Therapy of Moderate-to-Severe Psoriasis

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Second Edition, Revised and Expanded

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An Overview of Psoriasis

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I. INTRODUCTION

Psoriasis has traditionally been considered an inflammatory skin disorder of unknown etiology producing red scaly patches of mere cosmetic nuisance to patients. However, with recent knowledge gleaned from the immunopathogenesis and genetics of psoriasis together with what may be termed the biological revolution in therapy, all of which will be discussed in later chapters, psoriasis now has to be considered a dynamic, genetic, immunological, systemic disorder manifesting on the body surface as well as in the joints in a significant proportion of patients. Patients and dermatologists alike thus need to shift their focus from considering psoriasis as a mere skin disease likely to be controlled with topical therapy to a condition no different from other immune-mediated disorders such as Crohn's disease, rheumatoid arthritis, and lupus erythematosus, all of which have a vast range of clinical manifestations. Just as the full spectrum of these disorders of the immune system need to be carefully considered, so too does psoriasis need a careful clinical evaluation, taking into account the extent of disease, the form of the disease, and quality of life issues for each individual patient as well as the potential for coexistent psoriatic joint disease. All of this, particularly on an initial patient visit, will not be accomplished in a 5–10 min patient encounter. It will require time and dedication from the physician and his or her support staff to improve patient compliance as well as the disappointment factor

currently prevalent in the psoriatic population. Never has psoriasis been so much at the forefront; the buzz among researchers, clinicians, and indeed patients with the advent of new therapies, is palpable. It behooves us as dermatologists to rise to the challenge, refocus our energies and thought processes to the treatment of this most prevalent of all immune-mediated diseases, and take center stage along with our rheumatology and gastroenterology colleagues in biotechnology, target-based therapeutics. Certainly, we will continue to utilize the full therapeutic armamentarium currently available to us, as will be discussed later in this chapter. The explosion of this new knowledge, and with it new therapeutics, will enable patients and physicians alike to tailor therapy to individual forms of psoriasis as well as to individual patient needs.

II. CLINICAL MANIFESTATIONS

Psoriasis is defined by the Committee on Guidelines of Care and the Task Force on Psoriasis of the American Academy of Dermatology as follows: "A chronic skin disease that is classically characterized by thickened, red areas of skin covered with silvery scales" (1). The extent of skin involvement can range from discrete, localized areas to generalized body involvement. The joints, nails, and mucous membranes may also be affected with the disease. "Psoriasis has a tremendous range of phenotypic variability," with a range of clinical manifestations from mild disease with a few isolated discoid plaques to multiple different morphological variants together with more serious forms of the disease involving major portions of the body surface, and, finally, coexistent psoriatic joint disease. Psoriasis may be symptomatic throughout one's lifetime, may progress with age, or may wax and wane in severity. The disease may be readily apparent to others and cause functional impairment, disfigurement, and emotional distress out of all proportion to the actual extent of clinical disease. When severe, in the judgment of the patient, the effects of psoriasis can have a deleterious impact on work performance, social performance and acceptability, sexual function, and mental health. The diagnosis of psoriasis is normally relatively easy to make, although conditions such as cutaneous T-cell lymphoma (CTCL), mycosis fungoides, eczema, tinea infections, and secondary syphilis may occasionally cause confusion and should be considered in the differential diagnosis, particularly when patients' conditions fail to respond to traditional antipsoriatic therapy. A full medical, family, and personal history is likewise important (Table 1). The classic morphological variants are noted in Table 2.

While psoriasis normally remains true to form during one's lifetime with discoid plaques predominating, the whole range of morphological

Table 1 Important Factors in Patient's History

Medical history
Chronic scaling of the ears
Coexistent or previously diagnosed immune-mediated diseases
Long-standing "dandruff"
Atopy
Pruritus ani or vulvae
Associated joint problems
Family history
Atopy
Psoriasis
Rheumatological disorders
Precipitating factors
Antecedent infections, particularly streptococcal
Stress (physical, emotional, or metabolic)
Medications (see Table 7)

Source: From Menter A, Barker J, Fonelli WN. Psoriasis in practice. Lancet 1991; 338: 231–234.

subtypes may present in an individual patient either simultaneously or progressively with increasing age. Thus patients with palmar–plantar psoriasis may have no other clinical evidence of psoriasis, may have coexistent flexural psoriasis, or may have classic discoid plaque psoriasis involving a few anatomical sites or major portions of the body surface area. In addition, erythrodermic psoriasis also classically shows severe palmar–plantar involvement. It is likely that as we unravel the genetics of psoriasis (see below), this

Table 2 Morphological Variants of Psoriasis

Discoid
Elephantine
Erythrodermic
Flexural
Guttate
Palmar-plantar
Pustular
Localized
Generalized

Source: From Menter A, Barker J, Fonelli WN. Psoriasis in practice. Lancet 1991; 338: 231–234.

Table 3 Classification of Psoriasis

Mild psoriasis	Disease does not alter the patient's quality of life Patients can minimize the impact of disease and may not require treatment. Treatments have no known serious risks (e.g., class 5 topical steroids) Generally less than 5% of body surface area is involved with disease.
Moderate psoriasis	Disease does alter the patient's quality of life. The patient expects therapy will improve quality of life. Therapies used for moderate disease have minimal risks, (i.e., although these therapies may be inconvenient, expensive, time-consuming, and less than totally effective, they are not recognized as having the potential for altering short- or long-term health). Generally between 2% and 20% of body surface area is involved with disease.
Severe psoriasis	Disease alters the patient's quality of life. Disease does not have a satisfactory response to treatments that have minimal risks. Patients are willing to accept life-altering side effects to achieve less disease or no disease. Generally more than 10% of body surface area is involved with disease. Other factors Patient's attitude about disease Location of disease (e.g., face, hands, fingernails, feet, genitals) Symptoms (e.g., pain, tightness, bleeding, or severe itching) Arthralgias/Arthritis

Source: Adapted from Ref. 2.

clinical range will have a genotypic basis. The recognition that psoriasis is a condition of wide clinical variability, just like lupus erythematosus, will make evident that what we call psoriasis is in reality an umbrella term for more than one disease with a similar histopathological picture of a hyperplastic epithelium, and an inflammatory cell infiltrate in both the epidermis and the dermis consisting predominantly of T lymphocytes. Before considering the various clinical forms and manifestations of psoriasis more specifically, it is worthwhile to review definitions of mild, moderate, and severe psoriasis.

Psoriasis has traditionally been classified purely on the basis of body surface area: mild corresponds to less than 5% body surface area, moderate psoriasis equals 5–15% body surface area, and severe psoriasis over 15–20% body surface area. Krueger et al. (2) attempted to revise these definitions to include not only body surface area involvement, but also quality of life issues as well as the patient's perception and his or her ability to withstand as well as deal with side effects relating to their individual treatments (see Table 3).

III. THE GENETICS OF PSORIASIS

A. Psoriasis Relating to Age of Onset

Traditionally, two distinct forms of psoriasis have been noted: Type I disease with early onset (before age of 40), likely genetic in origin: and Type II late-onset (over 40 years of age), less likely to be genetic. In a recent clinical and epidemiological study from Spain (3), 1774 patients were studied. In this population, the disease started at a wide range of ages, with a mean age of onset of 29.1 years, with a slight female preponderance for earlier age of onset. In accordance with other studies, over 60% of patients experienced their psoriasis before the age of 30. As in similar prior studies, this large cohort of patients confirmed the association of a positive family history (in up to 40% of patients) with early-onset psoriasis showing an increasing family history of disease. From a morphological point of view, the only significant relationship between the age of onset and clinical forms of the disease related to guttate psoriasis (more frequently seen in patients with early-onset psoriasis) and palmar–plantar pustular psoriasis (more prevalent in late-onset psoriasis). In addition, patients with the early-onset form tended to have more extensive disease and a more severe clinical course.

In a large series of patients followed at the University of Kiel, Germany, a bimodal age of onset of psoriasis was noted with one peak occurring in young patients (mean age 16–22 years), and a second peak occurring in older patients (mean age 57–60 years) (4), which are similar findings to the Spanish study. The features of psoriasis in these two patient groups, Type I and Type II disease, are summarized in Table 4.

Thus in the Kiel population, Type I psoriasis had a strong association with a human leukocyte antigen (HLA)-Cw6 genotype with 85% having this gene compared to 15% of Type II psoriatics. Overall, about 70% of psoriatics were classified as having Type I disease, with the clinical course of Type I psoriasis tending towards more severe involvement.

The genetic influence on psoriasis is best illustrated in twin studies comparing the development of this disorder in monozygotic and dizygotic twin pairs (5). In dizygotic (not genetically identical) twins, psoriasis was

Table 4 Characteristics of Type I and Type II Psoriasis

Characteristics	Type I	Type II
Age at onset	Peak around age 20	Peak around age 60
Family history	Common	Rare
HLA association	Cw6 definite, B13 and B17 probable	Rare
Clinical course	Tends towards more generalized refractory or severe disease	Milder

Source: Adapted from Ref. 4.

found in both individuals in about one-fourth of the pairs, whereas in monozygotic (genetically identical twins), psoriasis was found in both individuals in about two-thirds of the pairs. The significantly higher prevalence of psoriasis in identical twins strongly suggests a genetic component to its development. However, since in only one-third of identical twin pairs only one individual developed psoriasis, there is also an epigenetic influence on its expression. The genetic transmission of psoriasis has been evaluated in some families in which this trait occurs in a higher percentage of individuals (6). Its transmission in some of these families suggests that a dominant gene is responsible, but that, as in the twin studies, acquiring the gene does not always produce the condition (variable genetic penetrance). In large population studies, a clear grouping of psoriasis in families has been confirmed, but the transmission has not followed simple autosomal dominant or recessive patterns. It has thus been proposed that its inheritance in the broad population is multifactorial, combining both a genetic component and an environment influence.

B. Recent Research

Let us now consider the most recent research relating to the genetics of psoriasis. It has been known for years that there is a significant association between HLA and psoriasis, specifically, class I antigens HLA-B57, B13, Cw6, and Cw7, with HLA-Cw6 appearing to confer the highest risk. The first susceptibility locus at the distal end of chromosome 17 was described in 1994 in a publication in Science (7). This came about as a result of research at the National Psoriasis Tissue Bank based in Dallas at Baylor University Medical Center, sponsored by the National Psoriasis Foundation. In 1997, the Michigan-Kiel Group confirmed this susceptibility locus (8). In this study

of 224 sib-pairs, Nair and colleagues found linkages in the HLA region as well as additional loci on chromosome 16q and chromosome 20p. Of interest was the overlap in the 16q region with a previously described locus for Crohn's disease: psoriasis appears more commonly in patients with Crohn's disease. Furthermore, an Italian group has shown a locus on chromosome 1: i.e., 1q21 (9). Drs. A. Bowcock (the discoverer of the original 17q locus) and Bhalerao in 1999 also confirmed this Italian finding (10). Other susceptibility loci have also been found on chromosomes 3 and 4 with no confirmation of these findings to date yet published for these two loci. The various psoriasis loci have been designated:

Psors1 = 6p
Psors2 = 17q
Psors3 = 4q
Psors4 = 1q
Psors5 = 3q

The majority of interest and work in this field of psoriasis genetics has been confined to Psors1 on chromosome 6p21.3, which is considered the most important locus for psoriasis susceptibility in the majority of populations studied. Fortunately in 1999, the full sequence and gene map of the human MHC was described (11). In a study from the United Kingdom published in *Lancet* in 1999 (12), the polymorphic S gene ("S for skin") that lies 160 kb telomeric of HLA-C showed significant evidence for gene linkage and disease association, thus supporting evidence that the S gene plays a major role in psoriasis susceptibility. This S gene encodes the corneodesmosin protein, which plays a role in epidermal differentiation as well as the adhesion of the stratum corneum. It was the authors' conclusion that the S gene was a more attractive potential candidate gene than HLA-C itself. Subsequently, other genes in this region including the HCR gene have been considered to play a role in the pathogenesis of psoriasis. Despite intensive investigation within and around this HLA-Cw6 region, the definitive candidate gene in this area has hitherto not been identified. More recent evidence suggests that the S gene (also called the CDSN gene) may not appear to account for disease susceptibility any better than HLA-Cw6 itself, as underscored by a recent paper in 2000 from the Michigan-Kiel group (13). In this paper, Nair and co-workers defined the psoriasis susceptibility gene as a 60 kb region between HLA-C and HCR, suggesting that this region is the region most likely to carry the disease allele at the 6p 21 locus.

