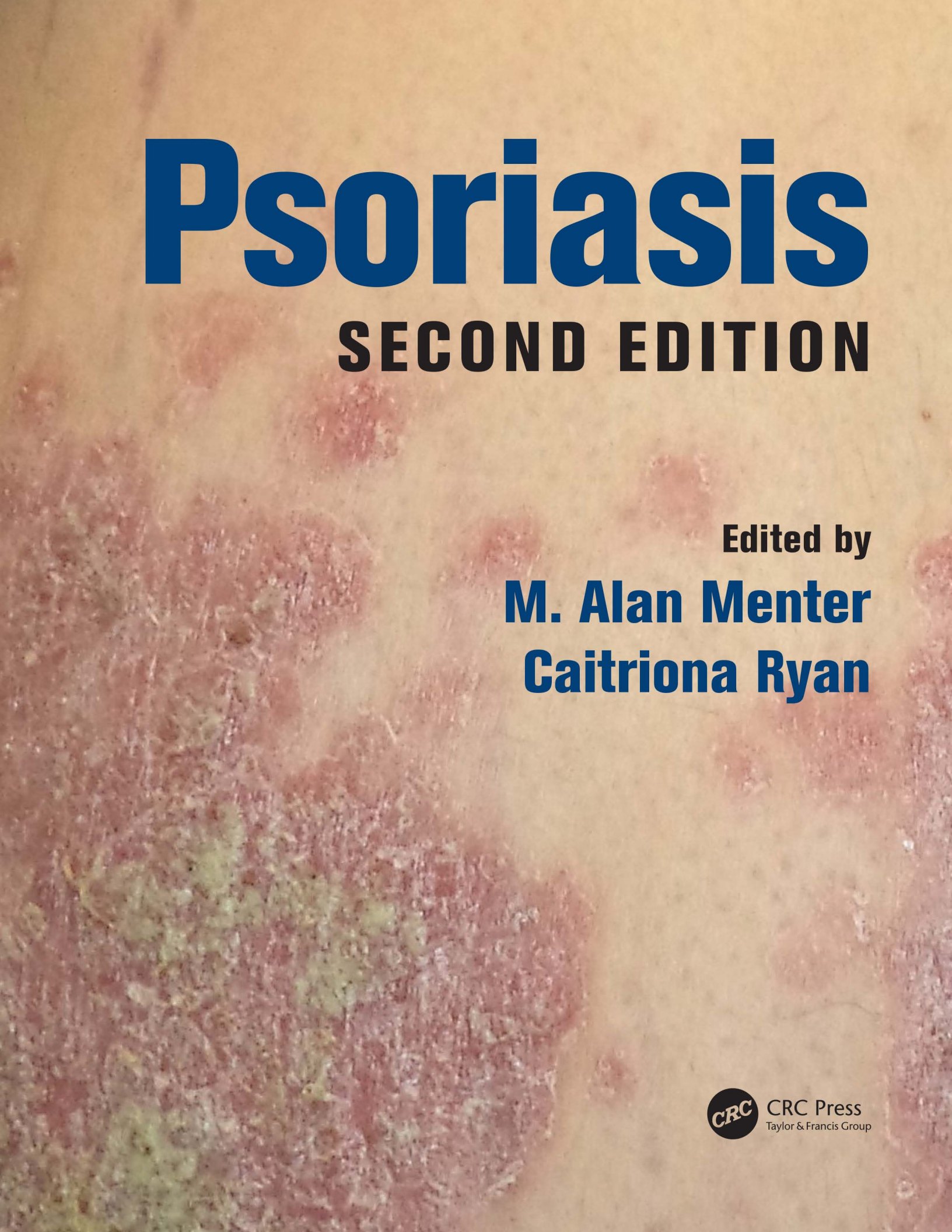
Psoriasis
SECOND EDITION
Edited by
M. Alan Menter
Caitriona Ryan
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Psoriasis

