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Prof. Dr. Michael J. Parnham PhD
Director of Preclinical Discovery
Centre of Excellence in Macrolide Drug Discovery
GlaxoSmithKline Research Centre Zagreb Ltd.
Prilaz baruna Filipovića 29
HR-10000 Zagreb
Croatia

Prof. Dr. J. Bruinvels
Sweelincklaan 75
NL-3723 JC Bilthoven
The Netherlands

Treatment of Psoriasis

Edited by Jeffrey M. Weinberg

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Editor
Jeffrey M. Weinberg
Department of Dermatology
St. Luke's-Roosevelt Hospital Center
1090 Amsterdam Avenue, Suite 11 D
New York, NY 10025
USA

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List of contributors

Rahat S. Azfar, Department of Dermatology, University of Pennsylvania, 3600 Spruce St, 2 Maloney, Philadelphia, PA 19104, USA

Allison J. Brown, Department of Dermatology, Murdough Family Center for Psoriasis, University Hospitals Case Medical Center, 11100 Euclid Ave, Cleveland, OH 44106, USA

Paru R. Chaudhari, Mount Sinai School of Medicine, Department of Dermatology, 5 E 98th St 5th Floor, New York, NY 10029, USA; e-mail: paru.chaudhari@mssm.edu

Alissa Cowden, University of Pennsylvania, Philadelphia, PA 19104, USA

Neil J. Korman, Department of Dermatology, Murdough Family Center for Psoriasis, University Hospitals Case Medical Center, 11100 Euclid Ave, Cleveland, OH 44106, USA; e-mail: neil.korman@uhhospitals.org

Mark G. Lebwohl, Mount Sinai School of Medicine, Department of Dermatology, 5 E 98th St 5th Floor, New York, NY 10029, USA; e-mail: mark.lebwohl@mssm.edu

Marissa D. Newman, UMDNJ-Robert Wood Johnson Medical School New Jersey, New Jersey, 08902, USA; e-mail: marissa.newman@gmail.com

Edward M. Prodanovic, Department of Dermatology, Murdough Family Center for Psoriasis, University Hospitals Case Medical Center, 11100 Euclid Ave, Cleveland, OH 44106, USA

Maria R. Robinson, Department of Dermatology, Murdough Family Center for Psoriasis, University Hospitals Case Medical Center, Cleveland, OH 44106, USA

Sejal K. Shah, St. Luke's-Roosevelt Hospital Center, Department of Dermatology, 1090 Amsterdam Avenue, Suite 11D, New York, NY 10025, USA; e-mail: sejalshah151@yahoo.com

Amanda B. Sergay, Department of Dermatology, St. Luke's-Roosevelt Hospital Center and Beth Israel Medical Center, New York, NY, USA; e-mail: asergay@yahoo.com

Matthew Silvan, Department of Dermatology, St. Luke's-Roosevelt Hospital Center and Beth Israel Medical Center, New York, NY, USA

Dana K. Stern, Mount Sinai School of Medicine, Department of Dermatology, 5 E 98th St 5th Floor, New York, NY 10029, USA

Abby S. Van Voorhees, Psoriasis and Phototherapy Treatment Center, 2M44 Rhoads Pavilion, 3600 Spruce Street, Philadelphia, PA 19104, USA; e-mail: vanvoora@uphs.upenn.edu

Jeffrey M. Weinberg, Department of Dermatology, St. Luke's-Roosevelt Hospital Center and Beth Israel Medical Center, 1090 Amsterdam Avenue, Suite 11D, New York, NY 10025, USA; e-mail: jmw27@columbia.edu

Preface

Psoriasis is an inherited skin disease that has been diagnosed in 4.5 million adults in the US. About 10–30% of people with psoriasis also develop psoriatic arthritis, which causes pain, stiffness and swelling in and around the joints.

The past 25 years of research and clinical practice have revolutionized our understanding of the pathogenesis of psoriasis as the dysregulation of immunity triggered by environmental and genetic stimuli. Psoriasis was originally regarded as a primary disorder of epidermal hyperproliferation. However, experimental models and clinical results from immunomodulating therapies have refined this perspective in conceptualizing psoriasis as a genetically programmed pathologic interaction between resident skin cells, infiltrating immunocytes and a host of proinflammatory cytokines, chemokines and growth factors produced by these immunocytes.