Thus, in conclusion, to quote A. D. Burden in his 2000 review (14),

> Classical HLA loci are not themselves psoriasis genes, but by virtue of their position, are in strong linkage disequilibrium with a non-HLA

susceptibility locus. In addition, it is quite likely that different ethnic groups may have produced different disease-associated haplotypes which possibly could explain both the different HLA associations as well as the decreased incidence in the Chinese population as compared to the Caucasian population (15).

In summary, the identification of the specific gene/s for psoriasis has been narrowed, with multiple loci almost certainly implicated. Once a specific candidate gene on chromosome 6p21.3 (Psors1) is identified, potential interactions (epistasis) between this gene and other psoriatic loci previously discovered (Psors2–Psors5) appear likely to be confirmed. The collaboration between molecular geneticists around the world, under the sponsorship of the National Psoriasis Foundation, certainly is bearing fruit and the potential exists for the exact molecular defect underlying psoriasis susceptibility being discovered in the not too distant future.

IV. PATHOPHYSIOLOGY OF PSORIASIS

A. Epidermal Hyperproliferation

The histopathology of the psoriatic epidermis was always noted to have many mitoses. In 1963, Van Scott determined that there was a marked increase in mitoses per surface of psoriasis in comparison to the normal epidermis. He developed the concept called the hyperplasia of psoriasis (16). This information was then expanded in a series of studies using radioactive isotopic techniques to examine both static and dynamic aspects of psoriatic epidermal hyperproliferation. The data showed that the transit time of psoriatic basal cells moving upward to the beginning of the stratum corneum took only 2 days in comparison to the normal epidermis, which had a slower upward movement of about 12 days through a much thinner epidermis (17). Further studies using tritiated thymidine injected in vivo into psoriatic skin determined a cell cycle of approximately 37 h compared to about 300 h in normal skin (18). While finding that psoriatic cells were hyperproliferative, it did not reveal the mechanism(s) by which the skin would change its pattern of proliferation and conversion into the phenotype of psoriasis. However, it did suggest at least one reason why a drug such as methotrexate might be active in the treatment of this disease. Additional studies indicate that lymphocytes are more sensitive to methotrexate than epidermal cells, suggesting that methotrexate may affect at least two different cellular components of psoriatic tissue (19).

B. Immunology of Psoriasis

Since the mid-1980s, evidence has appeared that there might be an immunological component to the pathogenesis of psoriasis. This concept was expanded by the serendipitous observation that patients receiving an immunosuppressive drug, cyclosporine, who also had psoriasis, found that their skin disease was clearing. This is not unlike a similar serendipitous observation in 1951 that the folic acid antagonist, aminopterin (later replaced by methotrexate) produced clearing of psoriasis. The immunological milieu of psoriatic skin includes the presence of many T lymphocytes, particularly CD4+ (helper) and CD8+ (suppressor/cytotoxic) cells. Related to these and other cells, many cytokines were and are still being discovered that influence the inflammatory aspects of psoriasis and trigger, directly or indirectly, the hyperproliferation of psoriatic keratinocytes.

The science of immunology as it pertains to many diseases is now being utilized to develop new therapeutic approaches to diseases including psoriasis, rheumatoid arthritis, psoriatic arthritis, multiple sclerosis, Crohn's disease, and others. From research on the immunopathogenesis of psoriasis, these findings are creating an extensive pipeline of new drugs described in this book (20,21) (see Chapter 11).

V. CLINICAL MANIFESTATIONS

A. Scalp Psoriasis

The majority of patients with psoriasis will show evidence of scalp involvement. Despite the full range of therapeutic modalities now available, including topicals, light treatments, and systemic therapies including the new biological agents, scalp psoriasis remains one of the most difficult areas to control. Psoriasis is classically a highly symmetrical disease, but lesions on the scalp are frequently asymmetrical, almost certainly related to the inevitable koebnerization of scalp psoriasis due to the patient's picking, scratching, and harsh shampooing. This leads to lichenified plaques with involvement usually on the posterior scalp or above either ear (i.e., areas of easy accessibility). When scalp psoriasis predominates with or without associated facial involvement, overlap with seborrheic dermatitis may produce the clinical variant known as sebopsoriasis.

B. Guttate Psoriasis

This form is well known to most dermatologists, often presenting in young adults or children with a prior history of a streptococcal throat infection.

Numerous other trigger factors, such as viral infections, medications, major stress episodes, and rapid discontinuation of systemic therapy (steroids, methotrexate, or cyclosporine) may also produce this inflammatory, papular form of psoriasis. In addition, patients with previous stable plaque psoriasis may experience, at intervals, guttate flares, either related to the aforementioned trigger factors or spontaneously. It is fortunate that pure guttate psoriasis is one of the forms of psoriasis most amenable to treatment with phototherapy and, if necessary with culture-proven streptococcal infection, concomitant antibiotics. Parents of children presenting with guttate psoriasis as a first indication of the condition should be counseled about the likelihood of more classic discoid-type psoriasis supervening in young adult life as well as the need to interact with their pediatrician for future interventions with subsequent upper respiratory infections, particularly streptococcal ones.

C. Discoid Plaque Psoriasis

This most common form of the disease usually presents as symmetrical plaques ranging in size from small coin-sized plaques to larger plaques that may coalesce to form large geographic areas (Fig. 1). As discussed in the definitions of mild, moderate and severe disease, it is essential to do a full-body evaluation of the patient's plaque involvement to ascertain whether topical therapy, for instance, is likely to be both of value as well as appropriate for each individual's needs and potential long-term compliance.

D. Erythrodermic Psoriasis

This inflammatory severe form of psoriasis, fortunately affecting only a minority of patients, is frequently precipitated by trigger factors such as infections, inappropriate systemic steroid usage, or burns incurred during phototherapy. Other trigger factors may relate to abrupt discontinuation of systemic therapy, particularly methotrexate and cyclosporine. It is important to differentiate other forms of erythroderma, particularly in patients with no known prior history of stable chronic plaque psoriasis. Thus, eczema of all forms, particularly atopic in nature, Sézary form of cutaneous T-cell lymphoma, pityriasis rubra pilaris, and drug-related causes may need to be differentiated. Despite the continued decrease in hospitalization of psoriasis patients, erythrodermic psoriasis is the one form of the disease that frequently necessitates inpatient therapy. In our experience, it is critical to rule out systemic sepsis prior to initiating specific antipsoriatic therapy since a certain proportion of patients will have staphylococcal sepsis. In fact, a

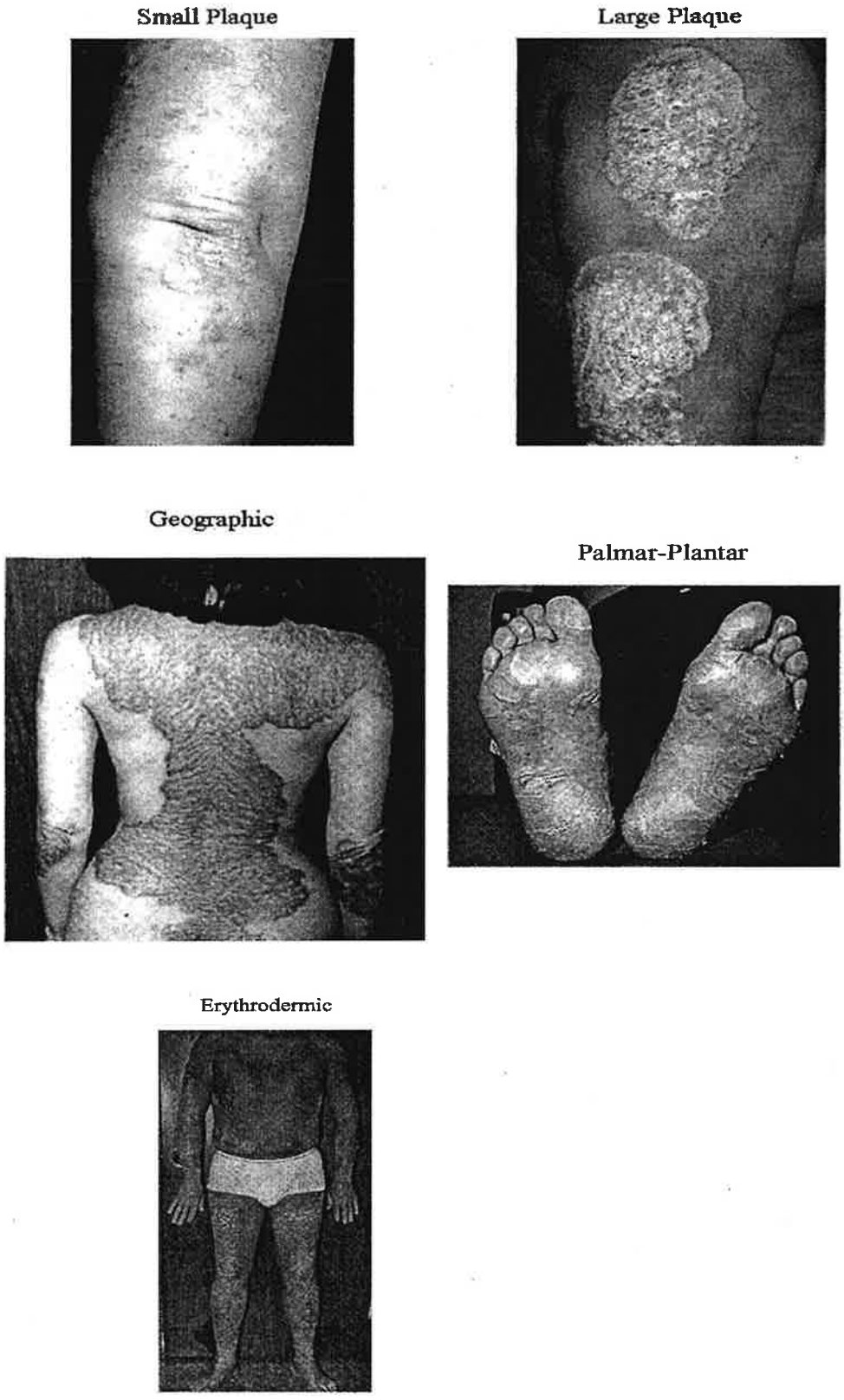

Figure 1 Morphological variants of psoriasis: Is this one disease? (Refer to the color insert.)

recent referral to our clinic in Dallas was a young patient with prior stable plaque psoriasis well controlled on cyclosporin who experienced sudden worsening and increased inflammation. The dosage of cyclosporin was increased by his referring dermatologist to 5 mg/kg/day, despite which his psoriasis continued to worsen. Coagulase-positive *Staphylococcus* was cultured in his blood, on initiation of appropriate systemic antibiotics, his psoriasis responded dramatically with no further need for antipsoriatic therapy. Likewise, it is important to observe these patients for evidence of cardiac and renal failure, particularly in elderly patients in whom these organ systems may already be compromised. A certain proportion of these patients do respond to hospitalization and treatment with wet compresses, dilute topical steroids with or without occlusion, and supportive therapy, such as fluid balance control (22).

