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MEDICAL GRAND ROUNDS

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INTRODUCTION

The outer portion of the skin acts as a physiologic barrier which has been placed between man and his environment. That portion of the skin which comprises a barrier to molecular exchange resides within the outer portion of the epidermis, or stratum corneum. This structure which measures 10 microns in thickness, is made up of dead, flattened corneocytes which are locked together into a laminated membrane. Barrier properties of the stratum corneum are similar to that of 10 micron polyeythlene film, and an important aspect of stratum corneum function is that individual cells are continuously replaced, since a lamellar exfoliation of cells occurs at the outer surface. This loss is replaced by obligate proliferation and maturation of cells within the viable portion of the epidermis beneath.

To illuminate epidermal structure and function, one may develop an extended analogy with erythrocyte structure and function. This analogy begins with the definition. The erythron is the combined mass of immature and mature erythrocytes. Eighteen months ago I introduced a new word, the keraton, which was defined as the combined mass of mature and immature keratinocytes. The analogy extends farther. Both cell lines are terminal, in that the functional cell is incapable of cell division. Both cells begin in a proliferative pool, mature while accumulating a specialized protein and eventually lose their nuclei. As functional cells both survive for a finite period of time, 120 days for erythrocytes and 14 days for corneocytes, at which point they are destroyed or lost. An important aspect of this analogy is that it allows one to visualize a less familiar disorder by comparing it to a better known one.

Psoriasis is an idiopathic hyperproliferative disorder of the epidermis which is characterized by the excessive release of corneocytes to the stratum corneum. Nucleated cells are seen frequently, indicating a premature release from the maturation compartment. Both the proliferative and maturation compartments are greatly enlarged, increasing many times in size. Each corneocyte, however, may function normally, but as an aggregate, stratum corneum barrier function is faulty. Psoriasis treatment consists of the removal of excess corneocytes with keratolytic agents and the inhibition of cell division with drugs and ultraviolet light.

Polythemia vera has been defined as an idiopathic hyperproliferative disorder of the erythron. It results in a sustained elevation of the hematocrit, hemoglobin and red cell count. The total red cell mass may range up to three times normal. Reticulocytosis is present and occasionally nucleated erythrocytes may be seen, indicating a premature release from the bone marrow. The bone marrow itself is vastly hyperproliferative, replacing much of the yellow fatty marrow. Erythrocytes which are produced function relatively normally, but as an aggregate they may cause vascular insufficiency. Treatment consists of removal of erythrocytes by venesection and inhibition of cell division with chemotherapy. Although this extended analogy breaks down when carried further, it does provide an interesting perspective for visualizing both diseases.

Several aspects of psoriasis must be considered in 1979: a) Psoriasis is an important disorder for both clinical and scientific reasons.

b) Recent observations have greatly expanded the understandng of its pathogenesis. c) New methods of treatment are in continuous development. and d) Psoriasis accounts for 5% of office visits to dermatologists(1).

CLINICAL PRESENTATION

The primary clinical lesion of psoriasis is a small, red papule with superimposed scale. It is said to be asymptomatic but this is frequently not the case. Such papules have a predilection for change, particularly expansion. Individual papules may expand or coalesce into large red plaques, also covered or superimposed with scale. The scattering of visible light which strikes the surface gives it a silvery appearance. An important clinical features is that when such areas are scraped, pinpoint bleeding occurs (Auspitz phenomenon). Furthermore, the erythema of psoriasis may be compressed out (diascopy). These two features indicate that the erythema of psoriasis results from vasodilitation and that these vessels are close to the skin surface. As is seen in the histopathologic preparations, this is indeed the case. When psoriasis involutes spontaneous it frequently clears at the center of a plaque, leaving an annular ring.

In a series of papers, Farber and his associates have done us great service by confirming many commonly held assumptions about the clinical setting of psoriasis. With an extensive questionnaire study Farber and Nall identified characteristic historical factors in 5600 patients with psoriasis(1a). The median age of onset for psoriasis was 24 years in

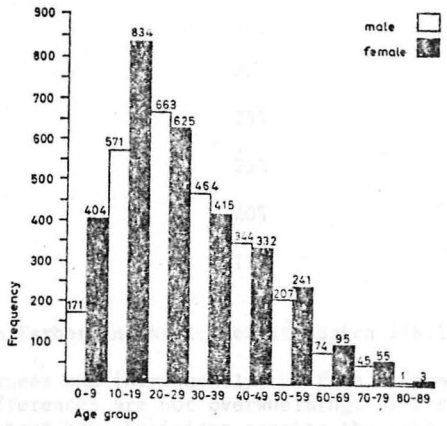


Fig. 2. Distribution of age at onset for 5,544 psoriasis patients . (1a)

the group which at the time of the study had a median age of 44 years. It should be noted that 10% of these patients had an onset before age 10, and 35% before age 20. In some patients the expression of psoriasis

begins before two years of age(2), and this historical factor is important when it is recognized that severe psoriasis as an adult is more common when the psoriasis began in childhood(3,4).

From the patients questioned by Farber and Nall there was a 47% incidence of psoriasis among first degree relatives and a 15% incidence among all relatives (first, second, and third degree)(1). Both values are biased toward including relatives who do have psoriasis but these data are consistent with the universal interpretation of a genetic predisposition toward psoriasis(2). This has subsequently been confirmed by the HLA associations which are discussed later. Of the biological offspring of these subjects 5% had psoriasis with a mean age of 18 years. Obviously this value is artificially depressed since many children have not yet expressed their disorder.

These same investigators also determined the frequency of occurrence of psoriatic lesions among seven cutaneous sites. The most frequent site was the scalp followed in order by the elbow, leg, trunk, arm, knee and face. It has been stated that psoriasis frequently affects the

CUTANEOUS SITES AFFECTED BY PSORIASIS

	Onset of psoriasis	Time of study
Scalp	38%	54%
Elbow	33%	55%
Leg	33%	65%
Trunk	29%	60%
Arm	23%	52%
Knee	20%	41%
Face	11%	28%

(from Farber and Nall: Dermatologica 148:1, 1974)

scalp, elbows, and knees and infrequently the face. From this data it is true, but the differences are not overwhelming. The statement probably says more about how physicians examine the skin, a cursory look at the face, elbows and knees without further examination.

Environmental conditions also affect the expression of psoriasis. Farber and Nall observed that cold weather made the majority of patients worse, warm weather better and as one is prepared to expect sunlight made the majority better. Another frequently asked question is the

EFFECT OF CLIMATE ON PSORIASIS

	Better	Worse
Cold weather	11%	89%
Hot weather	78%	22%
Sunlight	80%	20%

(from Farber and Nall: Dermatologica 148:1, 1974)

effect of pregnancy on psoriasis. Thirty-eight percent of the female patients had been pregnant at some time. Of these patients, 32% reported improvement, 18% worsening and 50% were not certain of any effect. Although these data show a statistically significant difference, it does not allow the physician to make a reliable prediction as to the expected effect of pregnancy on psoriasis.

Psoriasis frequently develops in areas of trauma. Such trauma may occur from cutaneous inflammation, physical pressure, ultraviolet burns, heat, or from incision of the skin. A particularly frequent occurrence is the observation that psoriasis extends or exacerbates after a severe sunburn. Many cases of acute psoriasis follow beta-hemolytic streptococcal pharnygitis, a fact which was recognized sixty years ago(6). There must be some direct relationship.

A final and important factor related to the precipitation of psoriatic activity is emotional stress. To assess this factor, Seville studied 132 psoriasis patients whose psoriasis had recently cleared completely with dithranol and ultraviolet light(7). Fifty-one (39%) recollected specific stress occurring within a month prior to the onset of psoriasis. This retrospective study supports previous studies in which stress appeared to precipitate the onset of psoriasis(8,9). Of greater interest was the prospective observation that those patients whose psoriasis apparently was exacerbated by stress were more likely to remain clear three years later (17/26 = 65%) when compared with patients without a stress history (5/24 = 17%) ($P < 0.001$). This prospective observation is a clear demonstration that these two populations were different whether or not stress was conclusively demonstrated by the retrospective data. These clinical observations taken together are important conceptually because they imply that psoriasis is a threshold disease, that is that the defect is frequently not expressed and that it may become expressed with the correct (inflammatory) insult.

Psoriatic arthritis occurs in as many as 5% of patients with psoriasis although its existence as a distinct disease entity has been doubted by some investigators(10). Most rheumatologists and dermatologists now accept it as such(11,12,13,14,15,16). Part of the confusion has arisen from the wide spectrum of clinical presentations of this disorder. Some patients with arthritis remit completely, some have remissions and

relapses while a few pursue a progressive unremitting course. Moll and Wright brought light to the clinical confusion by classifying their patients into five categories(15):

a) Classical psoriatic arthritis in which the DIP joints are primarily involved.

b) Arthritis mutilans often complicated by digital telescoping resulting from severe osteolysis. These patients often have sacroiliac involvement.

c) Symmetrical arthritis indistinguishable, except for negative serology, from rheumatoid arthritis.

d) Asymmetrical involvement of single or a few small joints. This pattern usually affects scattered DIP, PIP, and MIP joints.

e) Rheumatoid spondylitis

Leonard, McDuffy and Rogers described 77 consecutive hospitalized patients at the Mayo Clinic during six months in 1976 and 1977. Then obviously observed a higher percentage of patients with arthritis than would be expected in the general population of psoriasis patients since hospitalized patients have more severe psoriasis and since arthritis occurs more frequently with severe psoriasis. Despite this, their data provides prospective into the clinical presentation of this disorder. Joint disease occurred in 40 out of 77 patients (52%).