The main focus of this volume will be the evolving paradigm of therapy for psoriasis. The first segment of the volume provides a background for the disease. The first two chapters will review the history of psoriasis and psoriasis therapy, and the pathophysiology of psoriasis. The third chapter provides a detailed clinical review of psoriasis and psoriatic arthritis.

The review of therapy begins in the next segment of the volume. Chapters 4 and 5 review the myriad of topical therapies available for psoriasis, and Chapter 6 discusses the spectrum of ultraviolet therapies and novel laser therapies for the treatment of this condition. Prior to the advent of biologic therapies, a number of oral therapies were the mainstay of systemic treatment for psoriasis. The efficacy and safety of these agents will be reviewed in Chapters 7 and 8.

Over the last few years, one of the major focuses in psoriasis research has been the development of biologic therapies for this disease. The aim of these therapies is to provide selective, immunologically directed intervention with fewer side effects than traditional therapies. Chapter 9 will review biologic therapy for psoriasis, providing an overview of infliximab, etanercept, adalimumab, efalizumab, and alefacept. Biologic and oral therapies in development will be discussed in Chapter 10.

Psoriasis-related quality of life is a broad term that aims to incorporate the physical, psychosocial, and economic implications of the disease, and their cumulative impact on the patient. The final chapter will address the important topic of quality of life issues in psoriasis.

The treatment of psoriasis is truly an evolving field. In the volume, an outstanding group of authors have provided the most recent clinical data, encom-

passing proper applications, efficacy, and safety. We hope that you will find the information useful in the scope of your research or practice. We urge you, however, to keep abreast of this field after reading this volume, as the flow of new information is constant.

Jeffrey M. Weinberg, MD New York, August 2007

Treatment of Psoriasis
Edited by J.M. Weinberg

Introduction: History of psoriasis and psoriasis therapy

Alissa Cowden and Abby S. Van Voorhees

University of Pennsylvania, Philadelphia, PA 19104, USA

Introduction

This chronicle of psoriasis begins in ancient times when psoriasis, leprosy, and other inflammatory skin disorders were thought to be the same condition. The identification of psoriasis as a distinct entity did not occur until the 19th century, when clinical descriptions distinguished it from other cutaneous disorders. Histopathologic descriptions in the 1960s and 1970s shed some light on the pathophysiology of psoriasis, but many aspects of the disease remain unknown to this day. As Bechet expressed, "Psoriasis is an antidote for dermatologists' ego" [1].

Given the lack of understanding of its pathophysiology, early psoriasis therapies were discovered serendipitously. Chance observations by early clinicians of psoriatic improvement in patients prescribed medications for other conditions led to advancements in therapy. As our understanding grew, this serendipity evolved into detailed targeting of specific immunological processes. These newly directed therapies clarified aspects of the pathophysiology and treatment of psoriasis and other immune-mediated diseases.

Ancient history: Lepra, psora, psoriasis

The roots of the identification of psoriasis lie in Ancient Greece. The Greeks, who pioneered the field of medicine, divided skin disease into the categories of *psora, lepra* and *leichen* [2]. *Psora* referred to itch, while *lepra* was derived from the Greek words *lopos* (the epidermis) and *lepo* (to scale) [3]. Hippocrates (460–377 BC) was one of the first authors to write descriptions of skin disorders. He utilized the word *lopoi* to describe the dry, scaly, disfiguring eruptions of psoriasis, leprosy, and other inflammatory skin disorders [4].

Similar to Hippocrates' works, the Old Testament also lumped together many cutaneous disorders. The biblical term *tsaraat,* or *zaraath,* described a range of skin conditions including leprosy and psoriasis. Lepers were often

ostracized because they were considered divinely punished, and cruelty was imposed upon those who suffered from psoriasis and leprosy alike [5, 6].

Many historians credit the Roman thinker Celsus (ca. 25 BC–45 AD) with the first clinical description of papulosquamous diseases [1, 2, 5]. Celsus described impetigines and specified that the second species of impetigo was characterized by red skin covered with scales. This description suggested a type of papulosquamous disease, such as psoriasis [7].

Galen (133–200 AD) first utilized the term psoriasis, but his description was not consistent with the disorder that we now call psoriasis. He described psoriasis as a pruritic, scaly skin disease of the eyelids and scrotum. Although he used the term psoriasis, his description is now believed to most likely represent seborrheic dermatitis [4, 5, 8].