E. Flexural Psoriasis

This form of psoriasis, like scalp psoriasis, is frequently resistant to traditional forms of therapy. In obese patients, areas such as breast folds and groin folds may frequently be complicated with secondary candidiasis necessitating specific anti-*Candida* therapy. In addition to standard antipsoriatic therapy, such as dilute topical steroids, the newer nonsteroidal topicals tacrolimus and pimecrolimus both appear to be effective in this location compared to their rather poor effect in other cutaneous sites except for the face.

F. Palmar–Plantar Psoriasis

This is classically divided into the hyperkeratotic form and the pustular form. In many instances there is an overlap between these two polar types with fissuring, erythema, crusting, and pustules coexisting in individual patients, with or without evidence of cutaneous disease on other anatomical sites. Intensive topical therapy is frequently difficult. A significant proportion of patients have disease that is not well controlled on purely topical therapy leading to problems in quality of life, particularly in day-to-day activities, including ambulation, and manual activities. Many patients with this form of psoriasis will require systemic therapy and/or phototherapy.

G. Psoriatic Arthritis

Why is it important that the dermatologist recognize this condition? First, psoriatic arthritis is far more common than has previously been considered (23). It has always been considered to affect only about 10% of patients with

psoriasis, yet it is well known that over 35% of patients with psoriasis will complain of joint tenderness without necessarily having confirmed psoriatic arthritis. According to a recent National Psoriasis Foundation survey, up to 20% of patients may indeed have psoriatic arthritis. Psoriatic arthritis is often considered a relatively benign arthropathy associated with cutaneous psoriasis. However, it can frequently be debilitating and disabling, and, like rheumatoid arthritis, is frequently progressive leading to disability and eventual need for surgical intervention. Five clinical patterns of psoriatic arthritis have been recognized that can coexist with overlapping clinical expressions (Table 5).

Patients with distal interphalangeal (DIP) disease are likely to have psoriatic nail changes, and thus it is imperative that at all clinic visits the dermatologist inquire whether the patient has morning stiffness and/or joint pain or swelling elsewhere (Table 6).

While we do not ask all dermatologists to delineate the type or degree of psoriatic arthritis, because we are frequently the portal of entry for psoriatic patients, diagnosis by us and/or referral to our rheumatological colleagues may prevent further disability and progression of the disease. This is especially important with the array of medications, particularly the new biological agents, currently available.

Table 5 Classification of Psoriatic Arthritis: Types and Incidence

Type	Key clinical features	Incidence (%)
Asymmetrical polyarthritis or oligoarthritis	Morning stiffness, distal (DIP) and proximal interphalangeal (PIP) involvement, nail disease, ≤4 joints involved	> 47
Symmetrical polyarthritis	Simultaneous development of psoriasis and arthritis	25
Ankylosing spondylitis	Progressive low back pain, morning stiffness, sacroiliac and axial joint involvement	23
Distal interphalangeal joint disease	Nail and joint involvement (DIP) predominate	Rare
Arthritis mutilans	Destructive form of arthritis, telescoping, joint lysis, typically in phalanges and metacarpals	Rare

Source: Courtesy of Amgen Corporation.

Table 6 What is the Role of the Dermatologist in Identifying Psoriatic Arthritis?

No one expects dermatologists to be rheumatologists
However, dermatologists should be aware of, and vigilant for the arthritic component of psoriasis and refer as needed

Dermatologists should:

Examine for	*Ask about*
PIP and DIP involvement	Morning stiffness
Tender and/or swollen joints	Persistent joint pain or other arthritic symptoms
Nail involvement	Fluctuations of joint pain with exacerbations of psoriasis
	Family history of psoriatic arthritis

Source: Courtesy of Amgen Corporation.

VI. ITCHING IN PSORIASIS

Most major texts state that itching of psoriasis, while present in a fairly significant proportion, is frequently mild in nature. Prevalence is frequently higher in patients with more severe disease. In this regard, a study of 200 psoriasis patients found that 92% had pruritus at some time (24). In a study of patients from a psoriasis outpatient clinic with significant plaque involvement, pruritus was a feature in 84% of 108 patients, being daily in 77% of patients, weekly in 18% of patients, and less frequently in 5%. All body sites were affected, with the back, legs, and arms the most commonly involved. The face and neck were less commonly involved (25). Important in this study was the fact that the pruritus in the majority of patients was unresponsive to treatment with traditional antipruritics. Phototherapy also did not significantly relieve the itch. Thus itching is a symptom, like many other symptoms of psoriasis, that has a negative impact on the quality of life in the majority of patients with psoriasis. This will be discussed in more detail subsequently.

VII. FACTORS AFFECTING REMISSIONS AND FLARES

Since psoriasis is a chronic condition that often waxes and wanes in severity, it is clearly desirable to identify factors that can worsen disease activity or prolong the duration of therapy-induced remission. Much more is known about circumstances under which psoriasis worsens than about favorable conditions or treatments that will significantly extend a period of remission or

low-level disease activity. Presently many psoriatic patients are continued on standard therapeutic agents following clinical clearing of their disease in order to suppress recurrences (maintenance therapy). Other than maintenance therapy, there are no specific treatments for extending remission periods, except through efforts made to avoid skin injury or drugs for other therapies that will lead to worsening of psoriasis. Warm weather, summertime, and rest and relaxation in beach-type vacation environments may provide significant periods of improvement without accompanying medical treatments. The relaxation component may be the most significant part of the improvement in a stress-prone patient. Factors that have been shown to exacerbate psoriasis are summarized in Table 7.

Expression of active, lesional psoriasis is linked to mitotic and biochemical activation of both keratinocytes and immunological cells within a localized area of skin. Because both sets of cells are functionally activated by common cytokines, it is not surprising that psoriasis can be triggered by a variety of different stimuli that activate either epidermal keratinocytes or lymphocytes locally in skin. Any form of injury to the epidermis that triggers resting keratinocytes into a wound repair pathway can also trigger psoriasis in susceptible (Koebner-responsive) patients. Thus tape stripping, superficial or deep abrasions, lacerations, thermal burns, sunburns, or other physical injury can locally trigger psoriasis (26). In normal individuals, each of these forms of injury would lead to a transient period of altered epidermal activity (termed regenerative epidermal maturation) or an alternative pathway of keratinocyte differentiation that would repair the injury. In this regard, the difference between Koebner-responsive psoriatics and nonresponsive individuals is probably the ability to turn off or downregulate a physiologically relevant cell growth pathway. Another physiological cell-activation process that can occur locally in skin is delayed-type hypersensitivity local T-cell activation via antigen presentation by epidermal Langerhans cells. The most common expression of this pathway in skin is contact allergy to an external substance, but local immunity can also be triggered by focal skin infections, vaccinations, or reactions to systemic medications. Each of these conditions that activates cellular immunity has also been shown to cause a flare of psoriasis in some susceptible individuals. Flares of guttate psoriasis, especially in adolescents, are often attributed to antecedent pharyngeal infections with group A streptococci. Although the skin is not directly infected with this organism, systemic immunological activation may lead to increased T-cell activation in skin as the initiating reaction in a guttate flare. It should also be emphasized that widespread systemic immune dysfunction induced by human immunovirus (HIV) sometimes leads to a form of psoriasis that, paradoxically, worsens with decreasing T-cell counts (27).

Table 7 Factors that Can Induce or Exacerbate Psoriasis in Susceptible Individuals

Physical trauma to skin
Superficial abrasion
Blister
Laceration/incision
Thermal burn
Phototoxic reactions
Solar
Ultraviolet B
PUVA-induced
Activation of local cellular immunity
Contact allergens
Immunizations in skin
Infections in skin (bacterial or viral)
Systemic immunological activation or alteration
Hypersensitivity to drug or other antigen
Group A streptococcal infections
HIV infection
Systemic drugs (probable action through pharmacological properties of the agent)
Corticosteroids
Interferons
Lithium
Antimalarials (chloroquine, hydroxychloroquine, quinacrine, quinidine)
Beta-blockers (adrenergic receptor antagonists: many different agents both selective and nonselective)
Nonsteroidal anti-inflammatory drugs
Angiotensin-converting enzyme inhibitors
Gemfibrozil and a number of other drugs in case reports
Emotional stress

Psoriasis can be exacerbated or induced in some susceptible individuals by a number of systemic drugs (28, 29). Drugs that have been reported to worsen psoriasis include lithium, β-adrenergic receptor blockers, antimalarials, nonsteroidal anti-inflammatory drugs, angiotensin-converting enzyme inhibitors, gemfibrozil, and corticosteroids (Table 7). In individuals with demonstrated or suspected worsening of psoriasis due to one of these agents, it is desirable to discontinue the suspected drug or to try an unrelated alternative if the patient's medical condition permits and other therapeutic options are available. Although systemic corticosteroids are occasionally used to treat psoriasis, the response in this regard is limited by significant

exacerbation of baseline disease activity (termed rebound or flaring), including induction of pustular flares, following their discontinuation. Unless a concurrent medical condition dictates the need for systemic corticosteroids, their use in the treatment for psoriasis should be avoided because of their tendency to worsen psoriasis after withdrawal. In a study of 103 patients with generalized pustular psoriasis, over 30% had previously received treatment with oral steroids (30). Such exacerbations of psoriasis have also have been seen after extensive use of topical corticosteroids, particularly when they are applied under occlusion. Rebound and flaring of psoriasis following discontinuation of systemic corticosteroids are probably not obligate consequences of systemic immunological suppression, since psoriasis recurs without rebound or pustular flares less frequently following discontinuation of cyclosporine therapy.

VIII. STRATEGY OF THERAPY

The strategy of therapy starts with an educational process that informs the patient as to the nature of psoriasis and the therapeutic capabilities available today for the type and extent of disease in the particular patient. The initial visit with a patient will usually include consideration of topics that pertain to the current disease manifestations, exacerbating factors, familial hereditary concerns, and psychological factors (Table 8). The discussion soon reaches the major goal, which is to improve the patient's quality of life without producing undue harm medically, fiscally, or emotionally. The physician is challenged with presenting to the patient a realistic but, it is hoped, optimistic big picture of therapy, keeping in mind the chronicity of this disease. Extended therapy with any treatment leads to the potential for resistance and/or toxicity.