JOINT DISEASE IN 77 CONSECUTIVE PATIENTS
HOSPITALIZED FOR PSORIASIS

(Leonard, McDuffy, Rogers)(18)

DISEASE	PATIENTS	
	Number	Percent
Psoriatic arthritis	30	39
Degenerative joint disease	5	6
Gout	4	5
Degenerative disk disease	4	5
Aseptic necrosis	1	1
Rheumatoid arthritis	1	1
Reiter's syndrome	1	1

Cutaneous psoriasis preceeded arthritis in 26 of 30 and occurred simultaneously in 3 of 30 while in only 1 did the arthritis occur first. The mean interval between the onset of cutaneous and arthritis symptoms was about 10 years (35 to 45 years). Of greatest interest was the

significant positive association between the cutaneous involvement and the functional class of impairment of the arthritis.

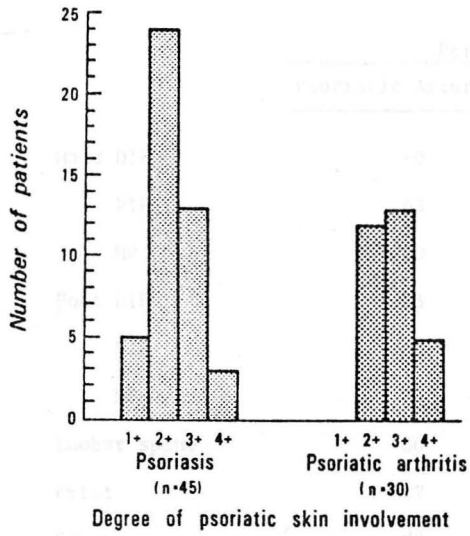


Fig. 1. Severity of psoriatic skin involvement (grades 1+ through 4+, see "Methods and Materials") in psoriasis group compared with that in psoriatic arthritis group. Psoriatic arthritis group has more severe skin involvement (grades 3+ and 4+) as compared with psoriasis group ($P<0.05$, chi-square test).

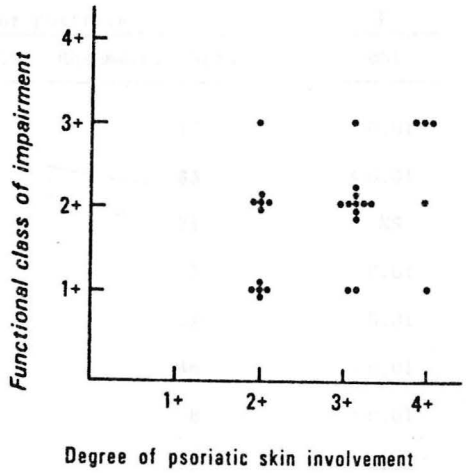


Fig. 2. Comparison of functional class of impairment to severity of skin involvement in patients with psoriatic arthritis. There is a significant positive correlation between functional class of impairment and degree of psoriasis ($P<0.02$, Spearman's rank correlation).

These same investigators compared the clinically involved joints in their 40 patients with the 532 patients with rheumatoid arthritis described by Short, et al.(19). These data clearly illustrate the clinical presentation of these two disease states are clearly separable.

CLINICALLY INVOLVED JOINTS IN PATIENTS WITH RHEUMATOID ARTHRITIS AND PATIENTS WITH PSORIATIC ARTHRITIS

(Modified from Leonard, McDuffy and Rogers) (18)

	Percent Positive		P
	Psoriatic Arthritis	Rheumatoid Arthritis	chi^2
Hand DIP	60	17	< 0.01
PIP	63	83	< 0.01
MP	70	71	NS
Foot DIP	63	23	< 0.01
PIP	60	23	< 0.01
MP	73	46	< 0.01
Lumbar spine	30	8	< 0.01
Wrist	27	79	< 0.01
Elbows	27	50	< 0.01
Ankle	27	68	< 0.01
Knee	50	78	< 0.01

Furthermore these patients with psoriatic arthritis had joint involvement distribution which were similar to those in the patients described by Moll and Wright(15).

CLINICAL PATTERNS OF JOINT INVOLVEMENT IN
30 PATIENTS WITH PSORIATIC ARTHRITIS

(Modified from Leonard, McDuffy, and Rogers)(18)

PATTERN	PERCENT	
	Leonard	Moll and Wright
Oligoarthritis	63	> 70
Symmetrical polyarthritis	23	15
Ankylosing spondylitis	7	5
Arthritis mutilans	3	5
"Classic" psoriatic arthritis	3	< 5

It is clear from all of this data that the clinical spectrum of disease is significantly different for psoriatic arthritis compared with rheumatoid arthritis.

We may summarize by saying that psoriatic arthritis is a distinct clinical entity which occurs in as many as half of hospitalized patients. In virtually all cases, skin lesions occurred first, averaging 10 years before the onset of arthritis. Clinical characterization of these patients is difficult in that five characteristic patterns may be found. Furthermore, most patients (70%) have asymmetrical involvement of single or a few small joints. Frequencies of involvement among selected joints are clearly different from those of rheumatoid arthritis. Distal hand joints are more frequently involved as is the lumbar spine while large extremity joints are less frequently involved. Finally "classic" psoriatic arthritis with exclusive involvement of most DIP joints is uncommon.

HISTOPATHOLOGY

The primary clinical lesions of psoriasis is a small papule with superimposed scale. Because skin is so accessible, an enormous amount is known about histopathologic events in psoriasis. In fact, so much is known that dermatologists have largely ignored the possibility that psoriasis may have systemic manifestations as well. In the psoriatic plaque the epidermis or epidermal compartment increases several fold in size. Since the epidermis itself is a syncytium this implies that there is a large increase in the number of cells populating the epidermis. Associated with this is an absolute and relative increase in the mitotic index, which led earlier investigators to the correct assumption that the most prominent alteration in the skin in psoriasis is an increase in

the rate of cellular replication and a consequent increase in the number of cells in all compartments. The rate of transit through these compartments is increased as well.

Other important histopathologic observations have been made and some of these have definite clinical counterparts as well. There is an accumulation of the functional cells, corneocytes in psoriasis. Either because of excessive numbers or because of incomplete attachment to each other they detach from the skin surface in large aggregates, commonly known as scales. Many of the corneocytes exhibit incomplete maturation. Since the DNA is not removed from prior to cornification, it may be found histopathologically and in the scales as well.

Prominent among the light microscopic changes seen in psoriasis is a dramatic increase in the number of high dermal blood vessels. Such vessels are dilated and they extend with the dermis through almost to the surface of the skin. This is reflected clinically as mentioned previously by fine pin-point bleeding sites when superficial scale is scraped off the skin surface. Although it has been largely ignored, there is a significant inflammatory infiltrate in the skin. I shall ignore it as well for now but we shall return to it later.

Psoriasis belongs to the clinical category of papulosquamous skin disorders, which are identified by elevated areas termed papules and which are topped with scale, therefore termed papulosquamous. The major components of the differential are listed in the table.

DIFFERENTIAL DIAGNOSIS OF PSORIASIS

1. Contact irritant dermatitis
2. Contact allergic dermatitis
3. Seborrheic dermatitis
4. Lichen planus
5. Dermatophytosis
6. Pityriasis rubra pilaris
7. Mycosis fungoides
8. Subacute cutaneous lupus erythematosus

A major warning must be introduced before proceeding into the clinical and diagnostic parameters which distinguish these disorders from psoriasis. It is that patients with psoriasis are subject to all other cutaneous

afflictions, and that it is not unusual for one to be superimposed on the other. Furthermore, an inflammatory insult at the skin surface will frequently elicit the phenotypic expression of psoriasis in that area. This is known as the Koebner phenomenon or the isomorphic response. It has been associated with physical injury and inflammatory insults. Therefore the secondary disorder will elicit psoriasis. The onset of psoriasis has been associated with allergy scratch testing, surgical incisions, sunburn, contact dermatitis and virtually every other skin disorder. Secondly, psoriasis is common enough, affecting about 2% of the U.S. population, that many patients will have their first phenotypic expression of psoriasis only with a second disorder.

Therefore the differential list for psoriasis is useful in several ways. It must be consulted when a patient with established psoriasis exacerbates or develops changes in his clinical presentation. Secondly, it must be consulted when a particular diagnosis in it is considered, because an underlying psoriatic diathosis must be considered for all patients who have such disorders. Such recognition may help to explain why a particular patient has not responded to treatment as expected.

PATHOGENESIS

The most obvious defect in skin involved with psoriasis is accelerated cellular (keratinocyte) proliferation. This defect which was suggested by the dramatic increase in the epidermal compartment size, the excessive amount of scale which is lost by patients, and the increased number of mitoses, was clearly identified by Van Scott and his co-workers in 1963 with the increased uptake of ^{3}H-thymidine by keratinocytes within the lesion of psoriasis(20). Since that time numerous reports have documented the increased proliferative behavior of psoriatic epidermal cells compared with normal epidermal cells(21,22,23). When psoriatic skin is removed from patients for in vitro studies, however, most investigators find no difference in proliferative rates(24,25). Harper, Rispler and Urbanek, however, have observed in their own in vitro skin organ culture system that both lesional epidermis and normal appearing skin from patients with psoriasis exhibit increased DNA uptake when compared with normal controls(26). This is consistent with the observation of Marks(27) and of others(28,29) that in vitro thymidine uptake is increased in psoriasis plaques as well as normal appearing psoriatic skin when compared with normal controls. This is not a trivial question since it has yet to be determined whether accelerated proliferation as seen in psoriasis is inherent to the epidermal cell(30,31) or results from the local environmental impact of vascular supply(32) or inflammatory insults.