Indiscriminate grouping together of all inflammatory skin diseases led to stigmatization of patients with psoriasis. For centuries, patients with psoriasis received the same cruel handling as lepers. They were required to carry a bell or clapper to announce their approach, and had to wear a special dress. In addition, they could only touch or dine with others considered lepers. In 1313, Phillip the Fair of France ordered that they be burned at the stake [1].

Distinguishing psoriasis as a distinct entity

In 1809, Willan built on Celsus's description of papulosquamous conditions by detailing features of what we now know as psoriasis. However, he described modern psoriasis under the term lepra vulgaris, which perpetuated confusion of psoriasis and leprosy. Lepra vulgaris was described as enlarging, sharply marginated erythematous plaques with silvery-white scale that occurred most frequently on the knees, and were associated with nail pitting [8, 9].

For decades after Willan's description, some authors favored using the term psoriasis [1, 2, 10–12], while others chose the term lepra [9, 13]. Physicians lacked clarity regarding the word psoriasis and the ability to distinguish psoriasis from diseases with similar cutaneous manifestations.

Finally, Gibert and Hebra matched Willan's description with the term psoriasis, ending much confusion. Psoriasis was now finally acknowledged as a distinct disease, leading to improved perception of psoriatic patients.

In his books, Gibert (1797–1866) used the term psoriasis, recognized secondary syphilis as a contagious entity, and established pityriasis rosea as a clinical syndrome. Gibert's pivotal publications included thorough accounts that made important distinctions between papulosquamous diseases [5, 10, 14]. In 1841, shortly after Gibert's works, Hebra further distinguished the clinical picture of psoriasis from that of leprosy. Only 165 years ago, this differentiation set the stage for psoriatic patient's freedom from extreme persecution [15, 16]. The distinctions made by Gibert and Hebra were essential to accurately diagnosing patients and developing tailored therapies.

Advancements in the description of psoriasis

The 19th century identification of psoriasis as a separate entity ushered in a period of increasingly accurate descriptions of the disease. One of Hebra's students, Heinrich Auspitz (1835–1886), noted bleeding points upon removal of scale in patients with psoriasis. We now refer to this as the Auspitz sign [14, 17]. Along with the Auspitz sign, the Köbner reaction is a characteristic feature of psoriasis. In 1876, Köbner described the propensity of psoriatic lesions to arise in areas of prior trauma. Köbner's observation provided insight into the importance of the vascular compartment in the initiation of the psoriatic lesion [18]. Two decades later, in 1898, Munro described microabscesses of psoriasis that are now known as Munro's abscesses [17].

The start of the 20th Century ushered in further descriptions of psoriatic lesions. In 1910, Leo von Zumbusch first described generalized pustular psoriasis, or von Zumbusch disease [19]. Additional descriptions included Woronoff's 1926 description of a pale halo referred to as the 'Woronoff ring' encircling a plaque of psoriasis [20]. The portrayals of the Auspitz sign, Köbner's phenomenon, Munro's abscesses, pustular prosiasis, and the Woronoff ring allowed physicians to more confidently diagnose patients with psoriasis.

Understanding pathophysiology

In addition to clinical observations, histopathologic descriptions of psoriatic skin advanced understanding of the roles of epidermal hyperplasia and the immune system in psoriasis. Epidermal hyperplasia in psoriasis was first observed in 1963, when Van Scott noted a significant increase in mitoses of psoriatic epidermis [21]. Three years later, Van Scott and Weinstein noted that psoriatic basal cells rose to the stratum corneum in only two days, in contrast to their 12 day transit through normal epidermis [22].

Therapeutic discoveries and histopathologic observations linked the immune system with psoriasis. In 1951, Gubner treated rheumatoid arthritis with the folic acid antagonist aminopterin, and serendipitously noted clearing of the skin in patients with psoriasis [23]. At that time researchers did not understand the mechanism of action of folic acid antagonists in psoriasis treatment, but later understanding revealed that these medications modulated the immune system. Two decades after Gubner's report, Mueller prescribed cyclosporine to prevent rejection in transplant patients, and found improvement of lesions in patients with psoriasis [24]. Reports of psoriatic improvement provided by immunosuppressive drugs implicated the immune system in the pathogenesis of psoriasis. Histopathologic observations, that cellular infiltrates in psoriasis were composed primarily of T cells and macrophages, further highlighted the role of the immune system in psoriasis [25, 26].

In spite of these discoveries, much remains unknown about the pathogenesis of psoriasis and other immune-mediated diseases including arthritis and inflammatory bowel disease. Psoriasis serves as a model for immune-mediated diseases because the response to therapy can be readily seen [27].