Table 8 Doctor–Patient Discussion of Psoriasis

Lesions/symptoms/diagnosis
Hereditary aspects
Systemic manifestations: arthritis
Exacerbating and favorable factors
Response to past treatments
Range of therapeutic options
Chronic long-term disease
Psychological ramifications
Optimism for tomorrow, new therapies in the pipeline

The therapeutic approaches to psoriasis today include topical or local medications, phototherapeutic modalities, and systemic drugs. The simplest and safest treatments are topical agents used primarily in patients with limited amounts of skin involvement. There is no precise definition of limited (or mild) disease. Our definition is that the location and amount of body surface area (BSA) affected can be practically and effectively treated with topical medications.

Quality of life comes into this consideration: smaller areas but those in critical areas (such as for employment or social appearance) may override consideration of a simple body surface area calculation (2). Topical therapy of BSA greater than 20% requires large quantities of medications with commensurate higher costs, time for applications, and inconvenience depending on the drug. Currently available topical therapy does not usually produce long-term clinical improvement. Patients with minimal disease undergo continual trials of different medications and accumulate a medicine chest filled with topical preparations. At some point, however, those frustrated patients with more disease (i.e., 10% or more BSA), or those unresponsive to topical therapy) become candidates for more aggressive forms of therapy, such as phototherapy and/or systemic drugs. In these patients, now defined as having moderate-to-severe disease, more effective therapies are, fortunately, available.

In 1993 a survey of American Academy of Dermatology members revealed that there were approximately 2.4 million visits annually to dermatologists by psoriatic patients, with each dermatologist seeing an average of 28 patients with psoriasis per month (31). Using a working definition of mild psoriasis as a patient being treated with topical therapy, 77% were estimated to have mild (limited) disease. The remainder of the patients received photo/systemic treatment and were considered to have moderate-to-severe disease. Other criteria frequently used to define moderate-to-severe disease are listed in Table 9.

In patients receiving topical therapy, corticosteroids are the choice of 85% of physicians. The remaining patients receive either topical calcipo-

Table 9 Working Definitions of Moderate-to-Severe Psoriasis

Greater than 20% of body surface area involved
Psoriasis not responsive to topical therapy
Extensive disease not economically feasible to treat topically
Psychologically stressful disease
Gainful employment prevented
Pustular or erythrodermic psoriasis

triene, topical tazarotene, or combinations of each with corticosteroids. See Chaps. 2 and 8. Within the steroid selection category, class I–II (potent-superpotent) steroids were chosen by 62% of the dermatologists and 37% selected the mid-potency compounds. Potent steroids generally produce good to excellent results, but the major problem is that these results do not persist for long periods of time. The survey information indicates that by 3 months after maximal improvement with steroids, relapse of disease is seen in about 50% of patients, even with continuing use of medication. The well-known phenomenon of tachyphylaxis somehow prevents the continuing responsiveness of psoriasis to topical steroids. Older therapies—tars and anthralin—are much less effective than the potent steroids and are used less today. In summary, while the potent topical steroids may be reasonably effective for the treatment of psoriasis, their value is limited by lack of long-term remission and maintenance. The frequency with which patients carry bags of different topical medications into their physician's office testifies to this frustrating dilemma.

The moderate-to-severe psoriatic patient presents a much more interesting, satisfying, and valuable therapeutic challenge. There is probably no other extensive (noninfectious) dermatological disease that has available such an armamentarium of effective therapeutic approaches. There are at least seven forms of psoriasis therapy (Table 10) for which much information has been acquired. These treatments are the subject of this book.

It is interesting to consider the advances in therapy of psoriasis that have occurred in the last half-century. These advances represent approximately half of all the new medications that have been developed for our most common dermatological diseases to the present (Table 11).

In the treatment of moderate to severe psoriasis, there are some interesting concepts worth noting. The moderate/severe patient population comprises 20–25% of all the psoriatics seen in the average practice (31).

Table 10 Therapeutic Approaches to Moderate-to-Severe Psoriasis

Phototherapy:UVB with or without tar
Photochemotherapy
Methotrexate
Acitretin
Cyclosporine
Isotretinoin (pustular psoriasis)
Immunomodulatory drugs (biologicals)

Table 11 Major Dermatology Drug Discoveries

Pre 1950	**Tar/UVB**; penicillin, antibiotic era begins
1950s	**Corticosteroid** era begins, **methotrexate,** griseofulvin, antifungals, antihistamines
1960s	5-fluorouracil, topical retinoids
1970s	Retinoids (isotretinoin), **PUVA,** acyclovir
1980s	**Retinoids (etretinate, acitretin)**
1990s	**Cyclosporine, topical calcipotriene, topical tazarotene**
2000s	Tacrolimus, **"immunomodulatory drugs"**

Bold names indicate psoriasis therapies.
The bold therapies used for psoriasis represent half of the therapeutic medical advances in dermatology.

Estimates of which therapies dermatologists use are presented in Table 12. It is readily apparent that ultraviolet B (UVB) phototherapy with or without tar is the most frequently utilized modality. This is followed in frequency by psoralen combined with ultraviolet A phototherapy (PUVA) and methotrexate. The oral retinoid, etretinate, now acitretin, is used to a significantly lesser extent. Since cyclosporine was approved at about the time of the survey, its usage is probably significantly higher now than found in the survey. Several other treatments are used for occasional patients. The data also indicate that a small percentage of physicians continue to use systemic steroids in about one-third of their patients. The concern with this treatment is the number of patients presenting with pustular psoriasis associated with recent or continuing use of systemic steroids.

Table 12 Selection of Photo/Systemic Treatments for Moderate-to-Severe Psoriasis

Therapy	% Dermatologists using this form of treatment	Mean % of patients receiving this therapy
Goeckerman; UVB ± tar	82	62
PUVA	56	25
Methotrexate	56	22
Etretinate	43	9
Cyclosporine	3	2
Sulfasalazine	18	15
Systemic steroids	11	35
Other (referral out)	8	44

Source: From Ref. 31.

In treating patients with a chronic disease such as psoriasis, treatment effectiveness, duration of effectiveness, and safety are integral components of a treatment plan. As indicated earlier, topical steroids may have good short-term effects but long-term lesion clearance is far from satisfactory.

The surveyed dermatologists were asked for their perception of the effectiveness of topical therapy for mild psoriasis in comparison to the effectiveness of photo/systemic treatments for more extensive psoriasis. The criteria for judgment included both quality and duration of improvement. Each of the photo/systemic treatments was perceived to work *better* than topical steroids (Fig. 2). In a recent report, an analysis of multiple studies on the effectiveness of these therapies was performed (32). This report quantitates the clearance rates of available treatments (Fig. 3). One can conclude that the available topical forms of therapy are not yet as effective for psoriasis, lesion for lesion, as the photo/systemic modalities. Subsequent chapters in this book will describe in detail the quality and duration of improvement achieved by these treatments.

With moderate-to-severe psoriasis the assumption must be made that this disease will generally remain active in some form for much of the patient's

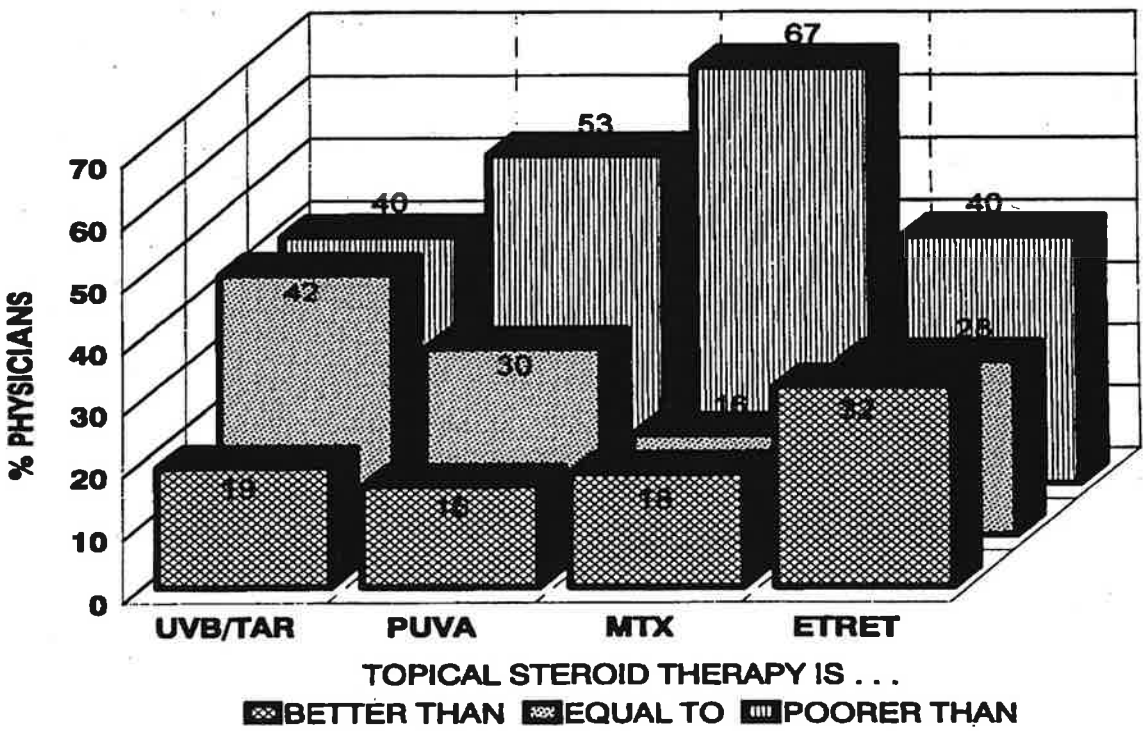

Figure 2 Comparison of efficacy of topical steroid therapy for mild psoriasis with photo/systemic therapy for widespread disease in the opinion of physicians surveyed. (From Ref. 31.)

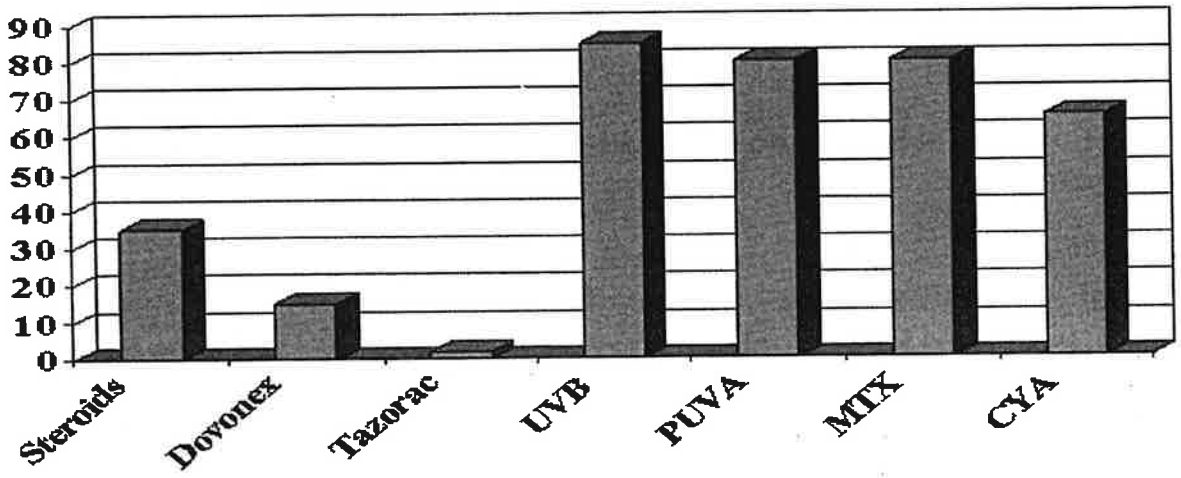

Figure 3 Clearance rate is not a realistic expectation of psoriasis treatment. (Courtesy of S. Feldman.)

future. Therapeutic planning must consider that the currently available treatments will be used for many years. Thus they must be used in a manner that will minimize long-term toxicity so that they can be safely used intermittently for possibly the remainder of the patient's life. For two of our major treatments, UVB with tar and methotrexate, we have clinical experience for over 70 and 50 years, respectively. Long-term experience with PUVA and the oral retinoids, etretinate and acitretin, is still being accumulated, while cyclosporine experience with psoriasis is about 10 years old. Unfortunately, all the current therapies are accompanied by toxicity to a greater or lesser extent. At some point during treatment, the therapeutic index for each therapy suggests that the risks may begin to outweigh the benefits. These risk factors appear to accumulate with continuing therapy, as seen, for example, in the liver changes accompanying large cumulative dosages of methotrexate or skin cancers following many PUVA treatments.