The knowledge that psoriasis is characterized by excessive epidermal proliferation became available at the same time that enormous progress was being made in chemotherapy for malignancies. Given that psoriasis is a disorder of excessive proliferation, it does respond quite well to therapy with metabolic antagonists. The only limit to investigation in this area is the obvious fact that psoriasis is a benign disorder. Therefore the long-term safety of any therapy is of utmost importance.

INFLAMMATION AND IMMUNOLOGIC OBSERVATIONS IN PSORIASIS

Non-immunologic factors which characterize psoriasis may be summarized:

1) The defect(s) which cause psoriasis result primarily in accelerated keratinocyte proliferation and disordered epidermal maturation.

2) These cutaneous changes are focal and have anatomic sites of predilection.

3) The clinical course of psoriasis is characterized by spontaneous exacerbations and remissions.

4) A familial inheritance pattern has been observed and it is most easily explained as a polygenic dominant influence.

5) Numerous biochemical and physiologic parameters are abnormal in the lesion of psoriasis and some relate in significant ways to pathogenesis of psoriasis. These include:

   a) accelerated DNA replication

   b) altered cyclic nucleotide ratios

   c) increased levels of prostaglandins precursors, and related substances, and

   d) altered carbohydrate metabolism.

6) The biochemical metabolism of uninvolved skin of patients with psoriasis is probably abnormal as well.

Observations made in the last ten years also identify psoriasis as a disorder which is associated with significant inflammatory and immunologic

INFLAMMATION (Celsus & Galen)

1. Redness
2. Swelling
3. Heat
4. Pain
5. Loss of function

phenomena. But the elucidation of these phenomena is still at a stage of discovery, when individual observations appear unrelated to each

other. It is at this state of investigation that learning is most difficult, because one must remember all observations --relevent, irrelevant and even the incorrect -- all without an appropriate conceptual framework to line them together. Despite this, enough is known to be able to place these observations into one of five areas: histopathology, HLA associations, psoriatic arthritis, auto-antibodies, and cellular alterations. And it must be stated from the onset that these observations and interpretations do not contradict the enormous biochemical and physiological literature mentioned previously(20,31).

Histopathology

The classical histopathologic features of psoriasis include acanthosis, increased numbers of mitoses, hyperkeratosis, parakeratosis, vascular dilitation and an inflammatory infiltrate(32a,33). This cellular infiltrate has been rediscovered and is now the subject of considerable interest. Inflammatory cells which may be found in both the epidermis and the dermis include lymphocytes, macrophages, mast cells, and neutrophils Lymphocytes and macrophages are primarily perivascular in the reticular dermis while mast cells and neutrophils are found most often in and around vessels of the papillary dermis.

HISTOPATHOLOGY OF PSORIASIS

1. Acanthosis, Hyperkeratosis, Parakeratosis Papillary Elongation, Vascular Dilitation

2. Inflammatory Infiltrate: Lymphocytes, Macrophages, Neutrophils, Mast Cells

An important goal has been to identify early cellular events in psoriat lesions, and in this way to provide insight into the responsible defect(s). In a series of histological studies, Braun-Falco and his associates have studied both normal appearing skin surrounding stable plaques of psoriasis and new lesions in exacerbating psoriasis. They consider several features to be early cellular events(34,35):

1) In clinically normal skin adjacent to lesions of psoriasis definite pathologic alterations occur. They include epidermal thickening and a perivascular dermal infiltrate of macrophages, lymphocytes and mast cells.

2) With endogenous initiation of new lesions an acute inflammatory reaction occurs in the papillary dermis. This is characterized by exocitosis of inflammatory cells, first macrophages and lymphocytes, followed by neutrophils in fully developed lesions(34,35).

Other investigators have observed a greater participation by neutrophils in early lesions of psoriasis. Pinkus and Mehregan reported neutrophil exocitosis from dilated papillary capillaries with apparent exocitosis into the epidermis. They concluded that this exocitosis was

the initial event(36). Soltani and Van Scott observed numerous lymphocytes and neutrophils in approximately equal numbers, in early lesions of psoriasis(37). Braverman and Yen demonstrated with electron microscopy the attachment of neutrophils to endothelial walls in lesions of psoriasis(38 On a histologic basis it is therefore clear that inflammatory cells, including neutrophils are an important feature within the lesion of psoriasis. But these observations do not identify the chemotactic agent(s) responsible for this participation and conversely what influence these cells and their products have on epidermal homeostasis.

Chemotaxis of neutrophils into the epidermis may occur by immunologic or by nonimmunologic mechanisms. Neutrophil chemotaxis may occur in response to complement activation at the site of anti-stratum corneum antibodies. On the other hand, Lazarus and his associates have isolated

NEUTROPHIL CHEMOTAXIS IN PSORIASIS

1. Anti-stratum corneum antibodies and complement activation (Beutner)

2. Complement activation by neutral proteinase (Lazarus)

3. 12L-Hydroxy-5,8,10,14-Eicosatetraenoic Acid (Voorhees)

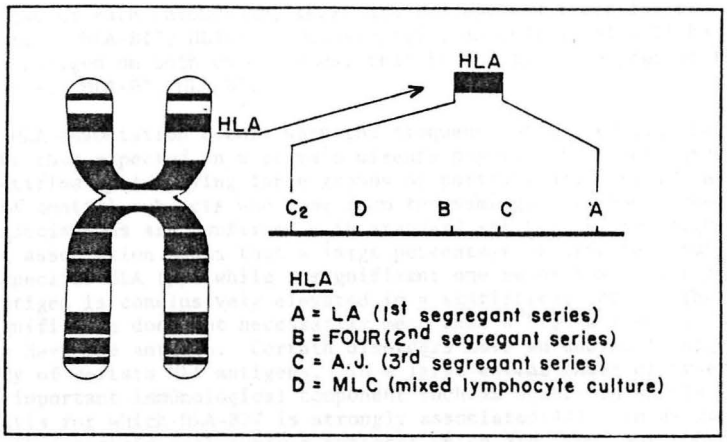
from psoriasis skin a proteinase, probably serine proteinase, in high concentrations with a high specificity for complement activation(39,40,41). They have identified the enzyme in whole human skin and in human epidermis, suggesting that cellular injury in these tissues might liberate this enzyme which then activates complement to cause neutrophil accumulation. Furthermore, an arachidonic acid derivitive, 12L-hydroxy-5,8,10,14-eicosatetraenoic acid (HETE) has been found in significantly elevated concentrations in the epidermis of active psoriasis(42). These local chemotactic mediators may play a significant role in the genesis of the neutrophilic infiltrate of psoriasis.

We may conclude that on a histologic basis, inflammation is a major factor in psoriatic lesions.

HLA associations

Human leukocyte antigens (HLA) are low molecular weight proteins found on the surface of certain cells(43,44,45,46). Since they are present in relatively small amounts, these proteins are most easily identified with immunological techniques. HLA antigens form the major functional barrier to tissue transplantation and they control specific interactions among cells of the immune system.

The genetic code for the molecular structure of HLA proteins system is located in the small segment of chromosome 6, and this genetic area as a whole is entitled the histocompatibility complex. Currently, four subregions (loci), each coding for a different protein, have been identified: HLA-A, HLA-B, HLA-C, HLA-D. The first three, A, B, and C,



(Farber, et al., 1977)

occur on the surfaces of all nucleated cells. When such cells are injected or transfused into a non-identical recipient (kidney transplantation or whole blood transfusion), the recipient forms antibodies against

HUMAN LEUKOCYTE ANTIGENS (HLA)

Distribution:

HLA-A, HLA-B, HLA-C: all cells
HLA-D: B-Lymphocytes, Macrophages
Sperm, Epidermal Langerhans Cells

Numbering: Sequential within each group

those HLA antigens which are foreign (alloantibodies). Such antibodies are easily detected by serologic tests.

HLA-D antigens have a more restricted cellular distribution. They are found on B lymphocytes, macrophages, sperm and epidermal Langerhans cells (macrophages?). They may not be identified by serologic studies (alloantibodies) but are identified by how cells interact when cultured with other cells. Specifically lymphocytes from two individuals have HLA-D antigens in common when they stimulate each others lymphocytes to proliferate. This is done in what is termed a mixed lymphocyte culture (MLC).

As each unique and specific antigen for a specific HLA locus is identified and confirmed, a number is assigned to it. Since individuals

inherit two of each chromosome, there are two antigen types for each locus: i.e., HLA-B17, HLA-B7. Occasionally, an individual will have the same antigen on both chromosomes, that is, he is homozygous at that locus: i.e., HLA-B7, HLA-B7.

An HLA association occurs when the frequency of a specific HLA type is higher than expected in a certain disease population. Such associations are identified by surveying large groups of patients and equally large groups of control subjects who come from the same genetic background. These associations are confirmed with standard statistical techniques. A strong association means that a large percentage of affected individuals have a specific HLA type while a significant one means that the frequency of an antigen is conclusively elevated in a statistical sense. Therefore, high significance does not necessarily mean that a high percentage of patients have the antigen. Certain disorders have an unusually high frequency of certain HLA antigens. To a large extent these disorders have an important immunological component such as occurs in ankylosing spondylitis for which HLA-B27 is strongly associated(47). An association implies that certain cell surface antigens which are important components in the system of immunological recognition and control confer on a patient an unusual susceptibility to a specific disorder. Alternatively, a closely linked nonimmunologic gene in the same area of the chromosome predisposes the individual to a disease. In this way those individuals with the disorder have a greater than normal chance of having that certain cell surface antigen.