Psoriasis
Second Edition

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Contents

Preface

It is with great pleasure that we present the second edition of *Psoriasis*. With all the advances in the field of immunopathogenesis, genetics, comorbidities, and therapeutic modalities in the field of psoriasis over the past few years, in collaboration with my colleague Dr. Caitriona Ryan, we have significantly expanded the number of chapters with grateful support from multiple colleagues worldwide. This book is written for clinical and research-oriented dermatologists, dermatology registrars, residents and fellows, medical students, and non-physician scientists. The authors also wish to reach general practitioners, such as family and internal medicine specialists and subspecialists. For academic and clinical dermatologists, we believe this book provides a full and thorough review of the evaluation, associated systemic disorders, and treatment of the multiple forms of psoriasis, to help facilitate the evaluation and care of their patients. The text also discusses current concepts in the ever-expanding field of psoriasis pathophysiology, with up-to-date graphic illustrations of key concepts. Emerging concerns, such as systemic disease associations, quality-of-life issues, and psoriatic arthritis, are also reviewed in detail. For research-minded dermatologists, recent advances in basic science and up-to-date clinical trial data particularly relating to the new anti-IL17 and 23 molecules together with new small oral molecules are discussed fully. In addition, examples of well-known and new and old validated assessment tools for psoriasis can be found in Chapter 19. Readers will hopefully find helpful a chapter devoted to differential diagnosis, with juxtaposed images illustrating the main differentiating features between psoriasis and other dermatoses, common and uncommon. For interest, the authors also present a brief historical and epidemiologic discussion of the disease. We hope that non-dermatologists, such as general and family practitioners, internal medicine specialists, rheumatologists, and specialty nurses, will also find the book valuable, as a substantial number of psoriasis patients continue to visit non-specialists for diagnosis and treatment. New associations between psoriasis and multiple systemic, comorbid conditions have recently been recognized and will play an important role in our further understanding of this complex disease. Knowledge of these will serve all physicians and healthcare professionals involved in the treatment of psoriasis, and their patients, well. For dermatology registrars and residents, this book lays a solid foundation for learning the various aspects of psoriasis, including clinical features, differential diagnoses, laboratory findings, and therapeutic strategies. In addition, the updated sections on immunopathogenesis and genetics will enhance their understanding of the molecular events underlying psoriasis pathophysiology and assist in preparation for their qualifying examinations. For medical students, this book opens a window to the intriguing world of skin disease with specific focus on psoriasis, a condition as pleomorphic and stigmatized as any other in dermatology. We hope to excite and encourage students to pursue further study into this exiting world of psoriasis or even to consider a career in this field. For non-physician scientists, this book bridges the gap between clinical and basic science, relating the pathomechanism of disease to therapeutic targets and systemic disease associations. Our goal is to stimulate their interest in the investigation of inflammatory skin diseases in general and psoriasis in particular. Ultimately, we hope the diverse content within this second edition of *Psoriasis* will elicit a range of positive responses from the full spectrum of medical professionals whom we believe will find this book, with all the various aspects of psoriasis, interesting, thought-provoking, and enjoyable. We sincerely hope this second edition will help maintain and improve optimal medical practices in the care of our underserved worldwide psoriasis population of approximately 120,000,000 patients.

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The history of psoriasis

M. ALAN MENTER and BOBBAK MANSOURI

BIBLICAL TIMES

Psoriasis is one of the many dermatological conditions, including leprosy, which has been described since Biblical times. In the Hebrew bible, the term "tzaraath," translated as leprosy, was used as a term of punishment or "ritual uncleanliness." In the case of Gehazi (2 Kings 5:27), there is a specific biblical reference to psoriasis, "But Naaman's leprosy will cling to you and your descendants forever. And Gehazi left his presence a leper, white as snow."[1] In addition, ancient Egyptian and neighboring lands' scrolls frequently mention the term "leprosy"—again, mistaken in many instances for psoriasis. In 550 B.C., Greek athletes used special showers and application of olive oil to heal and protect their skin, whereas ancient poets Aeschylus and Herodotus described "leprosy," "leuke," and "psora" as diseases of the skin. Finally, Hippocrates (460–377 B.C.) freed medicine from the realm of superstition and magic with his meticulous descriptions of many disorders, including conditions of the skin. Dry, scaly eruptions were grouped together under the term "lopoi" (meaning epidermis), which likely included both leprosy and psoriasis.[1]

FIRST CENTURY A.D.

Cornelius Celsus, the Roman author (25 B.C.–45 A.D.), described psoriasis as the fourth variant of "impetigo" in his work *De Re Medica*.[2] Thereafter, the Roman physician Galen (133–200 A.D.) first used the term "psoriasis vulgaris" derived from the Greek word "psora" (meaning itch) to describe an affliction of the skin for which he administered arsenic in many different forms as a "cure."[3] However, the confusion between leprosy and psoriasis endured for many centuries with psoriasis patients between the years 1000 and 1400 A.D. receiving brutal treatment, being isolated from both their communities and their church, and even being burned at the stake by Philip the Fair of France in the fourteenth century.[4]