The development of long-term toxicity in patients receiving large amounts of individual treatments has led to the concept of periodically *rotating* the different available therapies (33). In this way, a patient would not remain on a specific medication for a long enough time to reach early levels of predictable toxicity, but instead would be switched to an alternative treatment. If one were to rotate these treatments at 1–3 year intervals (depending on the intensity of usage), it would theoretically take several years to return to the original drug or phototherapy (Fig. 4). By that time, after a several-year rest period off that treatment, some of the cumulative toxic effects in the body might have diminished. With such an approach one can hope to extend the useful and safe duration of therapy for many years. As

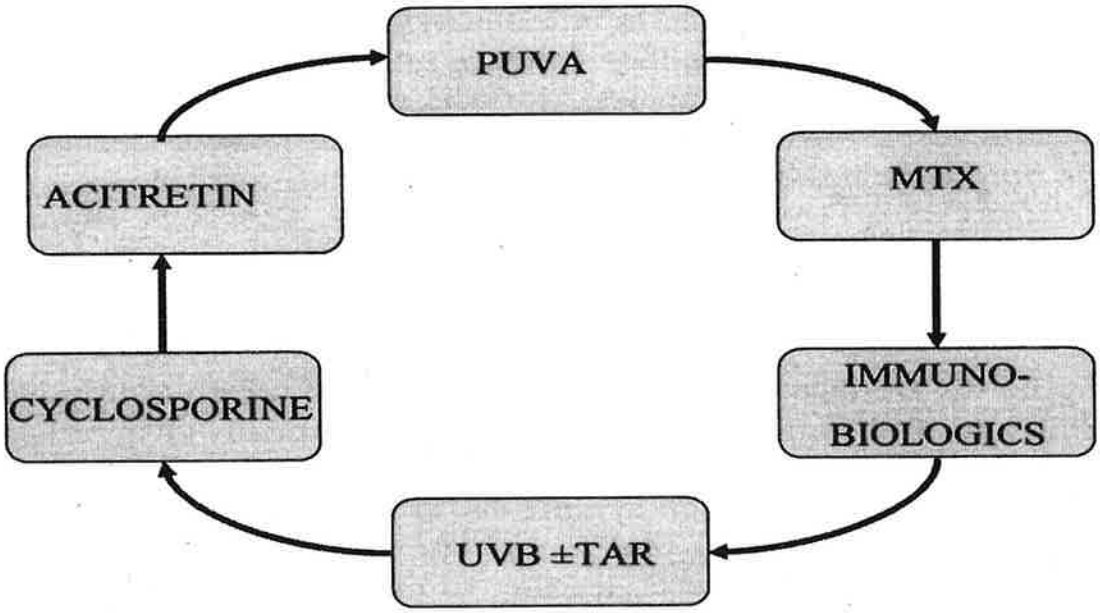

Figure 4 Multiple approaches to rotating available therapies for moderate-to-severe psoriasis. (Adapted from Ref. 33.)

new forms of therapy become available, which now includes cyclosporine and the newly available biologicals, the rotational circle then becomes larger and longer. (See Chap. 8).

Today, more than ever, the economics of therapy of a long-term disease psoriasis must be considered. Recent reports detail the annual costs of therapies for moderate-to-severe psoriasis (34). Outpatient forms of therapy range in cost from $1,400 to $6,600 (Table 13). Inpatient therapy, which is generally a modified form of the Goeckerman regimen, is substantially more expensive and is now used infrequently because of current health economic

Table 13 Mean Annual Costs of Psoriasis Care

Treatment	Total ($)	Lab Work	Drug
Outpatient Goeckerman (day-care setting)	3,914	0	0
PUVA	2,604	138	473
Outpatient UVB (3 times/wk)	1,966	0	0
Methotrexate	1,381	470	458
Etretinate	1,995	465	1,267
Cyclosporine	6,648	1,021	4,119

Source: From Ref. 34.

changes relating to hospitalization and length of stay issues. The overall costs of treating psoriasis may exceed $3 billion in the United States on an annual basis as of 1993, a figure that identifies psoriasis as a major health-care problem. Psoriasis, especially in those patients with moderate-to-severe disease, should not be viewed as a minor cosmetic problem.

IX. COUNSELING AND EDUCATION

As dermatologists we are faced with the very difficult and sensitive responsibility of discussing a chronically discomforting, cosmetically disfiguring disease. The physically discomforting problems of itching, dryness, irritation, fissuring, and a host of other symptoms are the more immediate difficulties that therapy is asked to overcome. The issue of cosmesis may be more distressing than anything else, leading to psychological difficulties because of an altered self-image. With new patients, particularly young adults who are socially distressed, it has always been of value to spend at least a short time discussing the emotional aspects of the disease. It often allows the patient to vent many pent-up feelings and frustrations to which the sympathetic physician can respond and offer encouragement. The availability of local support groups for psoriasis, and particularly the materials of the National Psoriasis Foundation, becomes very helpful. The patient needs optimism and education. Both of these needs can be discussed in terms of the considerable amount of research being done on psoriasis. The research has led to the development of several new therapies in the past 25 years, including PUVA, oral retinoids, cyclosporine, and the potential of the new immunomodulators or biologicals. As dermatologists accumulate more experience with each of the therapeutic modalities, additional patients with borderline severe disease may be included in the treatment groups for some of the drugs described in this book. With the basic mystery of psoriasis continuing to unravel and with more emphasis on immunological mechanisms, we are seeing new therapies that will attempt to interdict immunological pathways affecting the skin.

X. PSYCHOLOGICAL INTERVENTION

The physician's role is, and always has been, very much that of educator and psychotherapist. To know how to induce peace of mind in the patient and to enhance his or her faith in the healing powers of the health-care

provider requires psychological knowledge and skills, not merely charisma (36, 37). The practitioner's sensitivity to changes in body image and to fears of social rejection, and a willingness to listen to and understand the familial, social, and sexual impact of the disorder aids the recovery of the whole person. Within this supportive context, encouragement is more readily received.

The relationship between stress and psoriasis has been investigated by Baughman and Sobel, (38) and by Arnetz et al. (39) among others. Cognitive interpretation (how stressful life events are perceived by each individual) may be a crucial factor in what constitutes what we call stress (40). Cognitive interpretation, as an intervening variable, mediating between stressful life events and somatic reactivity, may explain why some patients with psoriasis believe their disorder is caused or exacerbated by stress while others do not. Thus, patients in Baughman and Sobel's sample are described as stress reactors and nonstress reactors. In contrast, the Arnetz et al. study suggests that, during stressor exposure, the psoriatic group reported significantly higher strain levels "accompanied by higher levels of urinary adrenaline and lower levels of plasma cortisol."

The continuing "stress and psoriasis" controversy makes research into treatment programs that combine state-of-the-art dermatological therapy with psychological intervention worth investigating. Yet self-control strategies and/or psychotherapy are not generally incorporated into treatment. Relaxation training and psoriasis-specific guided imagery as adjuvant treatment to dermatological therapy have been investigated (41). Twenty-five subjects with severe psoriasis were randomly assigned to one of three treatment groups: PUVA only; PUVA plus a series of individual psychotherapy sessions; or PUVA plus a self-control strategy; psoriasis-specific relaxation training/guided imagery. Each patient in the two psychological intervention treatment conditions met individually with a psychologist each week for 7 weeks. The dependent measures were qualitative evaluation of psoriatic lesional severity, and quantitation of percentage of psoriatic body involvement. At the 3 month follow-up, PUVA plus *either* of the adjuvant psychological intervention treatment conditions produced significant differences ($p < 0.05$) in both qualitative and quantitative dermatological measurements, indicating better psoriatic status compared with PUVA treatment alone. Both the adjuvant psychological treatment groups showed 80–89% psoriatic improvement in qualitative and quantitative measures compared with pretreatment values, while the PUVA-only treatment conditions showed 58–60% improvement. The results suggest a useful place for adjuvant psychological intervention in the management of severe psoriasis. There is a strong need for further research in this area.

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5

Therapy of Moderate-to-Severe Psoriasis with Methotrexate

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I. INTRODUCTION

A half century has passed since the serendipitous observation by Gubner that the folic acid aminopterin improved the lesions of psoriasis during a trial to assess its anti-inflammatory effects in patients with psoriatic arthritis (2). These observations were transferred into clinical trials utilizing a daily dosage schedule of aminopterin (3). In the late 1950s methotrexate (MTX) replaced aminopterin. During the next two decades alternative dosage schedules were developed based on cell cycle information and cancer chemotherapy concepts. Until the development of psoralen/ultraviolet A treatment (PUVA) in 1975, UVB phototherapy and methotrexate were the only effective treatments for moderate-to-severe psoriasis. Methotrexate was approved for psoriasis by the Food and Drug Administration (FDA) without the usual, at least by current standards, large double-blind clinical trials. Methotrexate usage for psoriasis appeared to be grandfathered in, in part related to guidelines for MTX therapy for psoriasis referred to below. Thus there are no large clinical trials to quantitate the efficacy and safety of the drug for the treatment of psoriasis. Its usefulness is based on many years of clinical experience and numerous clinical retrospective studies with more emphasis on side effects than efficacy (4–7). In recent years it has been estimated that 25,000–30,000 patients were receiving methotrexate therapy in the United States, although current data are not available.

In 1988, MTX was approved for the treatment of rheumatoid arthritis (RA) and has become one of the main choices of therapy for RA in the past decade. With a much larger population of patients with this chronic benign disease being treated with MTX in dosages similar to those used for psoriasis, much more data have become available on the relative safety of this drug. Guidelines developed by rheumatology organizations are similar to dermatology guidelines but have differed by not requiring liver biopsies prior to MTX therapy. This reflects a lack of significant liver toxicity found in RA in comparison to that discussed in detail in the dermatology literature (8).

II. PATIENT SELECTION

Patients with psoriasis involving greater than 15–20% body surface area were usually considered to have moderate-to-severe disease. Further thinking and experience have suggested that many patients may have lesions of a lesser amount but in critical areas of the body (i.e., face, hands, areas of occupational or social importance) that raise the importance of this type of disease to a moderate–severe degree rather than a limited or smaller percentage amount. Examples of patients who may warrant MTX treatment with lesser amounts of skin disease might include salespeople, actors, or young socially involved men and women. It is estimated that this population of patients makes up approximately 20% of psoriatic patients in the United States (9). Thus in recent years the criteria for using therapies like methotrexate have changed from a more rigid percentage body involvement to that of the location of the disease and its impact on quality of life (10). This extent/location of disease warrants more aggressive forms of therapy when topical therapy is not effective. Thus we consider treating these patients with a choice of several modalities including phototherapy, PUVA, retinoids, methotrexate, or possibly cyclosporine, based in part on quality of life concerns. The information in this paper is based in part on the concepts that have evolved in a series of guidelines on the use of methotrexate for psoriasis from 1972 to 1998 (11–14).

