Handbook of Psoriasis

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To all patients with psoriasis and their healers

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Preface

The *Handbook of Psoriasis* is intended to be a convenient reference work on the treatment of psoriasis. The format is designed for use by the busy practitioner, primary-care physician and specialist alike; each chapter stands on its own, but cross-reference to others may be necessary to fill in details. The *Handbook* may also be employed as a brief textbook on psoriasis to be read in its entirety by novices in dermatologic therapy: medical students, house officers, physician's assistants, and nurse clinicians.

The *Handbook* is an updated abbreviated companion to the complete hardcover text *Psoriasis* (Blackwell Science, 1994). The interested reader should refer to the latter for more in-depth discussions on pathogenesis and mechanisms of actions of drugs, critical review of the literature published prior to 1994, and many more references and color illustrations.

The *Handbook* emphasizes treatment protocols including new drugs such as vitamin D analogues, retinoids, and tacrolimus that were recently approved or studied. New sections on pediatric psoriasis, antimetabolites, and investigational treatments have been added. For ease of reading, only selected literature and reviews published since 1993 and important earlier articles are listed at the end of each chapter. Appendixes and tables containing lists of ultraviolet therapy equipment and accessories as well as formulae for evaluating psoriasis have been retained and revised. It is assumed that the reader will select the combination of treatments that works best for each individual patient.

C.C.

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Notice: The indications and dosages of all drugs in this book have been recommended in the medical literature and conform to the practices of the general medical community. The medications described do not necessarily have specific approval by the U.S. Food and Drug Administration for use in the diseases and dosages for which they are recommended. The package insert for each drug should be consulted for use and dosage as approved by the FDA. Because standards for usage change, it is advisable to keep abreast of revised recommendations, particularly those concerning new drugs.

Overview of Psoriasis

Charles Camisa

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Psoriasis is at once a common and complex disease. The prevalence of psoriasis in the population of the United States and United Kingdom is estimated to be 1% to 2%. The severity ranges from a single fingernail pit to skin lesions on a fraction of the skin's surface area to total-body skin involvement associated with disabling arthritis. Psoriasis usually does not take lives; it ruins them.

The cause of this vexing condition is still not known although it is agreed that the clinical lesions represent the end result of hyperproliferation and abnormal differentiation of the epidermis. Many hypotheses of the pathogenesis of psoriasis have been advanced. Some have been disproved outright or have just fallen out of favor. Other hypotheses remain viable candidates to explain the primary pathophysiologic alterations or else they have been validated only as epiphenomena.

Before the advent of modern technology with its sophisticated instrumentation for identifying and quantitating molecules in the skin, dermatologists relied on clinical and histopathologic morphology for correlating cause and cure to a skin disease (Table 1-1).

Referring to psoriasis, Goeckerman said, "The comparative frequency with which this disease occurs demands that not only the specialist but the general practitioner should be familiar with effective therapeutic measures directed against it." Many different treatments for psoriasis exist; they are individually and in combination frequently effective and nearly completely so in some subsets of psoriatic patients. Psoriasis is the third most common reason for office visits to dermatologists (behind acne and warts). It has been estimated that there are 1.5 million visits per year to hospital- or

Table 1-1. Clinicopathologic Correlations and Psoriasis Therapy

Clinical Morphology	Histopathologic Morphology	Treatment
Scales	Hyperkeratosis/parakeratosis	Keratolytics, emollients
Thickness	Acanthosis ("psoriasiform hyperplasia")	Coal tar, anthralin, retinoids, vitamin D analogues, phototherapy
Redness	Dilated and tortuous capillaries Lymphocytes in dermis	Corticosteroids, cyclosporine, tacrolimus
Pustules	Neutrophils in epidermis	Retinoids, methotrexate

office-based practitioners for psoriasis; 80% are to dermatologists and 20% to physicians of other specialties. Another 1.5 million visits are for outpatient treatment with ultraviolet B (UVB) or psoralen plus ultraviolet A (PUVA). Approximately 58% of new cases of psoriasis are first encountered by primary-care physicians, emphasizing the importance of recognizing psoriasis in practice and treating it competently. That market share is expected to grow in a managed-care environment that has seen the percentages of corporations and their employees selecting health insurance with a gatekeeper increase from 7% in 1993 to 19% in 1996.

In a study comparing the ability of physicians to diagnose the 20 most common skin diseases from color slides, primary-care physicians had an overall score of 54% (compared to a score of >90% for dermatologists). However, psoriasis was recognized 85% of the time by primary-care physicians, compared to 100% by dermatologists. In another study of 57 patients with varying diagnoses who were interviewed and examined by internal medicine residents and their board-certified attending physicians, the correct diagnosis was rendered in 43% and 52% of patients, respectively. These medical personnel frequently ordered inappropriate therapy for the patient's diagnosis. Computerized diagnostic algorithm systems do not improve these percentages and so far cannot replace the trained human eye and touch. Telemedicine consultations exploit mainly the visual expertise of specialists.

