similar condition with pruritus and “pustulary or scabby eruptions, in several parts of their body, but especially their foreheads, brows, and other parts of the face; which we find oftentimes over-run with dry and crusty scabs” (12). In 1806, French dermatologist Jean-Louis Alibert described another oozing and violently pruritic infantile dermatosis, calling it *teigne muqueuse*, which loosely translates to “mucosal ringworm” (11). These separate yet similar accounts of cephalic oozing in infants may represent historic forerunners of AD or seborrheic dermatitis, which can be difficult to distinguish. From antiquity to the present, it is clear that AD is an itchy disease and thus may be differentiated from seborrheic dermatitis by the fact that the latter is generally not pruritic.

The Hippocratic theory of humoral imbalance, the belief that skin lesions and itchiness were cutaneous rectifications of humoral disequilibrium deeper inside the body, influenced many physicians of the premodern era. The prevailing thought was that skin disease was an essential excretory process that, if disturbed,

would place patients in harm’s way (13,14). Daniel Turner wrote, “itching Humor...which if you go about to heal...you may ’tis certain quickly cure them of their itch, but you will as certainly put them into hazard of their lives, because you thereby pollute their blood and nervous fluid by driving back these excrements into the vessels” (12). This statement demonstrates the reluctance of physicians to provide symptomatic treatment for patients because of the likelihood that they might make things worse, although it is unclear whether available treatments for itching or eczema had any effectiveness at all, and therefore this statement may simply reflect overconfidence or perhaps wishful thinking.

The early 19th century brought with it a great transformation within the realm of dermatology. English physicians Willan and Bateman proposed a new classification scheme for skin disorders, grouping conditions according to their primary lesion (e.g., vesicle, papule, pustule) (11,15). This system was fundamental in building our modern morphologic diagnosis in dermatology but also had the unfortunate side effect of trapping physicians into believing that a disease could have only one type of elementary lesion. For example, Willan and Bateman coined the term “eczema” from the Greek *ekzein*, meaning to erupt or boil over. This condition was characterized by “an eruption of minute vesicles, non-contagious, crowded together” that “lacked surrounding inflammation and smarted rather than itched” (15,16). Although carrying a familiar name, this “eczema” does not appear to be an early description of AD but rather dermatoses related to external exposures such as the sun, irritants, and mercury (15). Willan and Bateman’s works contain an entity more closely resembling AD, *porrigo larvalis* (larvalis: “similar to the mask of a ghost”) (17), a pustular disorder of the head comparable with Alibert’s *teigne muqueuse* and “accompanied with considerable itching and irritation, which, in young infants, often greatly diminish the natural sleep” (16). Other possible precursors of AD found in Willan and Bateman’s works include *strophulus confertus* (strophulus: “a papular rash observed in children”; confertus “close, crowded, dense”) (18,19) and *lichen agrius* (lichen: “a true moss,” used to signify one of the papular diseases; agrius: “inflamed, derived from the word for angry, fierce”) (18,20).

Pierre Rayer first introduced the notion that eczema could be chronic in 1835 (11), writing, “Relapses are observed to happen in almost all diseases, but in none are they more frequent than in eczema...I have seen the disease get well and recur twelve or fourteen times within the space of a few

months” (21). Rayer’s concept of a relapsing and remitting pruritic dermatosis, although central in contributing to our current understanding of eczema, appears to have been muddled with other, unrelated chronic lesions resulting from sun and chemical exposures (15,21).

In 1860, Ferdinand von Hebra, a Viennese dermatologist, depicted a novel disorder that bore some resemblance to AD. “Hebra’s prurigo” was a chronic, relapsing condition arising in infancy as urticaria and later manifesting as itchy papules on the trunk and limbs (11). Hebra wrote, “the most intense form of the disease is displayed on the limbs, especially on their extensor surfaces” (22). Distinctive characteristics included excoriations, symmetric lymphadenopathy, and skin that was thickened, darker, and rough in the affected areas (22). Hebra’s prurigo met with much attention and controversy, because the condition that such an esteemed physician proposed was observed rarely in France and Britain (11,17). Although less frequently encountered and less typical in presentation than present-day AD, Hebra’s prurigo is often still considered a forerunner of our modern conceptualization of AD (20).