III. INDICATIONS

Methotrexate is indicated for the treatment of patients with moderate to severe psoriasis unresponsive to topical therapy. Administration of MTX for psoriasis must be an individualized decision, as we have learned from many years of experience. It is used in patients with moderate to extensive

Table 1 Indications for the Use of Methotrexate in Psoriasis

Erythrodermic psoriasis
Pustular psoriasis (acute and localized)
Psoriatic arthritis
Extensive psoriasis unresponsive to less toxic therapies
Psoriasis that significantly affects a patient's economic or psychological well-being
Lack of response to phototherapy, PUVA, or retinoids

plaque lesions as well as other variants of psoriasis including erythrodermic psoriasis, acute pustular psoriasis (von Zumbusch), psoriatic arthritis, and localized pustular psoriasis (Table 1). Its use is justified in certain other patients when the location or severity of the psoriasis jeopardizes the patient's economic, psychosocial, or physical well-being. While MTX is an extremely effective drug for psoriasis, it is the author's belief that phototherapy modalities (UVB or PUVA) should generally be the initial form of therapy for most patients prior to using MTX. Available information suggests that most patients are treated with UVB or PUVA because these are effective treatment modalities with less serious potential long-term toxicities. If light therapy is ineffective and/or has been used so extensively that the risks of side effects are increasing, then rotating therapy to MTX would be appropriate (3). In many patients, however, MTX may be the initial choice of therapy if the patient is light-sensitive, is unable to take light treatment for physical reasons, or is unable to travel or lives too far away from a physician's office to undergo light therapy. For patients being cared for by a physician other than a dermatologist, dermatological consultation is recommended for considering the use of MTX.

IV. CONTRAINDICATIONS

Relative contraindications to therapy with MTX are, in general, disease processes that may enhance the toxicity of MTX, particularly liver and kidney diseases (Table 2). Absolute contraindications include women who are pregnant or nursing and patients of either gender, who are attempting to conceive. An appropriate history and physical examination should allow the physician to detect any contraindications to therapy with MTX. In selected patients, circumstances may arise in which relative contraindications may be waived when it is considered that benefits of therapy may outweigh potential risks.

Table 2 Relative Contraindications to Methotrexate Therapy

Liver disease
Significantly abnormal liver function tests
Cirrhosis or severe degrees of histologically proven fibrosis
Recent or active hepatitis
Excessive alcohol consumption
Kidney disease
Significantly decreased renal function (elevated creatinine and BUN; decreased creatinine clearance). Decreased renal function is frequently seen in elderly individuals and compensation can be made using lower than standard dosages of MTX.
Hematopoietic abnormalities
Severe leukopenia, anemia, or thrombocytopenia
Active severe infectious diseases
HIV, tuberculosis, etc.
Concurrent use of trimethoprim–sulfamethoxazole antibiotics (absolute)
Active peptic ulcer
Fertility considerations
Pregnancy (absolute)
Male or female patients attempting to conceive (absolute)
Unreliable patient

V. MECHANISM OF ACTION

Methotrexate blocks the synthesis of DNA by inhibiting dihydrofolic acid reductase, preventing the donation of methyl groups during synthesis of purine and pyrimidine nucleotides and, particularly, thymidylate (15). Thymidylate, one of the four DNA precursors, is necessary for DNA synthesis and the cell division that follows within hours.

Methotrexate may exert a therapeutic effect in psoriasis by directly interfering with epidermal cell proliferation. Psoriatic skin contains twice as many proliferating cells and eight times as many cells in the *S* (synthesis) phase of cell division as normal skin. In addition, the proliferating cells have a cell cycle of 36 h, which is eight times faster than normal (16). Previous studies of MTX's mechanism of action indicate that after systemic or intralesional administration MTX inhibits DNA synthesis in psoriatic epidermal cells, followed within several hours by the cessation of mitoses (17). These data for many years suggested a direct effect of MTX on decreasing the rapidly proliferating psoriatic keratinocyte population.

With the discovery that cyclosporine, an immunologically active drug, was effective for the treatment of psoriasis (another serendipitous observation in psoriasis therapy), much evidence has accumulated for an immunological

basis for psoriasis. Based on that information, research in our laboratory has suggested an effect of MTX on both lymphocytes and keratinocytes. In vitro studies have revealed that keratinocytes are relatively resistant to MTX in culture at clinical concentrations reached in low-dosage MTX therapy (18). In comparison, activated lymphocytes are sensitive to MTX at concentration about 100-fold lower than those needed to affect keratinocytes. One may infer from these and other data that MTX may have a major immunosuppressing effect on psoriatic disease at levels that do not appear to produce a clinically immunosuppressive side effect profile in patients, based on the long experience with this drug.

VI. THERAPEUTIC EVALUATION/CONTRAINDICATIONS

The pretherapy evaluation starts with an appropriate history and physical examination that concentrates mainly on the patient's renal and liver function (Table 3). Methotrexate is excreted mainly by the kidneys; therefore, any underlying renal disease must be detected. This is especially important in older individuals who are more likely to have decreased renal excretory function, which could cause both higher and extended MTX blood levels resulting in increased toxicity at otherwise usual doses. A routine urinalysis, serum creatinine, and blood urea nitrogen (BUN) analysis are the standard tests for renal function. A more sensitive test of kidney excretion is the creatinine clearance over 24 h and may be especially important for older individuals whose renal function may be diminished significantly. Creatinine clearance less than 50 ml/min is indicative of at least moderate renal failure and may be a relative contraindication to therapy. In patients with decreased 24 h urine creatinine clearance rates, lower dosages of MTX should be used at

Table 3 Pretherapy Evaluation

History (including risk factors for liver and kidney disease) and physical examination
Liver function tests (SGOT, SGPT,[a] alkaline phosphatase)
Renal function tests (serum creatinine, BUN, 24 h urine or creatinine clearance)
CBC with platelet count
Chest x-ray (optional based on history)
Liver biopsy (before or shortly after initiation of therapy in patients with risk factors for liver disease)
HIV antibody determinations for patients at risk for acquired immunodeficieny syndrome

[a] Now AST and ALT, respectively.

the beginning of therapy and may be adequate. In these patients more vigilant monitoring for methotrexate toxicity will be necessary.

VII. PRETREATMENT OR EARLY LIVER BIOPSY

In all the years of MTX use for psoriasis, the issue of liver toxicity risk has received the most discussion and concern. In the 1998 guidelines for MTX (14), this issue was discussed in detail and is summarized below. While a history and physical examination and liver function tests may identify some patients with pre-existing risk factors for liver disease, the liver biopsy still remains the most reliable test for liver damage. In most studies in which patients *had no significant risk factors*, liver biopsies have found very few patients with fibrosis or cirrhosis.

Controversy exists as to the need for an early liver biopsy, but the current consensus (14) appears that it is not generally needed in patients *without* risk factors of liver disease.

The risk factors of concern are the following:

History of current excessive alcohol consumption (MTX toxicity is associated with a history of total lifetime alcohol intake before MTX therapy. The exact amount of alcohol that confers risk is unknown and differs among persons.)
Persistent abnormal liver chemistry studies
History of liver disease including chronic hepatitis B or C
Family history of inheritable liver disease
Diabetes mellitus, obesity (probably of secondary importance)
History of significant exposure to hepatotoxic drugs or chemicals

A. No Risk Factors

If there is no evidence of significant risk factors, it is rare for life-threatening liver disease to occur within the first 1–1.5 g of cumulative MTX. On this basis the guidelines have been **revised** to recommend *not obtaining* a liver biopsy until a patient has received this amount of MTX or is developing risk factors such as persistent elevated results of liver function tests (14).

B. Patients with Risk Factors

If risk factors are found prior to initiating MTX, it is advisable that a liver biopsy be done, when feasible, at or near the beginning of MTX treatment. Since it is possible that some patients will not continue taking MTX after the first few months because of adverse effects, lack of effectiveness, or other

reasons, it is reasonable to postpone the biopsy until after this initial period. If the drug is effective and its use will continue for long-term therapy, it provides more incentive for a patient to accept the decision for a liver biopsy. There is no information available that short-term use of MTX will cause clinically significant liver disease. Clinical experience has also suggested that a liver biopsy may not be warranted in the following situations:

Elderly patients
During acute illness and/or severe exacerbation of psoriasis
In the presence of medical contraindications for a biopsy (e.g., cardiac instability, bleeding problems, etc.)
In patients with limited life expectancy

VIII. DOSAGE/ADMINISTRATION

Dosage regimens for MTX in the treatment of psoriasis have gone through several stages of evolution. Initially, an empirically derived schedule was based on daily small dosages of aminopterin and, later, MTX (19). This daily schedule was subsequently found to produce greater liver toxicity. Using experience from oncological therapy schedules with MTX, weekly schedules of intramuscular MTX were found to be effective in the treatment of psoriasis (20). This regimen was then adapted for use as a single weekly oral dose (12).

The triple-dose schedule (MTX at 12 h intervals for three doses each week) was proposed in 1971 to provide a therapeutic level of MTX for approximately 36 h which is the duration of the psoriatic cell cycle (21).

Today, MTX is administered for psoriasis principally by two schedules: the triple-dose regimen or a single weekly dose, either orally or intramuscularly. A majority of surveyed dermatologists use the triple-dose schedule (Table 4) (9). The triple-dose regimen is initiated with a test dose of 5 mg (2.5

Table 4 Dermatologists' Preferences for Methotrexate Dosing Schedules: Results of a 1984 Survey

Dosing schedule	Percentage
Weekly divided oral doses	74
Weekly single oral dose	16
Weekly intramuscular dose	3
Other dosing schedule	7

Source: Data from Ref. 9.

mg every 24 h for two doses) (Table 5). The concept of a small test dose was initiated when weekly doses were first used to avoid possible serious side effects if a patient had a hidden or undiscovered medical or allergic sensitivity to MTX. Early use of MTX was given with much larger doses than are currently used and severe side effects were being found. A complete blood count (CBC) is repeated after 7 days. If these results are normal and there is no unusual sensitivity to the test dose, the first triple dose is started at a dosage of one 2.5 mg tablet every 12 h for three doses (1/1/1), totaling 7.5 mg for the week. One week later, if there are no adverse effects, the dosage is increased to 4 tablets (2/1/1), for a total of 10 mg. Over the following weeks the dosage is increased by one 2.5 mg tablet per week every 2–3 weeks, depending on the effectiveness of the drug and the patient's ability to tolerate a given dosage regimen. In the typical 70 kg patient, the dosage is usually plateaued at 2/2/2 (15 mg/wk), although larger patients or those with more resistant psoriasis may require a higher dosage. This schedule is continued until the patient's psoriasis is under adequate control. Most patients begin to see improvement in 6–8 weeks.