History of treatment of psoriasis

The history of the treatment of psoriasis is relatively short, and initially treatment discoveries were serendipitous. Early psoriasis therapies included arsenic and ammoniated mercury use in the 19th Century. In the first half of the 20th Century, anthralin and tar were discovered as effective psoriasis treatments. Corticosteroids were developed in the 1950s. These therapies were followed in the 1970s by use of methotrexate and PUVA on psoriasis. In the 1980s, psoriasis treatment discoveries included narrowband UVB, retinoids, and vitamin D therapies. From the 1990s to the present time, manipulating the immune system to treat psoriasis has been explored first with cyclosporine and more recently with targeted molecules.

19th Century – Arsenic and ammoniated mercury

Throughout history, arsenic has been utilized as both a poison and therapeutic. In 1806, Girdlestone reported on the efficacy of Fowler's Solution with 1% arsenic in treating many dermatologic conditions including psoriasis [1, 28]. With similar toxic potential, ammoniated mercury was used as a medication before the 20th Century [16, 29]. In 1876, Duhring recommended mercurial ointments to treat psoriasis [30].

1900–1950s – Anthralin and tar

In 1876, Squire inadvertently discovered anthralin as a treatment of psoriasis. Squire prescribed Goa powder, which was until then known only to be effective in ringworm, and the patient's psoriasis improved. The active ingredient of Goa powder is chrysarobin, also known as 2-methyl dithranol [31]. During World War I, this treatment was further refined, as a synthetic form of chrysarobin called antralin, or dithranol, was formed. In 1916, Unna reported the effectiveness of dithranol as an antipsoriatic treatment [32].

The next advancement in psoriasis treatment was coal tar. Hippocrates and other ancient physicians treated dermatologic conditions with pine tar and other types of tar. Coal tar became available when coal gas production developed in the late 19th Century, and Goeckerman found that coal tar was particularly useful in psoriasis therapy [33, 34]. Many observed that psoriasis improved with summer sun. In 1925, Goeckerman reported an additive bene-

fit of coal tar and UVB radiation in psoriasis treatment [16, 35]. Goeckerman's method remained the mainstay of psoriasis treatment for decades. In 1953, Ingram reported the successful treatment of psoriasis with a combination of Unna and Goeckerman's modalities. He established the first day care center for psoriasis in which patients were treated with a tar bath, then UVB therapy, and lastly with 0.42% dithranol in Lassar's paste [36]. This treatment improved the morbidity of psoriasis for many patients, but was time intensive.

1950s – Corticosteroids

In the 1950s, the corticosteroid era began and revolutionized the treatment of many diseases. In 1950 Hench, Kendall, and Reichstein received the Nobel Prize for the development of cortisone [37, 38]. A mere 2 years later, Sulzberg and Witten reported that compound F, or hydrocortisone, was the first moderately successful topical corticosteroid in inflammatory skin diseases including psoriasis [39]. From that time forward, additional topical corticosteroid preparations were developed to treat inflammatory dermatoses such as psoriasis.

1970s – Methotrexate and PUVA

Although methotrexate was first developed in the 1950s, it was not used to treat psoriasis until the 1970s. In 1946, Farber developed aminopterin to treat leukemia [40]. Five years later, Gubner reported that aminopterin used in the treatment of rheumatoid arthritis also cleared psoriasis [23]. In 1958, Edmundsun and Guy introduced methotrexate, a more stable derivative of aminopterin with lower toxicity [41]. Investigators initially believed that folic acid antagonists prevented keratinocyte hyperproliferation, but later the effect on lymphocytes in psoriatic lesions was elucidated. In 1972, the FDA finally approved the use of methotrexate for psoriasis [42].

Also in the 1970s, PUVA therapy was reported to be effective in psoriasis. PUVA, based on the interaction between UV radiation and a photo-sensitizing chemical, has its own rich history [43]. The concept originated in about 1'500 BC when Egyptian healers treated vitiligo with a combination of sunlight and ingestion of plants known as psoralens, including fig and limes [44]. An article published in 1974 reported the efficacy of oral PUVA therapy in a group of patients with psoriasis [43]. Three years later, a multi-center study confirmed that most patients with psoriasis experienced clearing of their skin using oral PUVA [45]. Shortly after the development of oral PUVA, alternative bathwater delivery systems of psoralens were also created to minimize adverse effects associated with oral PUVA [46].