Disorders with significant HLA associations frequently have certain characteristics in common(46). As previously mentioned, such disorders often have an immunologic component, but their etiology is unknown. As might be expected in disorders with a genetic susceptibility, they also have a familial inheritance pattern. Such disorders are usually chronic with spontaneous exacerbations and remissions. All this is true of psoriasis.

In 1972, two groups of investigators reported independently an association between psoriasis and the histocompatibility system(48,49). At present the association is best established for HLA-B13, BW-17, BW-16, and BW-37(48,49,50). Furthermore, there is a significant increase in the frequency of HLA-B27 in patients who develop arthritis associated with psoriasis and with pustular psoriasis(51). There is also an association between HLA-BW38 and peripheral psoriatic arthritis(52). As described, the implication of such associations is that these surface antigens, which are coded in the histocompatibility complex, confer an increased

Psoriatic arthritis

Psoriatic arthritis has been discussed under Clinical Presentation. Given that arthritis is a distinct clinical manifestation of psoriasis in a small percentage of patients with psoriasis, it then becomes important conceptually when dealing with the pathogenesis of psoriasis. One must consider that a general or systemic defect rather than an isolated epidermal defect is etiologically responsible for the disorder.

Auto-antibodies

We associate autoimmune inflammatory disorders with the generation of auto-antibodies. In fact, a variety of auto-antibodies have been described in patients with psoriasis, and they fall into three categories. Whether any one is pathogenic is still open to question. Furthermore,

AUTO-ANTIBODIES IN PSORIASIS

Antinuclear antibodies

Anti-stratum corneum antibodies

IgG-Antiglobulins (IgG Rheumatoid Factor)

the of at least three different auto-antibody type implies that the defect which gives rise to such autoantibodies is at a more fundamental level of immunoregulation. Furthermore, the presence of such antibodies does not mean that they necessarily contribute to the pathogenesis of psoriatic plaques. It is more easily conceived that they may contribute to the pathogenesis of psoriatic arthritis.

Anti-nuclear antibodies: Cormane and his associates have partially characterized an antibody against basal cell nuclei in patients with psoriasis(53,54,55). Direct immunofluorescence studies have shown immunoglobulin and complement bearing cells in the dermis, epidermis, and Munro microabscesses of psoriatic plaques. The frequency of immunoglobulin bearing neutrophils in the peripheral blood of patients with psoriasis vulgaris was increased significantly over control subjects. This observation suggests that circulating neutrophils, remote from the cutaneous lesions of psoriasis, have altered surface membranes. These surface immunoglobulins were eluted from the cells and shown to be reactive with the nuclei of epidermal basal cells. It did not react with nuclei above the basal cell layer, implying that the antibody was directed against a non-histone protein.

Anti-stratum corneum antibodies: Several groups of investigators have observed both immunoglobulins and complement within the stratum corneum

ANTI-STRATUM CORNEUM ANTIBODIES

Antibody

Complement

Complement cleavage products

of psoriatic plaques(56,57,58,59,60,61). These have been demonstrated with immunofluorescence, immune adherence, mixed agglutination and immunoelectron microscopy. Complement has been identified in the

majority of specimens identified as well. Tagami and Ofugi eluted a potent chemotactic substance from psoriasis scale(62). By chromatography this substance eluted as if the chemotactic substance were a C5 cleavage produce resulting from an antigen-antibody reaction in the stratum corneum. Anti-stratum corneum antibodies are not unique to psoriasis. Such antibodies may be found in the serum of many normal subjects. What is unusual for psoriasis is that they have access to the stratum corneum to initiate an inflammatory reaction based on complement activation and the consequent attraction of inflammatory cells.

IgG antiglobulin antibodies

Antibodies directed against other antibodies constitute the rheumatoid factor. For rheumatoid arthritis these antibodies are predominantly in the IgM class. Recently it has been observed that the majority of patients with seronegative (negative rheumatoid factor) rheumatoid arthritis have elevated levels of IgG antiglobulin and it is proposed that these antibodies are significant in the pathogenesis of their arthritis(63). Howell, et al. investigated the presence of IgG antiglobulin in patients with ankylosing spondylitis, psoriatic arthritis, psoriasis, gout, and osteoarthritis(64). Elevated levels were found in the great majority of patients with psoriatic arthritis and psoriasis. However, the extent and severity of disease bore no relationship to the IgG antiglobulin level.

Rimband, et al.(65) have demonstrated anti-IgG activity on the surface membrane of peripheral blood lymphocytes. Furthermore, rheumatoid-like factors were identified in IgA and IgG classes of immunoglobulins (64,66,67).

Guilhou, et al. determined immunoglobulin levels, salivary IgA levels and the presence of anti IgG in sixty patients with psoriasis.

	Controls (n=300)	Psoriasis (n=60)	P
IgG	127±27	146±41	<0.001
IgA	145±59	245±99	<0.001
IgM	177±66 (n=40)	167±84 (n=28)	NS
S-IgA	5.2±1.2	19.2±5.2	<0.001

Serum immunoglobulins and salivary IgA in psoriasis. (International Units) (Guilhou, et al BJD 94:501, 1976).

They observed a significant increase in serum IgG, IgA and salivary IgA (S-IgA). The increase in S-IgA was correlated in individual patients with the increase in IgA. Furthermore, 45% of 40 patients had anti-IgG antibodies while none of 50 age-matched controls had such antibodies.

	Controls	Psoriasis
Positive	0	18
Negative	50	22

Serum Anti-IgG activity in Psoriasis: IgG coated erythrocytes, Serum, FITC labelled anti-IgG. (Guilhou, et al. BJD 94:501, 1976.)

Turner, Schumacher and Myers investigated the physiologic effect of neutrophils caused by ingested IgG-rheumatoid complexes from synovial fluid(68). They observed that the ingestion of IgG-rheumatoid factor complexes by neutrophils resulted in a subsequent phagocytic defect for those cells. In two patients with psoriatic arthritis neutrophils were observed to contain inclusions made up of immunoglobulins and those cells exhibited decreased phagocytosis. The implication is that these "auto-antibodies" may have been partially responsible for their psoriatic arthritis.

Altered cellular function

In 1965 Epstein and Maibach sensitized patients with psoriasis to DNCB(69). Untreated patients had a small but significantly diminished rate of sensitization when compared with normal controls. (Psoriasis 5/13 = 42%; Norman 21/32 = 66%). Those patients treated with Imuran (100 mg/day) had an even more striking decrease when compared with control subjects treated with equal amounts of Imuran. (Psoriasis 4/26 = 15%, Normal 8/11 = 73%) This paper has set the stage for observation concerning altered cellular function in patients with psoriasis.

Clot, et al. evaluated lymphocyte subpopulations and T-cell functions in patients with psoriasis(70,71). Decreased absolute numbers and

		Control (50)	Psoriasis (60)	
E Rosettes	(T)	71%	62%	<0.001
HTLA	(T)	76%	69%	<0.001
Surface Ig	(B)	11%	12%	NS
EAC Rosettes	(B)	15%	15%	NS
EA Rosettes	(B)	11%	12%	NS
Peroxidase	(M)	7.9%	5.3%	<0.001

Peripheral blood lymphocyte subpopulations in psoriasis. (Clot, et al. Clin. Immuno. Immunopath. 9:389, 1978).

percentages of T-cells were observed in the peripheral circulation. This was based on three assays: sheep cell rosettes, active E rosettes, and anti-human T-lymphocyte antiserum. Furthermore, thymic factor levels were significantly higher in patients compared to age-matched controls.

Obalek, Haftek, and Glinski sensitized patients and control subjects with DNCB(72). Although the incidence of sensitization was similar in both populations, the intensity of acquired sensitization was similar in both populations, the intensity of acquired contact allergy was significantly diminished when compared with controls. Decreased intensities were

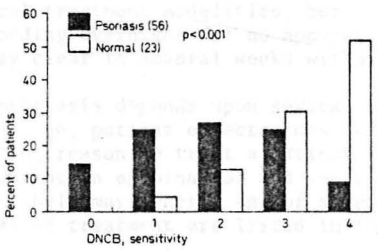


Fig. 1. The distribution of intensity of DNCB contact allergy in patients with psoriasis and normal population. Bars represent the percentage of total individuals studied in each group with a given intensity of the DNCB test in the 5-grade scale. The psoriasis group significantly differed from normals (χ^2 test; $p<0.001$).

(Obalek, Haftek, Glinski
Dermatologica 155:13, 1977)

correlated with the activity but not the extent of the disease. Decreased intensities were correlated with a decrease in E rosette forming lymphocytes.

Glinska, Haftek, Obalek and Jablonska also found that the percentage of E rosette forming lymphocytes was significantly reduced in patients with psoriasis when compared with controls(73,74). This depression correlated with the activity but not the extent of disease. EAC rosette forming cells were normal in number.

Krueger and Jederberg and their associates have identified mononuclear cell functional alterations in patients with psoriasis(75,76). In vivo they observed decreased erythema and induration to Varidase (streptokinase-streptodormase) dermal injections. In vitro they observed increased psoriasis peripheral blood mononuclear cell random migration and increased chemotaxis to Zymosan activated normal serum. Finally, increased peripheral blood mononuclear cell response to the mitogen conconavalin-A was observed in psoriasis. The presence of altered mononuclear cell function in psoriasis would seem to be established. Whether this alteration is primary or in response to existing disease has not been established.