To minimize the risk of side effects (in particular, severe liver toxicity), MTX dosages should be kept as low as possible to achieve and maintain what is termed adequate control of the disease. Total clearing of lesions is *not* the intended goal of therapy since that may require continuing increases in weekly dosages approaching toxicity. At the point of optimal response, the dosage is titrated down every month by 1 tablet per week until the lowest effective maintenance dosage, perhaps 1–3 tablets per week, is achieved. When possible, attempts should be made to discontinue therapy for several months at a time, the summer often being a good time. This limits the cumulative dosage, extends the time interval between potential liver biopsies, and permits longer-term use of MTX. New MTX patients are seen weekly for 2–3 weeks, then biweekly, and finally monthly as they develop a response pattern (Table 5). Clinical responses are titrated by 1 tablet up or down at monthly visits, reflecting very sensitive responses to changes of only one tablet.

Table 5 Drug Dosage Schedules

Divided oral dose schedule
2.5 to 5.0 mg at 12-hr intervals for 3 doses each week
Gradually increase by 2.5mg/wk every 2–4 weeks with appropriate monitoring of laboratory tests
Total dosage generally not to exceed 6–9 tablets per week (15–22.5 mg)
Weekly single oral dosage ranges from 7.5 to 30 mg/wk
If single weekly doses are used by intramuscular or IV administration, the dosages can go as high as 50 mg/wk . Intravenous drips of MTX should not be used. As the dosages are increased, the CBC should be monitored more frequently.

The dosage schedule using single weekly oral doses is initiated with a 5.0–7.5 mg test dosage and is subsequently increased by 2.5 mg per week. The total weekly maintenance dosage is usually between 7.5 and 25.0 mg. However, dosages as high as 37.5 mg per week may be required. Occasionally MTX is administered in weekly intramuscular (IM) doses, usually for unreliable patients. The IM route may also be used when the effectiveness of oral MTX has diminished, or when gastrointestinal (GI) side effects are limiting treatment. Doses are somewhat higher than weekly oral doses because the half-life of MTX in plasma is shorter when given via the IM route.

Alternative methods of administration have been explored by rheumatologists, which include the use of subcutaneous injections of MTX, which can be self-administered by patients, and oral usage of injectable MTX preparations (22). If oral administration of a MTX solution is used, the parenteral solution is usually in 50 mg/2 ml aqueous vial. A syringe would be used to withdraw 0.1 ml or more of this solution, which is equal to a 2.5 mg tablet, and put into a small amount of water or other drink. According to available information, administration by tablet or the equivalent carefully measured solution has equal effectiveness. Regardless of the dosage schedule or route of administration, the same principles previously described for adjusting dosages for individual patients to minimize the cumulative MTX dosage should be followed (Table 6).

Table 6 Instructions to Patients Taking Methotrexate for Psoriasis

Great care is needed when taking methotrexate
Methotrexate is usually taken only three times per week (*not* daily). Each pill is taken 12 hours apart. Sometimes methotrexate is given as single weekly doses orally or by injection.
Take only the prescribed, correct dose of methotrexate at the *same time and day* each week.
Do *not begin or change* the dosage of *any medication* (including nonprescription medications) unless your physician has approved it.
Avoid alcoholic beverages.
If you have side effects or any symptoms of dehydration, notify your physician before the next dose.
If you develop cough, fever, and shortness of breath or have any problems with sore throat; infections, including skin infections; or skin or mouth ulcers, STOP METHOTREXATE AND CALL YOUR PHYSICIAN.
See your physician regularly, usually every 4 weeks (more frequently at the beginning of therapy).
Do not miss doctor's appointments or blood tests.
Notify your physician at once if an accidental overdose has occurred.

Table 7 Duration of Methotrexate Treatments to Achieve a Cumulative Dose of 1.5 g

Weekly dosage (mg)	Months to 1.5 g
7.5	50
15.0	25
22.5	17

How long can or should a patient be maintained on MTX? As clearing is obtained, weaning of dosages is started, with the goal of achieving the *lowest* possible long-range dosing schedule. If a patient can be maintained with as little as 2–3 tablets per week, the calculated cumulative dosage would be 260–400 mg/year. Using a 1.0–1.5 g cumulative dose as the range within which liver changes may develop (Table 7), a patient could receive low-dosage MTX *continuously* for over 3 years. If rest periods off MTX consisting of several months each year were successful, even longer durations of MTX could be utilized before reaching this cumulative dose range. However, if a patient were to require higher maintenance dosages, such as 15 mg/week (2/2/2), then a cumulative dosage warranting concern about liver toxicity could be reached in 1.5–2.0 years. At that time we would recommend stopping MTX and rotating the patient to another form of therapy. At some future time the patient could restart therapy with MTX, it is hoped, with some reversal of any cumulative liver toxicity (23–25). If MTX needs to be continued, a liver biopsy would have to be considered.

IX. MONITORING THERAPY

Patients receiving MTX are monitored for the drug's effect on hematopoietic and liver function as they are reflected in laboratory tests (Table 8). During the first several weeks of initial therapy a CBC is obtained every week initially, then biweekly, and thereafter at the time of each visit, usually monthly. The CBC should be obtained at least 7 days after the last dose since MTX causes a maximal depression in the leukocyte and platelet counts 7–10 days after drug administration. Dosage reduction or a brief interruption of therapy is warranted when the counts drop below the minimum normal levels. The appearance of oral mucosal ulcerations, previously used to clinically monitor MTX toxicity, is now infrequently observed due to the use of lower-dosage regimens and careful monitoring of hematopoietic function.

Table 8 Monitoring Therapy

CBC and platelet count (every 1–4 weeks, drawn at least 1 week after the last dose).
Serum chemistries, including routine liver and renal function tests (every 3–4 months, at least 1 week after the last dose).
Chest x-ray (annual) if there are pulmonary symptoms.
Liver biopsy:
In patients without risk factors:
First biopsy at 1.0–1.5 g cumulative MTX
In patients with risk factors
First biopsy after 2–4 months of therapy
Subsequent biopsies after each 1.0 g cumulative dose

It is now recommended to obtain liver function tests (LFTs) every 2–3 months during therapy (see below). Since MTX can cause a transient and clinically unimportant elevation in liver enzymes 1–3 days after drug administration, these tests should also be obtained at least 7 days after the last dose. If liver enzymes are significantly elevated at that time, MTX therapy should be interrupted for 1–2 weeks and the tests repeated before restarting therapy. In most cases, the LFTs will return to normal. However, if significant elevations persist, a liver biopsy should be considered before continuing MTX therapy.

In the absence of abnormal liver enzymes, the 1998 Guidelines recommend liver biopsy after each cumulative MTX dose of 1.5 g (14). In patients who have one or more risk factors for cirrhosis, signs of liver disease, or significant liver enzyme abnormalities a liver biopsy should be considered after each 1.0 g MTX or more frequently. It is suggested that this procedure be performed at least 2 weeks after the last dose of MTX to minimize any acute histological liver changes. Liver biopsy may not be in the best interest of older patients or patients with acute diseases or other contraindications to liver biopsy. The risk of liver biopsy versus the risk of continued MTX therapy must be carefully assessed in these patients. There are also occasional reluctant patients who refuse to allow a liver biopsy. In the absence of evidence of liver changes, it then becomes the option of the physician to continue using MTX or consider the availability of other therapies, using benefit/risk considerations. It is recommended that the patient's chart reflect the discussions on this point and the patient's decision not to undergo liver biopsy. We would suggest that the patient sign such a notation in the chart.

Additional monitoring of patients on long-term MTX therapy includes hemoglobin/hematocrit and renal function tests every 3–4 months. A chest x-ray should be performed in the event of acute or chronic pulmonary changes

that might suggest a so-called MTX pneumonitis, seen rarely in psoriatics but more frequently in rheumatoid arthritis patients taking MTX.

X. SIDE EFFECTS

Short-term side effects of MTX such as nausea, anorexia, and fatigue are dose-related and rapidly reversible with a decrease in dosage or brief interruption in therapy. As an alternative, rotating between triple-dose and weekly oral or IM dosage may alleviate severe symptoms that may otherwise cause a patient to discontinue therapy with MTX. However, utilizing the IM route does not necessarily reduce GI side effects. In patients receiving higher dosages of MTX, nausea may be psychologically triggered in anticipation of the next dose. Food and occasional antiemetic drugs may be necessary to permit drug administration. Re-evaluation of renal function is prudent, especially in the older patient, or in a patient who suddenly develops symptoms after adequately tolerating a specific dosage regimen. A decline in renal function can result in persistent blood levels of MTX, leading to greater toxicity at a given dosage. A review of the patient's concurrent medications might likewise reveal a potential drug interaction causing increased MTX toxicity (see discussion of Drug Interactions below).

A. Folic and Folinic Acid Supplements

Several reports have suggested that concomitant administration of folic acid (1–5 mg/day) can reduce side effects such as nausea and megaloblastic anemia without affecting the effects of MTX. Folinic acid, the direct antidote for MTX, if given on days when MTX is not administered (the other 5 days of the week), will also reduce side effects such as nausea (26, 27).

B. Liver Toxicity

The major limitation in the use of MTX is the potential for severe drug-induced liver fibrosis and cirrhosis. Even with lower dosage regimens, long-term use of MTX can cause life-threatening cirrhosis (28). Data from several studies suggest that MTX's effects on the liver are mainly related to the cumulative dose. The incidence of cirrhosis is 3% in the range of 1.5–2.0 g cumulative dose, and as high as 20–26% with a cumulative dose of 4.0 g (12). The incidence of MTX-induced cirrhosis in the United States appears to be lower than in Scandinavian populations, although the reasons for this are unclear (29, 30). As mentioned previously, potential candidates for MTX therapy must be questioned about underlying risk factors for liver disease

that may be present prior to therapy. The prevalence of fibrosis and cirrhosis in patients with psoriasis could be the same as that for the population at large, as estimated from autopsies in the general public. A history of heavy alcohol consumption or intravenous drug use, or the presence of diabetes mellitus, obesity, suboptimal renal function, or pre-existing liver pathology, is a risk factor for the development of severe liver toxicity (31). It is recommended that any patient with moderate-to-severe psoriasis avoid or at least minimize alcohol consumption prophylactically to maintain the option for MTX treatment use in the future.

Fibrosis or cirrhosis due to methotrexate can be detected and may improve once therapy with MTX is discontinued, as demonstrated by repeat liver biopsies (24). Some researchers believe that MTX-related cirrhosis is not aggressive, as evidenced by little or no progression of liver histopathological findings in patients with documented cirrhosis who continued taking MTX (23). A few of these patients with cirrhosis even showed improvement. However, most would agree that if the liver biopsy shows grade III B or grade IV (moderate-to-severe fibrosis or cirrhosis), MTX should be discontinued (Table 9). Severe liver disease, as well as a few deaths, have occurred in patients receiving long-term methotrexate. To the author's knowledge, most have occurred in situations of significant deviations from appropriate patient/doctor safeguards (28).

Liver toxicity can often be detected by monitoring liver enzymes as recommended. Unfortunately, these tests are not always reliable; in fact, severe liver disease, including cirrhosis, can be present in the absence of elevated liver enzymes (32). As a result, other tests of liver function have been investigated as an indicator of liver disease that might obviate the need for liver biopsies. Levels of serum amino terminal propeptide of type III procollagen (PIIINP) have been correlated with liver histological findings

Table 9 Classification of Liver Biopsy Findings

Grade I	Normal; mild fatty infiltration/portal inflammation
Grade II	Moderate-to-severe fatty infiltration/portal tract inflammation
Grade III	A: Mild fibrosis
	B: Moderate-to-severe fibrosis
Grade IV	Cirrhosis
Clinical Interpretation of Liver Biopsy Results	
Grade I or II	Continue MTX therapy
Grade III A	May continue MTX therapy. Repeat biopsy after 6 months of continuous MTX therapy.
Grade III B	Discontinue MTX therapy.
Grade IV	Discontinue MTX therapy.