THE RENAISSANCE PERIOD

The "Renaissance" was a time of revival. Classical learning and wisdom brought to the fore the emergence of a more scientific understanding of psoriasis. Medicine experienced a rebirth with the cities of Vienna, Paris, and London becoming the center of the newly found specialty—dermatology. In Vienna, Joseph Jacob Plenck wrote of psoriasis in 1776 as being among the group of desquamative (scaly or scale-like) diseases but did not differentiate it from other dermatoses. Subsequently, in the late eighteenth century, two Yorkshire-born English dermatologists, Robert Willan (1757–1812) and Thomas Bateman (1778–1821), differentiated psoriasis from other skin diseases. Willan is considered to have first described psoriasis and identified two varieties of the disease. "Leprosa Graecorum" was used to describe the condition when scaling of the skin was predominant, whereas the second term, "Psora Leprosa," described a more eruptive variant of the condition.[5] Willan wrote the first textbook entitled *Cutaneous Disease* (published in 1798), which contained color photographs of psoriasis and established him as the father of modern dermatology. Bateman, on the other hand, was the first to consider a link between psoriasis and arthritic symptoms.

Despite these important writings, psoriasis continued to be confused with leprosy until 1841 when the Viennese dermatologist, Ferdinand von Hebra, gave the condition its definitive name "psoriasis," derived from the Greek word "psora" meaning "to itch," and eliminated "lepra."[6] Von Hebra improved on Willan's original system of classification by relating clinical disease to pathologic anatomy.

In 1872, Heinrich Koebner (1834–1904) described the induction of lesions of psoriasis within areas of prior trauma in an address delivered to the Silesian Society for National Culture. This has since become known as the "Koebner" phenomenon.[7] Subsequently, Heinrich Auspitz (1835–1886) described both the characteristic histological features of psoriasis and the eponymous clinical sign of pinpoint bleeding on the removal of psoriatic scale.[8] Finally, in the descriptive era on the origins of psoriasis as a separate disease, Leo

Ritter von Zumbusch (1874–1940), a Viennese physician, was the first to document generalized pustular psoriasis in the early 1900s after observing a single male patient through nine hospital admissions over a 10-year period.[9]

EVOLUTION OF MODERN THERAPIES

Arsenic: For centuries arsenic was used to treat psoriasis and other skin diseases with historical records showing its use as far back as Hippocrates. Thomas Fowler developed a treatment that was a solution of potassium arsenite compounded with a tincture of lavender for color and taste. Known as "Fowler's Solution," it was "peer reviewed" by Thomas Girdlestone in a paper entitled "Observations on the effects of Dr. Fowler's Mineral Solution in Lepra and Other Diseases." Arsenic was actually still used in the treatment of psoriasis as recently as the 1950s.

Tars: Tars were also used by Hippocrates. In the late 1800s, tar was used topically in conjunction with arsenic. Coal tar became available with coal gas production in the second half of the nineteenth century and still maintains a role in the treatment of psoriasis. The slogan "The Heartbreak of Psoriasis" originated in the advertising campaign for Tegrin®, which was a coal-tar based ointment. In 1921, Goeckerman initiated the use of coal tar in a hospital-based regimen with phototherapy, 24 hours a day at the Mayo Clinic.

Goa Powder or Chrysarobin: Goa Powder was a Chinese remedy, derived originally from the pith of a tree from Goa, a Portugese enclave off India. Goa Powder was mixed with water, lime juice, or vinegar to make a paste that was spread onto the skin. It was often also mixed with cold lard.

During World War I, when Goa Powder was difficult to obtain, Bayer synthesized a substitute called dithranol in Europe or anthralin in the United States. After the application of anthralin, patients were wrapped in a dressing for 24 hours, a technique pioneered by Ingram in Leeds, England, in 1948. Although effective, anthralin therapy was time consuming and often caused irritation and/or staining of the skin. These difficulties ultimately led to modifications of the regimen, and by the 1970s, the 24-hour period had been reduced to 6–9 hours a day, similar to the newly developed day care schedule of the Goeckerman regimen. Thereafter, at Stanford, shorter contact anthralian therapy (SCAT), i.e., 1–2 hours application time, was introduced by Eugene Farber in the early 1980s.

Folic Acid Antagonists: The folic acid antagonists, aminopterin and amethopterin, were used in dosages from 1.5 to 2 mg daily with improvement in the condition generally observed after 2 weeks. Initial studies were commenced in California in the 1950s under the supervision of Rees B. Rees.[10] Toxicity was, however, a constant problem, with aminopterin still being used as late as the 1960s, before being definitively replaced by its metabolite, methotrexate,[11] the first oral drug approved by the U.S. Food and Drug Administration (FDA) for the treatment of severe psoriasis in 1971.