THERAPY

In discussing psoriasis treatment I am reminded of the dictum that whenever there are more than two methods of treating an illness, none are satisfactory. One should not be quite that disenchanged with current modes of psoriasis therapy, but it is quite clear that all methods alter the expression but not the source of disability. Furthermore, one must temper enormous patient desires with good clinical judgment, strict attention to small details, and one must approach the patient with enthusiasm, conviction, and a sense of humor. This is not different from the treatment of any chronic disease: diabetes, rheumatoid arthritis, or chronic depression.

Psoriasis is a capricious disease. The majority of patients respond to any one of several treatment modalities, but stable lesions can become active, expanding overnight for no apparent reason, while long-standing lesions may clear in several weeks without treatment.

Treatment of psoriasis depends upon several factors: extent of involvement, patient age, patient expectations and the resources available. There is no compelling reason to treat a patient who is found incidentally to have psoriasis during an examination and who does not desire it. Patients who request help may receive any of several treatment modalities. The major categories of treatment are listed in the table.

PSORIASIS THERAPY

1. Topical Corticosteroids
2. Ultraviolet Light
3. Tar and Ultraviolet Light
4. Psoralens and UVA (Photochemotherapy or PUVA)
5. Anthralin (Dithranol)
6. Chemotherapy: Methotrexate, Hydroxyurea, Imuran (Mycophenolic Acid, Azaribine)

Not all of these treatments have the same popularity with the F.D.A. that they have with practitioners. Photochemotherapy with psoralens and UVA (PUVA) is in common use but is not approved by the F.D.A. Of the drugs used in systemic chemotherapy only methotrexate is approved for psoriasis; hydroxyurea and Imuran are available since they are approved for other uses; and mycophenolic acid and Azaribine are not available although Azaribine was approved at one time but was withdrawn later. In addition there are several unconventional or experimental modes of treatment. These will be commented because of the insight they provide into the pathogenesis of psoriasis.

PSORIASIS THERAPY (UNCONVENTIONAL)

8. Dialysis: Peritoneal, Hemodialysis

9. Topical alkylating agents: Nitrogen mustard, Lomustine

10. Other: Dapsone

Topical applications of corticosteroids have been a major part of psoriasis therapy since their introduction twenty-five years ago. For the patient with limited disease they provide exceptionally convenient and safe therapy. It is felt that they exert a direct antimitotic effect on the epidermis(77). In fact, the response of psoriasis to topical steroids and the vaso-constrictor assay(78) are the frequently used in vivo assays of steroid potency. All steroids have similar effects and the relative potencies of each preparation is primarily dependent upon three factors: a) the inherent potency of the steroid, b) its partition coefficient between vehicle and skin, and 3) the effect of the base on skin barrier function.

The manufacture and retailing of topical corticosteroids is obviously lucrative since a large number of the largest pharmaceutical companies are actively engaged in the manufacture or distribution of their respective agents: Syntex, Warner/Chilcott, Squibb, Johnson & Johnson, Upjohn, Lederle, ParkeDavis, Hoechst, Ciba, Dow, Schering, Lilly, Dome, Owen, Westwood, Marion, Texas Pharmacal, Dermik. In addition many secondary companies purchase from the manufacturer and distribute under their own names. Stoughton has brought some light to the mass of confusing names by comparing individual corticosteroid preparations and placing each into one of seven potency categories(79). Category I is the most potent and Category VII the least potent. Three factors are most important: a compound's inherent potency, its ability to penetrate into the skin, and the base in which it is formulated. Cream bases enhance potency the least, ointment base the most, with lotions and gels falling in between: cream lotion gel ointment. Fluorinated steroids are intrinsically more potent than non-fluorinated steroids.

Order of Potency*

I. Diprosone® ointment 0.05%
Halog® cream 0.1%
Lidex® cream 0.05%
Lidex® ointment 0.05%
Topicort ointment 0.25%
Topsyn® gel 0.05%

II. Aristocort® cream 0.5%
Diprosone® cream 0.05%
Flurobate® gel (Benisone® gel) 0.025%
Topicort cream 0.25%
Valisone® lotion 0.1%
Valisone® ointment 0.1%

III. Aristocort® ointment 0.1%
Cordran® ointment 0.05%
Kenalog® ointment 0.1%
Synalar® cream (HP) 0.2%
Synalar® ointment 0.025%

IV. Cordran® cream 0.05%
Kenalog® cream 0.1%
Kenalog® lotion 0.025%
Synalar® cream 0.025%
Valisone® cream 0.1%

V. Desonide cream 0.05%
Locorten® cream 0.03%

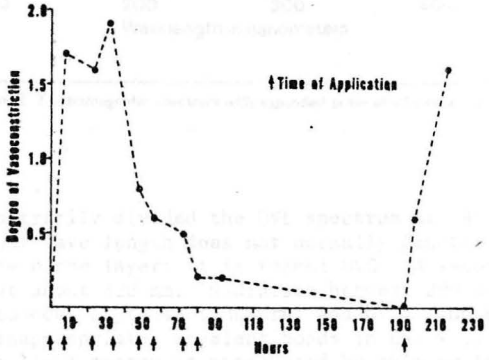
VI. Topicals with hydrocortisone, dexamethasone, flumethalone, prednisolone and methyl prednisolone

*Group I is the most potent and potency descends with each group to Group VI which is least potent. There is no significant difference of agents within any given group.

A word of caution reminds physicians that the newest preparations in Categories I and II are very potent. With continuous use or when applied under a plastic occlusive material they will produce atrophy and striae. When used over large portions of the body adrenal suppression may occur.

A second important factor concerning the use of topical steroids in psoriasis is the observation of patients and physician alike that when intensive use is required, their effectiveness diminishes. This is similar to the observation that when systemic steroids are withdrawn from patients with psoriasis there may be a serious exacerbation. DuVivier and Stoughton gave this assumption more credibility by demonstratin that tachyphylaxis occurs in response to topical steroid application(80,81).

Fig 2.—Tachyphylaxis after twice daily application of fluocinonide with recovery after four days without treatment.



Tachyphylaxis to Corticosteroids/du Vivier & Stoughton

In this table which is taken from their work, a decreasing branch response occurs after topical application. After several days the initial response returns. Topical steroids are effective for limited psoriasis but they become ineffective if continued use is required.

Light energy immediately above visible light in the electromagnetic spectrum has been defined as ultraviolet light (UVL). Since the wave length of this light decreases, its energy increases. Electromagnetic energy is contonuously emitted by the sun but only that portion of the spectrum which passes through the atmosphere reaches the earth's surface.

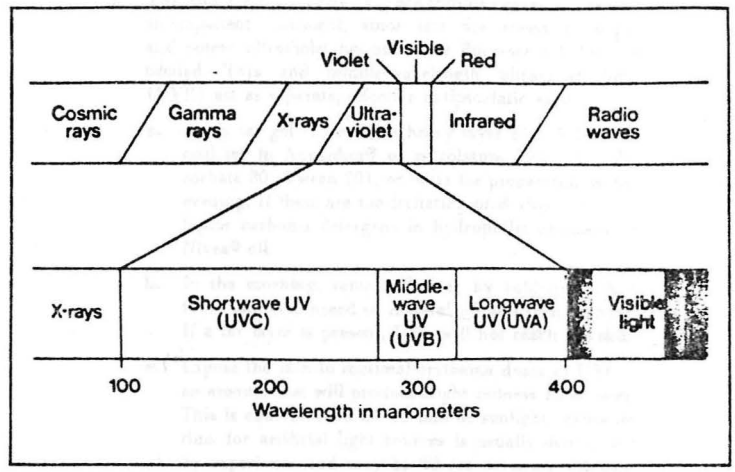


Figure 2. Electromagnetic spectrum with expanded scale of ultraviolet light.

This fact has arbitrarily divided the UVL spectrum at 290 nm. Light energy beneath that wave length does not normally penetrate because it is absorbed by the ozone layer; it is termed UVC. A second arbitrary division occurs at about 320 nm. Radiation between 290 and 320 nm produces both cutaneous erythema (sunburn) and by virtue of its ability to produce new, inappropriate, covalent bonds in DNA will produce cancer. Fortunately, such light energy is attenuated by skin so that only cutaneous carcinogenesis occurs. This category of UVL between 290 and 320 nm is termed UVB. Nearest to visible light, between 320 and 400 nm, is the UVA region. It has relatively few effects on biological systems except in combination with certain heterocyclic light absorbing molecules.

In 1931 Goeckerman published his experience using topically applied crude coal tar followed by ultraviolet light in the treatment of psoriasis(8 It quickly became the standard against which all other treatments were subsequently measured. In hospital therapy with ultraviolet light and crude tar is the safest, most active treatment of psoriasis(83).