(33). In psoriatic patients without arthritis, high levels of PIIINP appear to be an indicator of liver fibrosis. Patients with coexistent arthritis often have high levels of PIIINP in the absence of liver fibrosis. In addition, the test has a high rate of false negatives: 25–33% of patients in the study had fibrosis, albeit mild, in the presence of normal PIIINP levels. On a more practical note, this test is not widely available in the United States.

Attempts have been made to correlate imaging modalities with liver pathology. Magnetic resonance imaging and static radionuclide scanning have been unreliable (34, 35). Comparison studies of liver ultrasound and liver biopsy have demonstrated varied results, with a sensitivity in detecting liver fibrosis or cirrhosis as low as 11% and as high as 100% (36, 37). In a recent analysis, one investigator concluded that given the risks of liver biopsy, ultrasound, if performed by an experienced specialist, is a justified screening method and urged re-evaluation of the guidelines for routine liver biopsy (38). Imaging procedures have still not replaced the liver biopsy as a reliable indicator of fibrosis or cirrhosis.

To date, liver biopsy remains the gold standard for evaluating MTX-induced liver toxicity. Unfortunately, this procedure is not without risk and carries a general complication rate of 2.2% and a mortality rate of 9/100,000 (39). The risks of liver biopsies have tended to be lower in patients with psoriasis than with other diseases. Most adverse events occur in patients with internal hepatic problems related to other diseases. Notwithstanding, most would agree that, although uncommon, the risk of severe and life-threatening liver damage due to MTX outweighs the risk of liver biopsy. A qualified gastroenterologist who performs frequent liver biopsies should be consulted for appropriate patients. In addition, the pathologist should be familiar with the liver pathology classifications in MTX-treated patients as described in the 1998 Guidelines to provide the best clinicopathological correlations (14).

C. Hematological Complications

Methotrexate can suppress bone marrow function when high or incorrect dosages are used. Dosage errors by medical staff or patients have been reported. Specific directions, orders, and prescriptions should be legibly written and discussed with the patient. Periodic monitoring of the CBC should alert the physician to any significant changes. In rare cases, MTX can cause reversible agranulocytosis or pancytopenia at low dosages (40).

D. Methotrexate Overdosage

Causes of MTX overdosage include patient/physician/nurse/pharmacist errors, impaired renal function, or concomitant administration of drugs such

as trimethoprin or trimethoprim–sulfamethoxazole (Bactrim, Septra, and generics). If MTX overdosage is suspected, leukovorin calcium (citrovorum factor or folinic acid) should be administered immediately to prevent hematological toxic effects (Table 10). In overdoses of MTX used for cancer chemotherapy, the success of antidote administration greatly decreases if the last dose of MTX was received more than 24–48 h prior to rescue (41).

When MTX toxicity develops secondary to decreased renal function, leukovorin administration may be prolonged. If serum creatinine concentration has increased to $>50\%$ of baseline, leukovorin should be given intravenously at 100 mg/m^2 every 3 h until MTX concentration is less than 0.01 μmol/L. Alkalinization of the urine by means of sodium bicarbonate and fluid administration may be necessary to prevent precipitation of MTX in the renal tubules. All cases of suspected overdosage require vigilant monitoring for development of hematological or other toxic effects. Laboratory tests for MX blood levels should be obtained for guidance but these tests may not be readily available.

E. Drug Interactions

Reports of interactions between MTX and other drugs have been observed but, fortunately, are not common. Mechanisms of some drug interactions include interference with protein binding, renal tubular secretion, or intracellular transport of methotrexate (42). Other drugs may affect the efficacy or increase the toxicity of methotrexate. Barbiturates, phenylbutazone, phenytoin, probenecid, salicylates, and sulfonamides can displace MTX from serum albumin, causing elevated levels of free MTX and enhancing potential toxicity. Nonsteroidal anti-inflammatory agents, phenylbutazone, probenecid, salicylates, and sulfonamides can compete with MTX for active renal tubular secretion, thus increasing the half-life of MTX. Dipyridamole can interfere with intracellular transport of MTX and also prolong the effects of

Table 10 Leukovorin Rescue After Methotrexate Overdose

Serum MTX Level (μmol/L)	Leukovorin Dose (mg)
5×10^{-7}	20[a]
1×10^{-6}	100
2×10^{-6}	200
$> 2 \times 10^{-6}$	Proportionately increased

[a] The initial 20 mg dose of leukovorin is given parenterally, with subsequent doses given every 6 h either orally or parenterally.

MTX. **The combination of MTX and trimethoprim can cause severe suppression of bone marrow function and is best avoided** (43).

Methotrexate can be ineffective if given concomitantly with folic acid or vitamin preparations that contain folic acid. Folic acid, or more specifically folinic acid, may bypass MTX inhibition of the dihydrofolic acid pathway. In a patient not responding to MTX, concurrent medications should be reviewed for any vitamin preparations that may contain folic acid.

Methotrexate in combination with other systemic therapies for psoriasis should be used with caution. Historically, many of the early cases of severe side effects and deaths occurred with the concomitant use of systemic corticosteroids and MTX. Many of these patients had severe disease or pustular psoriasis. Methotrexate-induced leukopenia together with steroid suppression of immune function led to overwhelming infections. It is thus well appreciated that the combination of MTX and systemic corticosteroids should be avoided as much as possible.

In one report, 2 of 10 patients receiving combined therapy with MTX and etretinate developed life-threatening drug-induced hepatitis (23). Cyclosporine and MTX, through their respective renal and liver toxicities and metabolic pathways (liver and renal, respectively), can cause elevated levels of both drugs, thereby increasing the risk of severe side effects from both drugs (44). However, rheumatologists have used this combination successfully to treat rheumatoid arthritis (45).

F. Fertility

Methotrexate is a known abortifacient and possible teratogen even at the low dosages commonly used in psoriasis. A report of 10 pregnancies occurring in 8 women receiving MTX for rheumatic disease included 5 normal infants delivered at full-term, 3 spontaneous abortions, and 2 elective abortions (46). The authors conclude that MTX may have strong abortifacient properties even at low weekly dosages. However, their results do not demonstrate an association between low-dosage weekly MTX and teratogenicity. Another report of normal offspring born to women who had previously received higher dosages of MTX for choriocarcinoma does not show any increase in congenital malformations (47). One patient received high-dosage MTX for choriocarcinoma during pregnancy starting at 27 weeks and went on to deliver a normal infant (48). Nonetheless, female patients should take all precautions to avoid pregnancy while taking MTX and for at least 1 month (or, more conservatively, 3–4 months) after discontinuing MTX.

Oligospermia (49) and sperm abnormalities have been reported in men receiving MTX, yet we are aware of five male patients receiving MTX who

fathered normal offspring. Nonetheless, it is recommended that male patients taking MTX avoid fathering offspring during therapy and for 3–4 months after discontinuing therapy.

G. Pulmonary Complications

Pneumonitis due to methotrexate has been reported in at least 20 patients with rheumatoid arthritis (50). One patient, a 39-year-old woman, also had psoriasis and had been treated with MTX 15 mg/wk on a triple-dosage regimen for 5 months prior to developing symptoms of nonproductive cough and progressive dyspnea (51). The occurrence of MTX pneumonitis in psoriatics appears rarely in contrast to rheumatoid arthritis patients receiving MTX. Nonetheless, unexplained pulmonary symptoms in MTX-treated patient should be evaluated for MTX pneumonitis and the drug discontinued, at least temporarily.

H. Infectious Complications

A review of case reports of infectious complications of low-dosage MTX therapy includes varicella zoster, *Pneumocystis carinii* pneumonia, nocardiosis, and cryptococcosis (52). The patients described were all receiving low-dosage MTX for arthritic conditions. Three cases of disseminated histoplasmosis in patients receiving low-dosage MTX for psoriasis were also reported. Two had received a total of 7 and 8 g of MTX, respectively, and the third had received only 160 mg. Opportunistic infections should be considered in patients receiving MTX therapy who have unexplained prolonged fever. In the early years of MTX use some patients were treated with combinations of MTX and corticosteroids orally, which led to frequent infections and several deaths.

XI. COST

In the decision process of therapy today, one must consider the cost/benefit ratio as well as the benefit/risk ratios of different therapies. The limitations of health care resources have restricted access to some forms of therapy for many patients. For patients with moderate to severe psoriasis, the treatments available include phototherapy, PUVA, MTX, retinoids, and cyclosporine. In the near future it is likely that several biologicals will be available that will be significantly more expensive than the treatments listed above. Recently we quantitated the costs of several treatments (53). UVB phototherapy and MTX were significantly lower in cost than the other

treatments. In 1997 the average annual cost for UVB was approximately $1850 and MTX costs ranged from $1500 to $2150. For comparison, PUVA and etretinate were approximately $3000 and cyclosporine was $4000. These estimates did not include physicians fees.

Combination therapies tend to shorten the duration of therapies, (e.g., PUVA plus retinoid or MTX and cyclosporine). Ellis et al. created a simulation of treatment over 10 years of MTX alone compared with a rotational scheduled use of MTX and cyclosporine (54). For MTX alone, the cost was $33,000 ($3,300/year), which is higher than estimated above (53). When using MTX rotated with cyclosporine over 10 years, the cost was approximately $38,000. For the additional amount the rotated MTX/cyclosporine produced 4 years of clearing while MTX alone produced only 2 years of clearing. Assuming the efficacy and comparative safety of these two schedules over 10 years, one would have to decide whether the additional 2 years of clearing are worth an additional $5,000. In effect, this is another benefit, albeit economic, of the rotational approach to psoriasis therapy of which the major benefit is safety for long-term chronic therapy of psoriasis (25).

XII. CONCLUSION

We have been fortunate to have had access to MTX for the past approximate half a century. It is amazing that no other folic acid antagonists (after aminopterin) have become available to improve on the effectiveness and safety of MTX for the treatment of psoriasis as well as for cancer chemotherapy. We have learned that the drug is quite effective: producing at least 70% good improvement in at least 70% of patients being treated. Psoriasis has not developed resistance in most patients to intermittent or continued therapy, in contrast to what happens in some forms of leukemia.

Adverse events resulting from the short-term or continuing use of MTX have been relatively limited, with the exception of the concern for hepatic toxicity. In the early years of MTX use more problems were found when there was inadequate information on how to use the drug safely. In recent years, the prior problems of liver damage have been minimized because we have selected patients more carefully for this drug; tested patients more frequently for liver disease; and perhaps most importantly, treated psoriasis by rotating the additional new therapies so that MTX is not used as frequently or for so long at any time (55). In our experience the number of episodes of severe liver disease in recent years has been rare. This does not mean that MTX cannot cause problems. However from knowledge acquired from other physicians and malpractice litigation, these difficulties appear to arise in situations where

there is misuse or abuse by patients (28), or inappropriate use. Given this long and fortuitous experience, it remains an important drug for the therapy of moderate to severe psoriasis.

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