The expanding managed-care market has created new responsibilities for general practitioners (GPs) and dermatologists. Both groups must learn to practice in a more cost-conscious manner without compromising optimal medical care of the psoriasis

patient. Collaboration between the dermatologist and GP is essential: The dermatologist should educate the GP in differential diagnosis and the fundamentals of topical treatment. The two parties must come to terms as to what constitutes "primary care of the skin." Based on interest and available time, the GP may pursue more advanced dermatologic training via reading, attending continuing medical education courses, or spending time seeing patients with the dermatologist.

In May 1995, the American Academy of Dermatology published guidelines for the referral of a patient with psoriasis, but they seem to be written to favor early referral of all patients except those

Table 1-2. American Academy of Dermatology (AAD) Managed-Care Referral Guidelines for Psoriasis with Author's Commentary

AAD Guideline	Comment
1. Diagnosis is in question.	1. GP may perform KOH examination, culture, skin biopsy, serologic test for syphilis.
2. Lack of satisfactory response after 3–4 weeks.	2. Only medium- to high-potency topical corticosteroids would produce moderate to marked improvement in this time frame. The guideline seems to not allow for the use of coal tar, anthralin, and calcipotriene which usually take longer to work.
3. Pustular lesions are present.	3. Patients with generalized pustular psoriasis or erythrodermic psoriasis *should be referred*, but those with localized pustulosis may receive a trial of treatment prior to referral.
4. Arthritis is present.	4. Most dermatologists are not expert at distinguishing psoriatic arthritis from rheumatoid arthritis or osteoarthritis; consultation with a rheumatologist is preferred.
5. Special treatment such as phototherapy, immunosuppressives, retinoids, etc, are under consideration.	5. As these will be the most severe or recalcitrant cases, consultation and assumption of care are appropriate if GP does not have equipment or experience and comfort treating with potent but toxic medications.

GP = general practitioner; KOH = potassium hydroxide.

with the mildest symptoms (Table 1-2). However, topical steroids are prescribed for psoriasis at 70% of visits to dermatologists. The more complex systemic therapies (PUVA, methotrexate, retinoids, etc) for the more severe forms of psoriasis were prescribed at about 10% of visits to dermatologists.

For the purpose of this book, "psoriasis" is considered a single disease entity with several morphologic variants, and a full range of severity and expression based on 1) certain genetic influences (HLA type and genes), 2) environmental factors (such as trauma and climate), 3) associated diseases (particularly infections), 4) concomitant medications, and 5) immunologic status of the host.

The first four factors mentioned have been studied by direct observation, simple laboratory techniques, and statistical analysis, but the fifth had to await the development of in vitro assays of cellular function and the accurate measurement of nanomolar quantities of substances elaborated by cells in the blood and skin. Historically, polymorphonuclear leukocytes and mononuclear phagocytes were examined first because they were readily retrieved and purified in large quantities from circulating blood. The roles of lymphocytes and Langerhans' cells were subsequently explored by in situ monoclonal antibody labeling techniques. It was soon recognized that differences in the microenvironment of the skin could be influenced by soluble mediators secreted by all of the cell types involved including the keratinocyte itself. A "new" skin cell with antigen-processing capability, the dermal dendrocyte, has been proposed as the pivotal cell type in the autoimmune pathogenesis of psoriasis. The immunosuppressive drugs used in organ transplantation, cyclosporine and FK 506 (tacrolimus), block interleukin-2 production and the cascade of cytokines and receptors before slowing hyperproliferation and blunting the concomitant inflammatory responses in the skin. This finding suggests that some aberration in the regulation of interleukins, growth factors, or adhesion molecules is the primary pathologic process in psoriasis. Like many others preceding it, this theory may be partially or completely debunked in time, relegated to secondary status as epiphenomenon, or indeed may be accepted as the cornerstone of the psoriatic phenomenon at which future therapies will be directed.

Where then does arthritis fit into this picture? Although less common than the skin disease, occurring in about 5% to 7% of patients with psoriasis, psoriatic arthritis by its nature can be more physically disabling. A joint space is about as far removed anatom-

ically and functionally from hyperproliferative epidermis as one can get. Mucous membranes and the eye are more closely related to skin embryologically than is synovium and are rarely if ever affected by psoriasis. Is psoriasis a systemic inflammatory disease like lupus erythematosus? Other than the skin and the articular involvement in a minority of patients, it is dubious that other organ systems such as the liver and kidney are affected by psoriasis. The hypothesis of aberrant immunoregulatory control combined with genetic and environmental factors may help to explain the accumulation of inflammatory cells in such disparate sites and influence fibroblasts in the dermis and synovium to induce proliferation of keratinocytes or synoviocytes, respectively. While it is true that some systemic treatments (e.g., sulfasalazine, methotrexate, and cyclosporine) ameliorate both, the pathogenesis of the skin and joint disease may in fact be different.