2. ***Tar and UVL therapy (Goeckerman regimen)*** is best an inpatient treatment, since tars are messy to apply and potent ultraviolet hot-quartz or fluorescent lights are needed. Tars and middle-wavelength ultraviolet light (UVB) act as separate, effective antipsoriatic agents.

   a. Apply tar gel (Estar®), a heavy layer of 1–5% crude coal tar in Aquaphor® or petrolatum with 1% polysorbate 80 (Tween 20), or other tar preparation in the evening. If these are too irritating or drying, use 10% liquor carbonis detergens in hydrophilic ointment or Nivea® oil.

   b. In the morning, remove the tar by rubbing with a towel and cottonseed or mineral oil and then bathing. If a tar layer is present, UVL will not reach the skin.

   c. Expose the skin to minimal erythema doses of UVL – an amount that will produce slight redness 12 hr later. This is equivalent to 20–30 min of sunlight; exposure time for artificial light sources is usually determined by experience and may be 30 sec or many minutes. Production of a mild phototoxic effect (sunburn) is probably necessary for an effective response. Gradually increase the duration of light exposure daily.

   d. Bathe and remove scales with a stiff brush. Too vigorous brushing, however, may cause a Koebner reaction.

   e. After bathing, liberally rub tar onto involved areas. Alternatively, steroids with occlusion may be used during the day, being applied after UVL exposure, with tars applied only overnight. Using the latter method, lesions will flatten more quickly, but there will be no overall difference in the time necessary for total clearing or length of remission.

   f. After a 2–3-week in-hospital stay, most patients will clear and prolonged clinical remission of psoriasis will occur.

PUVA

John Howard Griffin is a retired investigative reporter now living in Fort Worth. In the 1950's he posed as a black educator and traveled through the South in search of work. His Pulitzer Prize winning book Black Like Me documents that journey(84). To accomplish his conversion from white to black he darkened his skin by the oral administration of psoralens followed by ultraviolet light (UVL) exposure. This medical procedure has been introduced decades earlier by El Mofty for the treatment of vitiligo(85).

Psoralen belongs to a group of heterocyclic organic compounds callcd furotoumarius which in turn are considered to be a derivitive of coumarin (1,2-benzopyrene)(86). Furoconmarins are synthesized when the furan ring is added to the suitably substituted coumarin derivitive. The medically important psoralen derivities are all plant-derived. Four common plant sources include celery, bergamat plants, leguminosae and the fig. Three derivitives, psoralen, 8-methoxypsoralen and 4,5',8-trimethylpsoralen have been studied most extensively. The ability to sensitize skin to ultraviolet light appears to be a unique capacity of

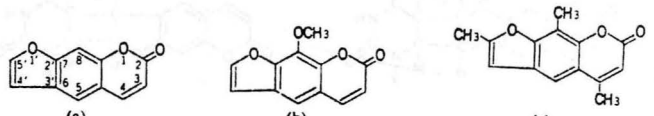


Fig. 3. Structure of psoralen(a), 8-methoxypsoralen(b), and 4,5',8-trimethylpsoralen(c).

these compounds, and in this regard an extensive literature documents a phototoxicity which results in increased melanogenesis and melanocyte proliferation(87,88).

In 1973 Walter, et al. observed that 4,5',8-trimethylpsoralen in association with "black" ultraviolet light (UVA) inhibited the incorporation of tritiated thymidine into mouse epidermis in vitro(89).

EFFECT OF TRIOXSALEN AND BLACK LIGHT ON
DNA SYNTHESIS IN MOUSE EPIDERMIS

Experimental		Control	P
Psoralen	45.2 ± 7.0	Saline 44.3 ± 4.6	NS
Psoralen & Light	14.3 ± 1.0	Saline 54.2 ± 7.6	0.001
Light	51.4 ± 6.1	Saline 46.1 ± 6.1	NS

(Walter, Voorhees, Kelsey, Duell. Arch Derm 107:861, 1973)

There was a three-fold reduction in thymidine incorporation into DNA while neither the drug alone nor the light alone had any appreciable effect. The currently accepted mechanism by which psoralen and UVA interrupts the accelerated cellular proliferation of psoriasis is that the absorption of UVA light raises the energy of the psoralen molecule

to the triplet state from which it reacts to form a covalent bond with pyrimidine bases in DNA(90).

Psoralen is highly reactive at several sites so that a variety of combinations occur with pyrimidine bases in DNA, primarily with thymidine. Pathak, et al. have demonstrated with several techniques that

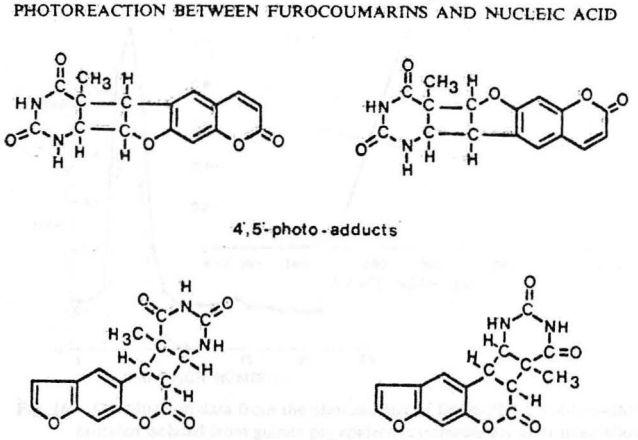


Fig. 2. Molecular structures of photoadducts between psoralen and thymine.

the bond between psoralen and DNA is permanent. In the figure below radioactive trimethylpsoralen has been exposed to guinea pig epidermis in the presence of UVA light. After the DNA is purified it is found that the radioactivity always accompanies the DNA. In this instance, after passage through a filtration gel the radioactivity (psoralen) is found in the fraction containing DNA. If the two were separable the psoralen should arrive in a much later fraction since it is much smaller in size than DNA.

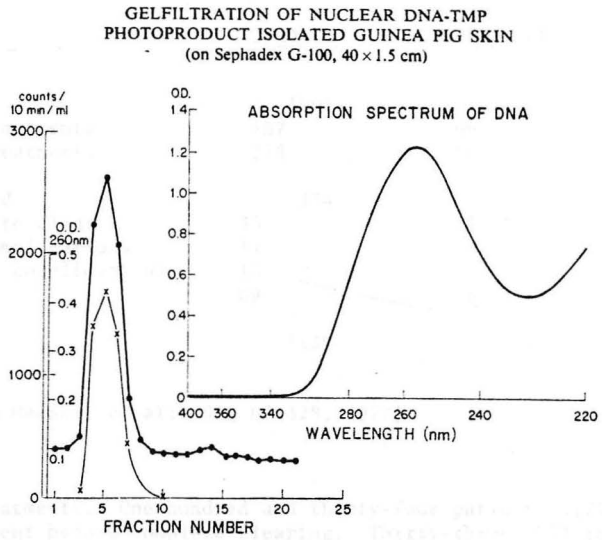


Fig. 16. Gel filtration data from the photoadduct of DNA-[^{3}H]-4,5′,8-trimethylpsoralen isolated from guinea pig epidermis immediately after irradiation. -x-=radioactivity; -•-=absorbance at 260 nm. The curve at the right corner shows the ultraviolet spectrum of DNA in 0.1 M sodium acetate buffer, pH 6.0.

On the basis of inhibition of thymidine incorporation, Walter et al. predicted that psoralen and UVL might be useful in hyperproliferative disorders such as psoriasis. One year later the successful use of psoralens and UVA in the treatment of psoriasis was announced at a press conference by investigators from Boston and Vienna(91). This was followed by additional reports(92,93).

The next year a randomized cooperative clinical trial was initiated among 16 centers to investigate in a systemic way the efficacy and short-term safety of PUVA therapy(94). 8-Methoxypsoralen dosage was weight dependent but was about 40 mg/treatment for a 70 kg adult. Two hours after drug ingestion, patients were exposed for increasing amounts of time to high-intensity fluorescent lights with the predominant output in the UVA spectrum (320-400nm). The results of this study clearly document the effectiveness of this treatment modality.

Eighty-eight percent (1005/1139) of the patients were effectively cleared of their psoriasis. Most patients (69%) cleared in fewer

PUVA THERAPY OF PSORIASIS

	Number	Percent
Cleared	1005	88
< 30 treatments	787	69
> 30 treatments	218	19
Discontinued	134	12
Failed to clear	33	3
PUVA complications	14	1
Medical complications	18	2
Other	69	6
Total	1139	100

(from Melski, et al: JID 68:328, 1977)

than 30 treatments. One hundred and thirty-four patients (12%) discontinued this treatment before complete clearing. Thirty-three (3%) failed to clear while 14 (1%) had complications which were directly attributable to PUVA therapy. This included five patients whose psoriasis exacerbated during treatment, two who developed burns, two with pruritus, two with nausea, and one each with tanning, pre-existing bullous pemphigoid, and claustrophobia. Other reasons for discontinuing therapy included unrelated and pre-existing medical problems, transportation, and expense.

Side effects were not uncommon. They included erythema or burns in nearly 10%. This was not unexpected in that phototoxicity (sunburn or lightburn) is a major component of the treatment making this side effect an extension of the therapeutic effect. However, only two

PUVA: IMMEDIATE SIDE EFFECTS

Side Effect	Percent
Erythema/burns	9.8%
Nausea	3.2
Pruritis	14.1
Headache	2.0
Dizziness	1.5

(from Melski, et al: JID 68:328, 1977)

patients (0.2%) discontinued treatment because of burns. Additional important side effects included pruritus in 15% and nausea in 3%. Three patients discontinued treatment because of these symptoms. Finally, headache and dizziness apparently occurred in 2 and 15 respectively but caused discontinuation in none. With respect to routine laboratory studies no clinically significant abnormal laboratory findings attributable to PUVA were made.

Three clinical categories of psoriasis responded differently to PUVA therapy. Guttate psoriasis as we will see in the second case report may be quite responsive to treatment. This was found to be true with respect to PUVA therapy as well. Those patients with guttate psoriasis cleared with significantly less treatment than did patients with other types.