1980s – Narrowband UVB, retinoids, vitamin D

Although often therapeutically successful, PUVA therapy carries an increased risk of skin cancer. Therefore, further study of UVB therapy was undertaken. In 1981, Parrish and Jaenicke demonstrated that UVB wavelengths between 300 and 313 nm caused the greatest remission of skin lesions [47]. Subsequent trials reported that the 311 nm spectrum showed improved clearance of lesions with less erythema [48, 49].

In the 1980s, researchers also established the use of retinoids in psoriasis treatment. Prior to its use in psoriasis, in the 1960s physicians prescribed retinoids for hyperkeratosis and acne. At this time, first-generation and synthetic topical retinoids did not have significant antipsoriatic activity [50, 51]. In the early 1980s, reports demonstrated the efficacy of the second-generation retinoids etretinate and its derivative acitretin, in the treatment of psoriasis [52, 53]. Although etretinate is no longer available in the US due to its lipophilia and protracted adverse effects, acitretin has a shorter half life and remains an important therapy in psoriasis [54]. Third-generation acetylenic retinoids developed in the 1980s allowed for the production of a topical retinoid, tazarotene, with demonstrated anti-psoriatic efficacy [55].

The next class of drugs developed for psoriasis, vitamin D and its analogs, was also developed by chance observations in the 1980s. In 1985, a patient who received oral vitamin D3 for osteoporosis experienced dramatic improvement of his psoriasis [56]. The active form of vitamin D3 plays a part in the control of intestinal calcium absorption, bone mineralization, keratinocyte differentiation, keratinocyte proliferation, and immune modulation [57, 58]. Despite extensive research, the exact mechanism of action of vitamin D analogs remains unknown. In 1988, a topical form of vitamin D proved useful in the treatment of psoriasis [59].

1990s – Cyclic immunosuppressive medications

In 1997, cyclosporine was FDA approved for psoriasis treatment. Cyclosporine was isolated in 1969 from a fungus and was screened for antibiotic properties. In 1976, Borel reported immunosuppressive properties of cyclosporine in animal models [60]. Three years later, Cyclosporine A was used experimentally in transplant patients to prevent graft rejection, and psoriatic patients in these trials experienced relief of their lesions [24]. FDA approval was delayed until the 1990s due to concerns about toxicity. Cyclosporine is prescribed for severe psoriasis that is not responsive to other therapies [61].

Psoriasis treatment discoveries of today and tomorrow

Although our understanding of the immunological basis of psoriasis had expanded greatly by the turn of the Millennium, many details still remain unknown. Understanding of the role of immunology in psoriasis, together with the knowledge of protein engineering techniques, has given us the capability to manufacture specific proteins that can selectively alter the immunological processes in psoriasis. These therapies continue to improve the treatment of psoriasis and shed further light into its pathogenesis.

Beginning in January of 2003, a number of biologic agents were approved by the FDA for the treatment of psoriasis including alefacept, efalizumab, etanercept and infliximab. Alefacept binds to CD2 to prevent the activation of T lymphocytes in psoriasis [27, 62], while efalizumab, binds to CD11 to inhibit T cell activation and migration into the skin [63]. Both of these therapies strengthened the understanding of the role of T lymphocytes in psoriasis. Tumor necrosis factor inhibitors also demonstrated efficacy in the treatment of psoriasis [64]. The efficacy and mechanism of etanercept, infliximab and adalimumab suggest that psoriasis pathophysiology also involves immunologic mediators in addition to T cells. Discovery of these biologic therapies opens the door of our understanding of psoriasis. The quest for developing additional biologics for the treatment of psoriasis and other immune-mediated diseases continues, and it will be the role of clinicians to measure the potential advantages of each therapy for individual patients [65].

Our understanding of psoriasis and ability to treat this disease has evolved tremendously in the past few decades. We not only recognize psoriasis as distinct from leprosy and other inflammatory disorders, but are beginning to more fully understand its pathophysiology. More importantly, our ability to treat patients and improve their quality of life has progressed. Although we initially stumbled upon treatments by chance, we are now developing targeted therapies. These innovative therapeutics not only improve patient symptoms, but also help elucidate the pathophysiology of psoriasis and other immune-mediated diseases. The rich history of our understanding of psoriasis and its treatment serves as inspiration for continued discovery about psoriasis and its therapy.