The total annual expenditure for cutaneous psoriasis treatment in the United States exceeded $1.5 billion even before the use of cyclosporine, currently the most expensive systemic treatment available. When tailoring therapy to the individual patient, physicians should base selections on efficacy, toxicity, accessibility, and cost. Sander and colleagues determined that excellent results can be achieved at high cost with the Goeckerman regimen in a psoriasis day treatment center (although it is less expensive than hospitalization) and that methotrexate was the most cost-effective systemic treatment (Table 1-3). While a cure for psoriasis is still

Table 1-3. Cost of Psoriasis Treatment

Treatment	Results	Estimated Cost/Year ($)
Cyclosporine	Excellent	6000
Day Goeckerman	Excellent	4000
PUVA	Good–excellent	2600
Outpatient UVB	Fair–good	2000
Etretinate	Good	2000
Methotrexate	Excellent	2000
Hydroxyurea	Fair	1400
Calcipotriene ointment	Good	1100
Potent topical corticosteroids	Fair	810
Commercial tanning bed	Poor–fair	280

PUVA = psoralen plus ultraviolet A; UVB = ultraviolet B.

Source: Adapted from Sander HM, Morris LF, Phillips CM, et al. The annual cost of psoriasis. *J Am Acad Dermatol* 1993;28:422–425.

lacking at the close of the twentieth century, the treatments listed in Table 1-3, as well as some of the newer and less popular ones discussed later in this book, offer incalculable advantages compared to those of less than a century ago.

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Clinical Variants of Psoriasis

Charles Camisa

2

The prevalence of psoriasis in U.S. and U.K. populations is 1% to 2%. The prevalence of psoriasis is much lower in native Americans, African Americans, and Asians. Most African Americans have ancestors in West Africa where the prevalence of psoriasis is 0.7%. There are between 150,000 and 260,000 new cases of psoriasis per year in the United States. The incidence by gender is equal. The mean age at onset is about 30 years, with the range being from birth to 100 years. Females may be affected earlier in life than males.

The cause of psoriasis remains an enigma.

The most common pattern of psoriasis is that of a symmetric inflammatory papulosquamous disease (Fig. 2-1). Recognition of the classic morphology of the skin lesions by an experienced clinician is usually sufficient for confirmation of the diagnosis, but simple diagnostic maneuvers such as examination of scales for hyphal elements using potassium hydroxide (KOH), serologic testing for syphilis, and skin biopsy may be necessary to rule out other considerations.

THE KOEBNER PHENOMENON

One of the hallmarks of psoriasis is the Koebner phenomenon or isomorphic response, which occurs in some patients with unstable or flaring psoriasis. Physical trauma results in linear or figurate patterns of psoriasis that conform to the localization of injury from a scratch, burn, surgical incision (Fig. 2-2), or skin graft donor site. Apparently injury to the epidermis alone can induce the Koebner phenomenon, as shown by "tape stripping," a technique commonly employed by investigators that removes the entire stratum corneum

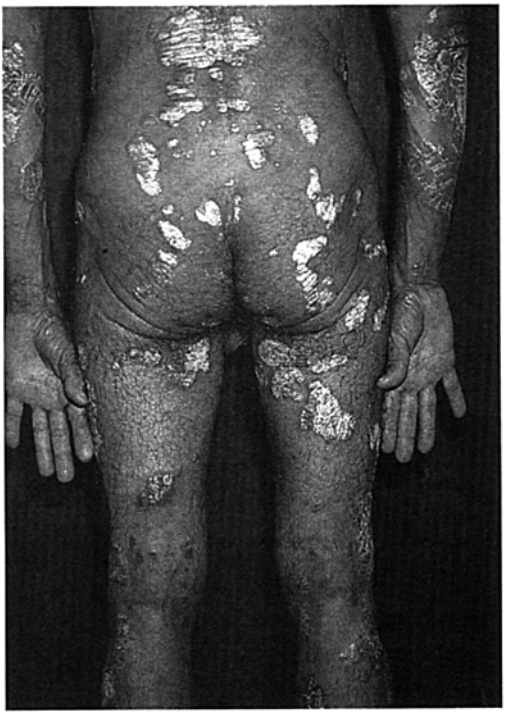

Figure 2-1. Fairly symmetric chronic plaques of psoriasis.

but leaves the granular layer and stratum spinosum intact. The isomorphic response is not unique to psoriasis: It can occur with lichen planus, lichen nitidus, vitiligo, and other skin diseases. Routine daily trauma may be partly responsible for the prominent involvement of the scalp, elbows, knees, hands, fingernails, sacrum, and genitalia. Because the scales of about 50% of psoriatic plaques are colonized by pathogenic staphylococci, it is important to clear psoriasis as much as possible prior to elective surgery, particularly orthopedic surgery, in order to reduce the risks of postoperative infection and psoriasis developing in the healing incision.