Erasmus Wilson (23) is credited with providing a thorough description of infantile eczema, an entity he deemed to be synonymous with Willan and Bateman’s *porrigo larvalis* and Alibert’s *teigne muqueuse*. Wilson’s description of infantile eczema was an eruption that “in young infants commences at the end of the first month or six weeks” and “may be prolonged in a chronic form until manhood, or may hang out for the remainder of his days” (23). It was characterized by severe itching that intensified at night (23). Wilson was the first physician to break free from Willan and Bateman’s method of disease classification, recognizing that, on the same child with infantile eczema “may be seen erythema, lichen, strophulus, eczema, impetigo, pityriasis, and psoriasis” (11,23).

In 1892, French physician and medical director of the Hôpital Saint-Louis, Ernest Besnier, presented at the Société Française de Dermatologie et de Syphiligraphie, introducing a novel skin disorder that would lay the groundwork for our modern-day perception of AD (15). The chronic disorder, which he called prurigo *diathésique* (a diathesis or tendency toward itching), focused on a predominant symptom of pruritus rather than lesional morphology (11,15). Another unique feature was the link to atopic processes such as asthma and hay fever, associations that had been alluded to before Besnier but not woven into a concise description as it was in Besnier’s prurigo (10). Some cite a minor flaw in Besnier’s work in that he did not draw a clear

relationship between prurigo *diathésique* and infantile eczema as a continuous spectrum (11,15). Other members of the French school who contributed to our understanding of AD include Brocq and Jacquet, who proposed the term diffuse (or generalized) neurodermatitis in 1891 to describe a constellation of symptoms that included psychiatric manifestations, chronic pruritus, and lesions in the areas scratched (15).

TWENTIETH CENTURY AND BEYOND

The 20th century brought a shift in nomenclature and studies investigating the etiopathogenesis of AD. Viennese pediatrician Von Pirquet first introduced the term “allergy” in 1906 to describe an abnormal reaction to any substance (17). Shortly thereafter, in 1923, Coca and Cooke proposed the concept of “atopy,” with a term that Edward Perry, professor of Greek at Columbia University, coined in 1923 from the Greek *atopia* meaning “strangeness” or “out of place” (24). They used the term to refer to a heritable hypersensitivity to allergens, typically manifesting as asthma and hay fever (17,25). Wise and Sulzberger furthered Coca and Cooke’s concept by introducing the term “atopic dermatitis” in 1933 to describe a diffuse and pruritic skin disorder characterized by a family history of atopy, flexural distribution, previous history of infantile eczema, certain blood serum components, and other features (1,26). The term “atopic dermatitis” placed emphasis on the association between the skin condition, asthma, and hay fever, although Sulzberger himself said that these were not a necessity for AD (15). The term “atopic dermatitis” eventually replaced the myriad of older names given to the disorder in the past, other than eczema and atopic eczema, which remain in use.

In 1916, Blackfan (27) performed cutaneous testing on individuals with eczema using food proteins, finding that a greater proportion of them had hypersensitivity reactions than did healthy controls. Blackfan and later Talbot discovered that restricting these foods improved patients’ disease (27,28). In 1933, Wise and Sulzberger (1) added to this discussion by stating that the presence of many positive wheal reactions during cutaneous testing with different allergens was a distinguishing characteristic of AD and that logically, therefore, patients should eliminate these allergens from their diet and environment (29). In the 1960s, scientists discovered high levels of serum immunoglobulin E (IgE) in patients with AD and, not long after, higher levels of IgE with more severe AD, as well as distinct IgE antibodies for specific allergens (30–33). These findings, in combination with the

initial food allergy studies, laid the foundation for future research exploring the role of allergy in AD.

In 1980, Hanifin and Rajka (34) published the first set of widely used criteria for AD diagnosis. Major criteria included pruritus, flexural surface involvement in adults or face and extensor surface involvement in infants, chronic and relapsing dermatitis, and personal or family history of cutaneous or respiratory atopy. In 1994, Williams et al (35) modified the Hanifin and Rajka criteria to develop the UK Working Party criteria, in which an individual must have itchy skin for 12 months along with other features.