PUVA TREATMENT vs PSORIASIS TYPE

Psoriasis (#)	Mean Total J/cm^2	Mean Number of Weeks
Guttate (122)	208	9.8
Plaque (831)	251	11.8
Erythrodermis (25)	368	16.4
	$p < 0.05$	$p < 0.01$

(from Melski, et al: JID 68:328, 1977)

Furthermore, erythrodermic psoriasis responded less favorably than plaque or guttate psoriasis.

An important aspect of this study was the observation that therapy at longer intervals was effective at a smaller total dosage of ultraviolet light and psoralen. As may be seen in the table patients treated twice

PUVA TREATMENT vs SCHEDULE

Schedule	Total J/cm^2 (mean)	Treatments (mean)	Weeks (mean)
Two times weekly	173	18.3	9.7
Three times weekly	201	20.3	7.6
	$p < 0.005$	$p < 0.01$	$p < 0.01$

(from Melski, et al: JID 68:328, 1977)

weekly in approximately 10 weeks while those treated three times weekly cleared in approximately eight weeks. The total number of treatments and the total dose of UVL received was less in the twice weekly group. This observation has become more important as long-term toxic effects have been observed and since the frequency of such may be a function of total dose.

An important consideration in this experimental therapy has been the possibility of eye damage, including possible cataract formation. To detect such changes, ophthalmologic exams including visual acuity, slit lamp and funduscopic tests were performed at the beginning of the study and periodically throughout the study. No statistically significant changes were observed.

It was concluded by these investigators that PUVA therapy for psoriasis is effective and that it exhibits short-term safety if administere by a competent physician.

The second large protocol study from 14 centers was reported in May of 1979(95). Data included 465 patients treated with a 48 tube cabinet over the 16 month period from October 1975 through January 1977. UVA exposure began two to three hours after methoxsalen ingestion and treatments occurred two or three times weekly. Methoxsalen dosages were variable but again were about 40 mg for a 70 kg adult. When patients had cleared, they were placed on maintenance therapy according to protocol (once every single week, two weeks, three weeks or as needed).

Of 388 evaluable patients 331 (85%) cleared, 23 (6%) dropped out and 17 (4%) failed to clear. Treatment was discontinued because of adverse reactions for 14 patients, although reasons for discontinuing treatment were not given. Predominant side effects included erythema, nausea, pruritus, headaches, dizziness, and edema. One or more of these side effects occurred in 30% of patients but they were generally mild and caused discontinuation of the treatment in fewer than 2%. These observations are similar to those of the first report.

An interesting aspect of this study was the listing of previous therapies used by these patients before treatment with PUVA. One must recognize first, however, that they had severe and disabling psoriasis and that they therefore required more aggressive treatment. The vast

PREVIOUS THERAPY BEFORE PUVA: TOPICAL

Therapy		Percent (N = 388)
Steroids:	topical	94
	systemic	35
UVL and Tar:	both	40
	tar alone	82
	UVL alone	53
Anthralin		22

majority had been treated with topical steroids and tar topical preparations. About half had received UVL alone, UVL with tar and methotrexate systemically One-third and one-quarter had received systemic steroids and anthralin

PREVIOUS THERAPY BEFORE PUVA: SYSTEMIC

Therapy	Percent (N = 388)
Methotrexate	44
Hydroxyurea	5
Azaribine	4
Mycophenolic acid	4
Grenz ray	16
Xray	13

(Arch Dermatol 115:576, 1979)

topically. More than ten percent had received low energy X-ray (Grenz ray) and X-ray iteslf. Both treatments are even used occasionally today although most of these patients were presumably treated many years ago. Approximately five percent had each received methotrexate, hydroxyurea, and azaribine.

The energy output of 64 fluorescent UVA tubes is approximately double that of natural sunlight. Therefore, Parrish, et al. extended their original work by employing oral 8-MOP followed by natural sunlight exposure(96). This is technically more difficult to do, but the majority of 51 patients treated improved substantially. Disadvantages included the eratic availability of sunlight and the difficulties of dosimetry. Advantages obviously included the reduced cost.

A second modification was introduced by Fischer and Alsins(97). They applied a dilute trioxsalen solution to the skin surface by having patients bathe in it rather than by oral ingestion. These investigators have predicted that toxic systemic effects are less likely under these circumstances.

In addition to the short-term hazzards of PUVA therapy there is considerable reason for concern about late changes as well.

Some reports have suggested the experimental production of cataracts in animals given large doses of 8-MOP and exposed to long-wave ultraviolet radiation(98,99,100). Lerman and Borkman observed that the oral ingestion of 8-MOP resulted in the uptake of the drug into the lens in rats(101).

Furthermore, it has been reported that psoralen administered orally may be found in human corneas in trace amounts long as seven days later(102).

The induction of cutaneous malignancies in patients receiving PUVA treatment was predicted by earlier animal studies. Griffin and his associates documented in a series of papers the unequivocal propensity of psoralen and UVA to induce cutaneous malignancies in albino mice (103,104,105).

The carcinogenic prophecy was demonstrated by 1979(106). In a prospective study of 1373 patients who received 8-methoxypsoralen photochemotherapy for psoriasis, 30 patients developed a total of 48 basal cell carcinomas and squamous cell carcinomas. This observed incidence of cutaneous carcinomas was 2.63 times that expected for a matched control population. Significantly, the increased relative risk was highest for patients with a previous cutaneous carcinoma (relative risk = 10.22). Two other observations were made which strengthen the thesis that PUVA itself does induce skin cancer. First, there was an increased

PERCENTAGE DISTRIBUTIONS OF CARCINOMAS
BY ANATOMIC REGION

Region	Tumor Type (percent)		
	Basal Cell(19)	Squamous Cell(29)	Total(48)
Head and Neck	63	3	27
Upper extremities	5	11	8
Trunk	21	31	27
Lower extremities	11	55	38
Totals	100	100	100

frequency of cancers on the trunk and lower legs, body areas not normally exposed to sunlight, but areas exposed during PUVA treatment. Secondly, there was a reversal of the normal predominance of basal cell carcinomas over squamous cell carcinomas in these patients. The majority of tumors were squamous cell carcinomas. In view of this it was stated that cutaneous carcinoma function was a definite result of PUVA therapy and that patients with fair skin and with prior histories of cancer were at greatest risk.

Of greater potential importance is the effect of PUVA on the immune system, particularly as translated through the effect on immune cells which circulate through the skin during UVB irradiation. Volden, Molen, and Thomsen observed that PUVA increased the threshold concentration of nitrogen mustard required to produce clinical dermatitis in five patients with mycosis fungoides who had been previously sensitized(107).

Kraemer and Weinstein found a reduction in thymidine incorporation of leukocytes after PUVA treatment in psoriatic patients(108). Inhibition of mitogen-induced lymphocyte reactions by 8-MOP plus UVA in vitro has been reported by several investigators(109,110,111,112). A depression of lymphocyte turnover(113), and of leukocyte chemotaxis(114), after exposure to 8-MOP and UVA light in vitro as well as an increase in chromosomal aberrations(115) and sister chromatid exchanges(116,117) have also been reported. This areas has recently been reviewed(133).

In August 1978 the F.D.A. issued a report concerning the use of psoralens plus ultraviolet light radiation(119). The one-page report contained the following comments.

1. PUVA is an effective therapy for severe debilitating psoriasis, but the treatment has not been approved because of unanswered questions about its long-term safety.

2. Although both psoralen and the PUVA light sources are legally available, the program itself has investigational status.

3. The F.D.A.'s Dermatology Advisory Committee reviewed PUVA in December 1977 and April 1978, agreeing unanimously that PUVA is effective. It withheld approval because of concerns about safety.

4. The potential risks of most concern were occular effects (cataracts), carcinogenesis, mutagenicity, effects on the immune system and actinic damage.

5. It was estimated by the Advisory Group that 30,000 patients were already receiving methotrexate.

Anthralin:

Following the initial burst of enthusiasm over photochemotherapy which clearly is effective in psoriasis, studies now indicate that it may not be more effective than earlier techniques. Rogers, et al. reported this year in Lancet a study in which 224 patients with chronic plaque psoriasis were randomly assigned to a standard anthralin regimen or to photochemotherapy with PUVA(120). All patients treated with anthralin were admitted to the hospital, where the anthralin was applied daily in a paste base. After 24 hours it was removed and the patient received UVB light. This was continued daily with increasing concentration of anthralin and increasing light exposure until clearing occurred. PUVA photochemotherapy was used as in previous studies. Clearance was not achieved in 8.8% (10/113) of the PUVA patients and in 18% (20/111) of the anthralin patients ($P > 0.05$). Two PUVA patients

PUVA: ANTHRALIN

	Patients	Percent Clear	Days to Clear
PUVA	113	91%	34.4
Anthralin	111	82%	20.4

(Rogers, et al: Lancet 1:455-458, 1979)

could not tolerate the procedure, while eight were unresponsive. Twelve anthralin patients could not tolerate it while eight were unresponsive. The mean time for clearance was significantly shortened for the anthralin-treated patients: 20 days compared with 34 days ($P < 0.001$). These investigators conclude in view of the known safety of anthralin, that PUVA should be reserved for patients in whom the balance of benefit and risk is more apparent.

C. Treatment for more severe or widespread involvement

1. ***The anthralin paste method*** is very effective for widespread lesions consisting primarily of thick plaques. Its disadvantages are that anthralin may be a primary irritant, it stains clothing and skin, and it is difficult to apply. Anthralin paste can be used on an outpatient or inpatient basis and will clear up the lesions on most patients within 2–3 weeks. The patient should use anthralin as follows:

   a. Bathe at bedtime in a coal tar bath (Balnetar®, liquor carbonis detergens, Polytar®, Zetar®) and scrub scales off.

   b. Liberally apply 0.1% or 0.2% anthralin with 0.2% salicylic acid and 5.0% hard paraffin in zinc oxide paste (Anthera®, Anthra-Derm®, Lasan® Unguent; see Farber and Harris 1970 for details) to lesions with a tongue blade or gloved fingers. The anthralin concentration may be gradually increased to 0.4% or greater.