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The pathophysiology of psoriasis

Marissa D. Newman[1] and Jeffrey M. Weinberg[2]

[1] *UMDNJ-Robert Wood Johnson Medical School New Jersey, New Jersey, 08902, USA*
[2] *Department of Dermatology, St. Luke's-Roosevelt Hospital Center and Beth Israel Medical Center, New York, 10025, USA*

Introduction

The past 25 years of research and clinical practice have revolutionized our understanding of the pathogenesis of psoriasis as the dysregulation of immunity triggered by environmental and genetic stimuli. Psoriasis was originally regarded as a primary disorder of epidermal hyperproliferation. However, experimental models and clinical results from immunomodulating therapies have refined this perspective in conceptualizing psoriasis as a genetically programmed pathologic interaction between resident skin cells, infiltrating immunocytes and a host of proinflammatory cytokines, chemokines and growth factors produced by these immunocytes. Two populations of immunocytes and their respective signaling molecules collaborate in the pathogenesis: innate immunocytes, mediated by antigen presenting cells (including natural killer T lymphocytes, Langerhans cells and neutrophils) and acquired or adaptive immunocytes, mediated by mature CD4+ and CD8+ T lymphocytes in the skin. Such dysregulation of immunity and subsequent inflammation is responsible for the development and perpetuation of the clinical plaques and histological inflammatory infiltrate characteristic of psoriasis.

Although psoriasis is considered to be an immune mediated disease in which intralesional T lymphocytes and their proinflammatory signals trigger primed basal layer keratinocytes to rapidly proliferate, debate and research focus on the stimulus that incites this inflammatory process. While psoriasis may represent an autoimmune reaction, researchers have not isolated self-antigens or defined the specificity of the auto-reactive skin lymphocytes. Our current understanding considers psoriasis to be triggered by exogenous or endogenous environmental stimuli in genetically susceptible individuals. Such stimuli include Group A streptococcal pharyngitis, viremia, allergic drug reactions, antimalarial drugs, lithium, beta blockers, interferon alpha, withdrawal of systemic corticosteroids, local trauma (Köbner's phenomenon) and emotional stress, as these correlate with the onset or flares of psoriatic lesions. Psoriasis genetics centers on susceptibility loci and corresponding candidate genes, particularly the psoriasis susceptibility (PSORS) 1 locus on

the major histocompatibility (MHC) class I region. Current research on the pathogenesis of psoriasis examines the complex interactions between immunologic mechanisms, environmental stimuli and genetic susceptibility. After discussing the clinical presentation and histopathologic features of psoriasis, we will review the pathophysiology of psoriasis through noteworthy developments including serendipitous observations, reactions to therapies, clinical trials and animal model systems that have shaped our view of the disease process.

Clinical presentations

There are multiple patterns of psoriasis including plague, guttate, pustular, inverse and erythrodermic. Approximately 80% of patients present with plaque psoriasis which is clinically characterized by well demarcated erythematous plaques with overlying scales. These lesions are distributed symmetrically and frequently occur on the elbows, knees, lower back and scalp. These plaques can be intensely pruritic and bleed when manipulated, referred to as the Auspitz sign.

In addition to the classic skin lesions, approximately 23% of psoriasis patients develop psoriatic arthritis with a 10 year latency after diagnosis of psoriasis [1]. The distal interphalangeal (DIP), wrist, sacroiliac (SI) and knee joints are most commonly affected with swelling, stiffness and loss of function. With longstanding disease, bone changes can be demonstrated on radiographs and bone scans. Psoriatic arthritis patients are rheumatoid factor negative which differentiates them from patients with rheumatoid arthritis. Additionally, nail involvement occurs in 30–50% of patients and may clinically resemble a fungal infection, with pitting, onycholysis, thickening, with hyperkeratotic debris under the nail plate [1].

Histopathology

The histology of psoriatic plaques is distinguished by excessive epidermal growth termed psoriasiform hyperplasia. This pattern includes a markedly thickened skin or acanthosis, elongated downward extensions of the epidermis into the dermis or rete pegs and aberrant keratinocyte differentiation. Mitotic figures are visible at the basal layer of keratinocytes demonstrating rapid proliferation and maturation responsible for incomplete terminal differentiation. Thus, keratinocytes retain their nuclei as visualized in the parakeratotic stratum corneum. The granular layer of the epidermis is also depleted. Additionally, the rapidly proliferating keratinocytes fail to secrete lipids that normally adhere the corneocytes to each other, thereby producing the classic scale of a psoriatic plaque. The tortuous and dilated dermal blood vessels are responsible for the erythema exhibited by psoriatic plaques.