The realm of AD has evolved and expanded in the new millennium. Scientific research has reached beyond simple studies on allergy and immunology to complex interactions between skin barrier function, environmental factors, genetic susceptibility, inflammatory mediators, and immunologic responses. This knowledge continues to rapidly evolve.

TREATMENT OF ECZEMA THROUGH THE AGES

The treatment of AD has likewise evolved through the ages, reflecting the predominant pathogenic theory of each particular era. Well into the 19th century, the etiology of AD continued to be based on the Hippocratic humoralist theory: a disequilibrium of humors inside the body (13,14). The cutaneous manifestations were thought to be the result of the body's attempt to restore balance (13,14). Accordingly, people were cautious in treating AD, fearing that the internal condition would worsen if the oozing and pruritus were to disappear (11,13,14). Although this probably hindered the development of therapies for AD, the dearth of effective treatments at the time may have confirmed belief in the humoralist theory itself. Many of the treatments were intended to cure the disease internally, including ingestion of sulfur, arsenic, or mercury (14). Some physicians even advocated methods of increasing oozing, such as mercury ointment applied near the affected areas to create blisters, or in the case of Colson in France, wrapping the body with rubber in a method known as *saignée séreuse* (serous bloodletting) (14). Bloodletting, leeches, diuretics, and laxatives were also used to accelerate elimination of toxic substances from the body (14). The great majority of physicians subscribed to the humoralist theory of medicine, but a notable exception was Austrian dermatologist Hebra, who gave due credit to the skin for its role in AD (22). Hebra proposed using local, topical remedies such as soaps, oils, lotions, ointments, and tar and

openly disagreed with the notion that quickly healing eczema would result in an incurable internal illness, adding that he was not aware that any rapid cure for the chronic disease even existed (22).

As the humoralist theory of medicine fell out of favor beginning in the late 19th century, other therapies for AD gradually began to emerge. The English physician Wilson advocated for systemic treatment, favoring arsenic, and emphasized diet (14). Noticing that the symptoms of AD often began in infancy, when milk was the only food ingested, some physicians proposed milk as the trigger for AD (17). This led to various attempts at changing the components of milk or replacing milk with wheat flour or "Moll's pudding" (originally designed for intestinal disorders and composed of rice, eggs, margarine, and sugar) and to some potentially dangerous recipes for atopic infants (14,16). In the 20th century, the advent of food allergy studies and allergy testing prompted the use of avoidance diets as treatment for AD, in which foods that yielded positive wheal reactions during skin tests were excluded from children's diets. This therapy gained considerable popularity, although no uniform method of food restriction was followed (15,25). This may have resulted in untoward side effects such as malnutrition and poor quality of life for affected children. The clinical benefits of these diets remain to be fully elucidated (25).

In 1952, Sulzberger and Witten (36) reported for the first time the effectiveness of compound F, or hydrocortisone, in improving erythema, pruritus, and scaling in patients with various dermatoses, including AD. The subsequent widespread acceptance of hydrocortisone and other topical corticosteroids as mainstays of AD therapy revolutionized management of the disease. This skin-based approach was a far cry from the days of Hippocratic humoralism, although the belief that AD can be "cured from the inside" may not have fully disappeared, possibly contributing to cases of treatment failure and steroid phobia seen today (14). More recently, therapies such as topical calcineurin inhibitors, phototherapy, and systemic medications have been added to the arsenal of effective treatments for AD, with exciting new treatments on the horizon.

CONCLUSION

This is an exciting time of dramatic advances in the conceptualization and treatment of AD, with new developments in the pathophysiology of skin barrier dysfunction and in complex immunology. Perhaps the Hippocratic theory is alive and well in a more modern

form, with intricate interactions between filaggrin, inflammatory mediators, and other factors representing the modern “humors.”

Studying AD from a historical perspective intimates that, perhaps in the future, today’s pathophysiologic mechanisms and treatments may seem as archaic as those of the past. Physicians should not be overconfident in their abilities to understand causation. Careful use of nomenclature in AD is important so that dermatologists in the future may be able to compare patients today and over millennia. The longer view shows how far things have progressed and perhaps suggests that there is still a ways to go in this 3,500-year quest to fully understand AD.

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