Certain drugs have been associated with a kind of "endogenous Koebner phenomenon," notably, lithium, antimalarials, and beta-adrenergic–blocking agents and interferons, which can induce psoriasis or aggravate preexisting disease in some patients. Flare-ups of psoriasis may be triggered by streptococcal tonsillitis or pharyn-

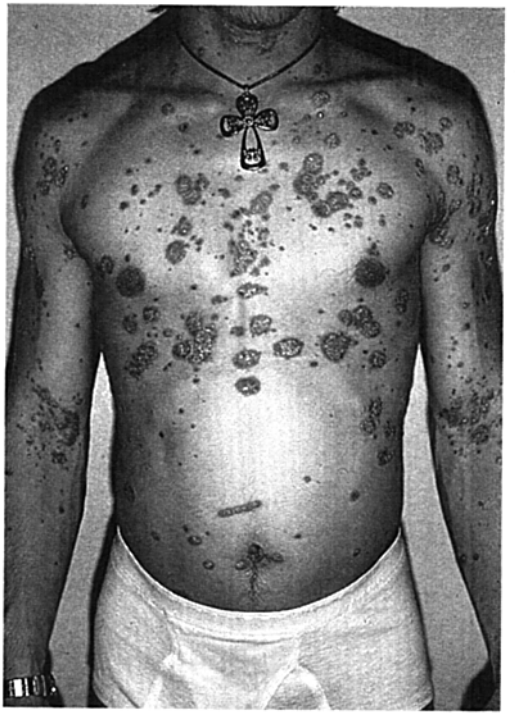

Figure 2-2. Generalized plaque psoriasis with linear lesion above the umbilicus secondary to laceration (the Koebner phenomenon).

gitis and upper respiratory viral infections. Acute guttate psoriasis is frequently the initial episode of chronic psoriasis.

GENETICS

There is no doubt that heredity plays a role in the development of psoriasis. Earlier onset of psoriasis tends to be associated with familial aggregation and more severe disease. For example, 40% of patients with onset at an early age had immediate family members who were affected. Farber and Nall found that of psoriatics indicating familial aggregation, 73% had onset before the age of 30 years. But when a patient developed psoriasis after the age of 20 years and no parent had psoriasis, only 3% of siblings had psoriasis. When psoriasis developed before the age of 15 years and one parent had psoriasis, 50% of siblings developed psoriasis by the age

of 60 years. Patients with severe psoriasis with onset at the age of 15 years or earlier were three times more likely to have siblings with psoriasis than were patients with onset after the age of 30. Twin studies showed 67% concordance for monozygotic twins compared to 18% for dizygotic twins. The lack of complete concordance in monozygotic twin pairs suggests that environmental factors are also important and supports the theory of multifactorial inheritance of psoriasis.

Christophers and Henseler distinguished two types of nonpustular psoriasis on the basis of family history, HLA associations, and age at onset. They designated as type I those patients with a positive family history, onset during the second decade, and a close association between HLA-Cw6, -B13, and -Bw57 (a subtype of B17). Type II psoriasis manifests during the fifth decade, does not involve parents and siblings, and is associated with HLA-Cw2 and -B27 with relative risks of developing psoriasis of 6.1 and 3.1, respectively. Swanbeck et al analyzed age at onset for 11,366 psoriasis patients and found a definite peak around puberty and maxima at about 30 and 50 years with a great deal of overlap.

Farber and Nall disputed the bimodal age incidence. Their peak age of incidence is in the second and third decades. They posited that the bimodal or trimodal curves reported may be an artifact of an excess number of HLA-B13– and -B17–positive patients who tended to have disease at an earlier onset.

A study of 12 families with 15 sibling pairs with psoriasis was analyzed for haplotype sharing. The results suggest that either more than one gene contributes to psoriasis susceptibility or there is a gene-dosage effect. All sib pairs shared at least one haplotype, and 13 of the 15 pairs were HLA identical compared to an expected frequency of 4. The extended haplotype Cw6-B57-DRB1*0701-DQA1*0201-DQB1*0303 was found in 35% of type I psoriatics and 2% of control subjects.

The development of psoriasis is related to the effects of one or more genes located near the HLA region that are able to influence autoreactivity. However, no differences in the patterns of T-cell receptor variable regions could be detected in lesional biopsy specimens from patients with type I or type II nonpustular psoriasis.

The Cw6 antigen is probably a marker for the gene determining susceptibility to psoriasis. Overall, the relative risk for developing psoriasis in patients with Cw6 is 13.3. The risk is doubled when Cw6 is associated with HLA-B57 (but not -B13), which may