Phototherapy and Photochemotherapy: Broadband ultraviolet B (UVB) was initially used in the treatment of psoriasis in the early 1900s, before being replaced by narrowband (NB UVB) phototherapy, initially in Europe over 40 years ago. After almost a century of various forms of UVB therapy, psoralen-ultraviolet light A (PUVA) was finally approved for the treatment of psoriasis in 1976 with the majority of research having been performed by John A. Parrish and his colleagues at Harvard.[13]

Systemic Retinoids: Etretinate was the first systemic retinoid developed for the treatment of psoriasis being approved by the FDA in 1986.[14] Acitretin, a second generation systemic retinoid, replaced etretinate shortly thereafter. Retinoic acid acts by modulating and normalizing the proliferation of the otherwise hyperproliferative epidermis in psoriatic lesions by activating retinoic acid nuclear receptors.[12]

Cyclosporine: Cyclosporine was discovered in the early 1970s and was originally used as an immunosuppressive agent in organ transplantation.[17] An anecdotal report of its efficacy in a psoriasis patient in 1979 changed the understanding of psoriasis from what was previously considered to be a keratinocyte-driven disorder to that of a T-cell-mediated disease.[18]

Cyclosporine acts by inhibiting the activity of calcineurin phosphatase by forming a complex with cyclophilin. As a result, important T-cell nuclear transcription factors are not phosphorylated leading to inhibition of the activation of T lymphocytes, natural killer cells, and antigen-presenting cells, depletion of lymphocytes and macrophages in the epidermis, and a host of other effects including inhibition of keratinocyte hyperproliferation.[15]

Biological agents

Over the past 13 years, the advent of biologic agents has revolutionized psoriasis therapy, leading to dramatically improved clinical outcomes in patients with moderate-to-severe psoriasis.

The first biologic injectable agent approved for psoriasis was Alefacept in January 2003. Alefacept inhibits the activation of $CD4^+$ and $CD8^+$ T cells by binding with CD2 on the T-cell membrane thereby blocking the costimulatory molecule lymphocyte function-associated antigen (LFA)-3/CD2 interaction and leading to apoptosis of memory-effector T lymphocytes.[19] Alefacept had limited efficacy in the treatment of psoriasis, and production was discontinued in 2011. Subsequently, a second T-cell biologic agent, efalizumab, was introduced in 2005.[20] Efalizumab binds to the CD11a subunit of lymphocyte function-associated antigen 1 to inhibit lymphocyte activation and cell migration out of blood vessels into tissues. Although efalizumab demonstrated efficacy in psoriasis, particularly in those with palmoplantar disease, it was removed from the market in 2009 due to three fatalities from progressive multifocal leukoencephalopathy (PML).[21]

The tumor necrosis factor-alpha (TNF-α) pathway has been an integral pathway targeted by psoriasis, psoriatic and rheumatoid arthritis, and inflammatory bowel disease therapies over the past two decades. Anti-TNF-α agents licensed for the treatment of psoriasis and psoriatic arthritis include adalimumab,[22] etanercept,[23] and infliximab.[24,25] These agents continue to play a major role in the biological therapy of psoriasis.

With advances in our understanding of the molecular pathways of psoriasis, newer, more targeted biologic therapies have been developed. The discovery of the critical role of interleukin-23 (IL-23)/Th17 axis in the immunopathogenesis of psoriasis has been the most fundamental advance to date in psoriasis research and has led to the development of many selective biologic agents that target this pathway. Ustekinumab, an antibody to the common p40 subunit of IL-12 and IL-23, has shown considerable efficacy in the treatment of psoriasis and psoriatic arthritis, and it was licensed for use in psoriasis in 2008 in Europe and Canada and in 2009 in the United States.[26,27] Finally, the first of the anti-IL-7 molecules, secukinumab and ixekizumab, have been approved for psoriasis in 2015 and 2016, respectively.[28,29] The third of these molecules, broadalumb, was approved by the FDA in July. Multiple, new targeted treatments are currently in clinical development for the treatment of psoriasis, including IL-23 inhibitors, and bispecific anti-TNF-α/IL-17A fusion proteins.

CONCLUSION

The history of psoriasis is rich. Much of our early understanding of the disease was guided by observation. More modern therapeutics were guided by serendipitous findings (e.g., cyclosporine). The last two decades have ushered in a new guard, biological therapies, which are the direct result of our improved understanding of the immunopathogenesis of psoriasis and a reminder of the progress we have made in treating this debilitating disease.

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