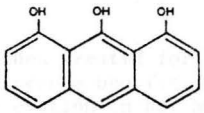
   c. Cover paste with powder and gauze dressing or stockinette, or simply wear old pajamas, and leave on 8–12 hr.

   d. Remove paste in the morning. Bath or mineral oil will aid removal.

   e. Apply a low-strength corticosteroid cream (fluocinolone 0.01%, triamcinolone 0.025%) to all lesions during the day.

   f. UVL treatment may be used but does not add appreciably to the final result.

   g. Use old sheets and bed clothing, since anthralin will stain them a violet color. Treat intertriginous areas cautiously with a 1:10 dilution of the paste and with sheeting separating body folds. Anthralin stain may be removed from the skin with 3–6% salicylic acid cream or ointment, which may also be used to rim lesions to limit the paste margins.



ANTHRALIN

Mrs. BJ is a 34 year old caucasian housewife who was first seen i the Dermatology Clinic at UTHSCD in January 1977 for her long-standing psoriasis. Nine years previously, at the age of 22, she developed generalized cutaneous psoriasis which responds only temporarily to topical care. One year later she fractured her hip and while hospitali noted the rapid onset of severe psoriatic arthritis for which she was confined to bed. Her arthritis responded only to systemic methotrexat (MTX) which was administered in weekly divided doses over the next fiv years. Four liver biopsies were performed during those years:

1971: (pre-MTX): severe fatty metamorphosis
1972: severe fatty metamorphosis, unchanged
1974: moderate fatty metamorphosis
1976: moderate fatty metamorphosis

On numerous occasions an attempt was made to discontinue her MTX but each time her disabling psoriatic arthritis exacerbated.

After January, 1977 I continued her on oral MTX in weekly divided doses of 7.5 to 15.0 mg. One year later, she had isolated elevations SGOT and SGPT at 117 and 188 respectively, and February they remained elevated at 112 and 196. All hematologic parameters and all other hepatic parameters were within normal limits. MTX was discontinued. Five weeks later the patient developed a generalized flare of guttate psoriasis associated with psoriatic arthritis which was limited to her toes and right knee.

Azathioprine (Imuran) was initiated at 50 mg/day and increased tw weeks later to 75 mg/day after her arthritis increased in severity. He generalized cutaneous psoriasis remained unchanged. Two weeks later, azathioprine was again increased to 100 mg/day and subsequently to 150 mg/day. Hematologic studies remained within normal limits, and by Apri her skin lesions and arthritis began to resolve, but the SGOT remained elevated at 150. Imuran was decreased to 100 mg/day and she had an exacerbation of cutaneous psoriasis. Daily natural sun exposure was then instituted without benefit.

In July the patient developed symptoms of a urinary tract infectic and was treated elsewhere with ampicillin, phenazopyridine (Pyridium), and allopurinol. Her psoriasis cleared rapidly and totally, and by Jul

26th her WBC count had decreased to 2,200/mm^3. Azathioprine was then discontinued. Her WBC subsequently fell to 2,000 and then increased slowly over the next month, and she noted a simultaneous exacerbation her psoriasis.

The patient was then treated for two months with oral hydroxyurea 1.0 g/day without noticeable benefit. Throughout this time she contir to have an isolated elevation in her SGOT, and in December she was hospitalized electively and received a liver biopsy which was interpre as showing mild cirrhosis.

Throughout the first four months of 1979 the patient was treated with Photochemotherapy, employing 8-methoxypsoralen and UVA light, without appreciable benefit. During this time she had extensive cutaneous psoriasis and minimal arthritis. In May she was admitted tc the Baylor Psoriasis Day Care Center with extensive plaque-type psoria on her trunk and extremities. She had marked scalp and nail involveme with distal arthritis in her fingers and toes. Treatment was institut with the Goeckerman regimen, employing tar baths, and UVB exposure twi daily and 5% crude coal tar in petrolatum topically. Four weeks later her psoriasis had cleared in all areas except the lumbosacral region a her arthritis resolved completely. After discharge she was continued outpatient ultraviolet therapy.

This patients long but still abbreviated history is presented to illustrate several points concerning psoriasis:

1) For some patients, psoriasis is a totally disabling disorder

2) Treatments which must be used for such patients have great potential toxicity

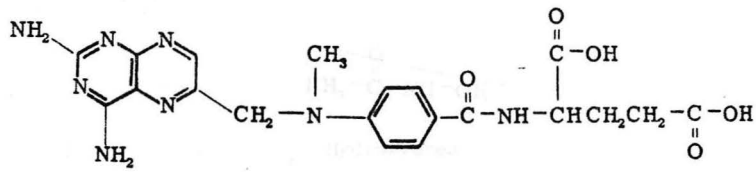
3) Tar following ultraviolet light remains the most effective treatment which is safe

SYSTEMIC CHEMOTHERAPY

Methotrexate continues to be the most frequently used systemic chemotherapeutic agent for the treatment of severe and disabling psoriasis(120a,121,122). Introduced in 1958 as the successor to aminopterin sodium(123), it has been shown to produce notable improvement for the majority of patients treated. By 1971, methotrexate was approved by the F.D.A. for use in treating psoriasis. Reservations concerning toxicity have resulted in guidelines for the use of methotrexate(124,125), and an international group has attempted to evaluate the extent of hepatic toxicity from methotrexate(126). In 1976 United States dermatologists were surveyed concerning their use of chemotherapeutic agents, including methotrexate, in the treatment of psoriasis(127). Methotrexate was used by 52% of dermatologists, while hydroxyurea was used by 10%. Seventy-five percent of dermatologists who used methotrexate currently treated ten or fewer patients with it. Multiple dose therapy with methotrexate divided over a period of 36 hours(122,128) was preferred schedule of

most dermatologists. Liver biopsy tests were obtained for 17% of patients prior to initiating therapy. The estimated number of dermatologist-treated psoriatics nationwide was estimated to be 25,000.

Large studies of patients undergoing liver biopsy for all types of liver disease indicate a mortality rate of about 1 in 6,000(129), although it is suggested by gastroenterologists that patients with severe liver diseases such as obstruction, cirrhosis, and malignant neoplasms, have the greatest risk. Finally, there would seem to be no



Methotrexate

increases of malignant neoplasms in patients receiving methotrexate. Balin, et al., in a large retrispective study, found no increased incidence of malignant neoplasms in patients treated with methotrexate(130).

One unanticipated result of the survey was the finding that 9% of patients treated with methotrexate received simultaneously prescribed systemically administered corticosteroids. This is high in view of the finding that a substantial number of methotrexate fatalities have occurred in patients who previously or concurrently received systemically administered corticosteroids for their psoriasis(131). Methotrexate is uncommonly associated with interstitial lung disease(132).

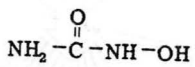
Baker reviewed in 1977 his experiences employing methotrexate in treating 260 patients with methotrexate over eleven years(133). In view of the extent and severity of psoriasis in patients who must be treated with methotrexate, the therapy is felt to be relatively safe.

JE was a 29 years old caucasian produce retailer who was first se in the Dermatology Clinic at UTHSCD in October, 1977, with a three-wee history of generalized guttate psoriasis. Ten years previously he experienced a similar episode following an acute pharyngitis. At that time he was treated unsuccessfully with topical corticosteroids. Systemic methotrexate and outdoor ultraviolet light exposure were then instituted. Under this regimen his psoriasis cleared in fifteen weeks methotrexate was discontinued and he remained free of disease for ten years.

Several weeks before his second exacerbation he experienced an acute pharyngitis which was not treated. At the time of his consultation he had acute guttate psoriatic lesions on his neck, trunk

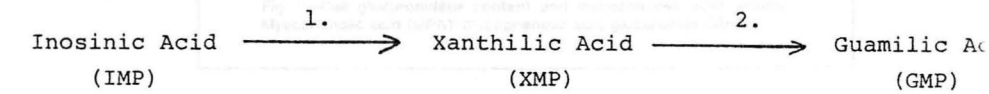
arms and legs. Natural ultraviolet light exposure was initiated and oral methotrexate was prescribed in divided weekly oral doses. Hepatic renal, and hematologic functions were monitored; all studies remained within normal limits. Three months later his skin was clear and the methotrexate, which was already prescribed in decreasing dosage, was discontinued. The patient experienced no subsequent exacerbation in hi psoriasis and he has remained clear since that time.

Hydroxyurea has been used successfully in the treatment of psoriasis (133a,134,135,136). Although long-term complications have not been reported, a major problem has been its relative lack of efficacy when compared with other drugs for extensive psoriasis(127).



Hydroxyurea

Mycophenolic acid is a fermentation produce of a penicillin mold with anti-tumor activity in certain systems(137). It blocks nucleic acid synthesis by inhibiting the interconversion of iosine monophosphate (IMP), xanthine monophosphate (XMP), and guanine monophosphate (GMP)(138).



1. IMP - dehydrogenase
2. GMP - synthetase

When mycophenolic acid is administered orally it is rapidly converted in the liver to the glucuonide which is excreted in the kidney(139). The glucmonide does not penetrate cells readily but those cells walls with high β-glucuronidase activity will liberate free mycophenolic acid to

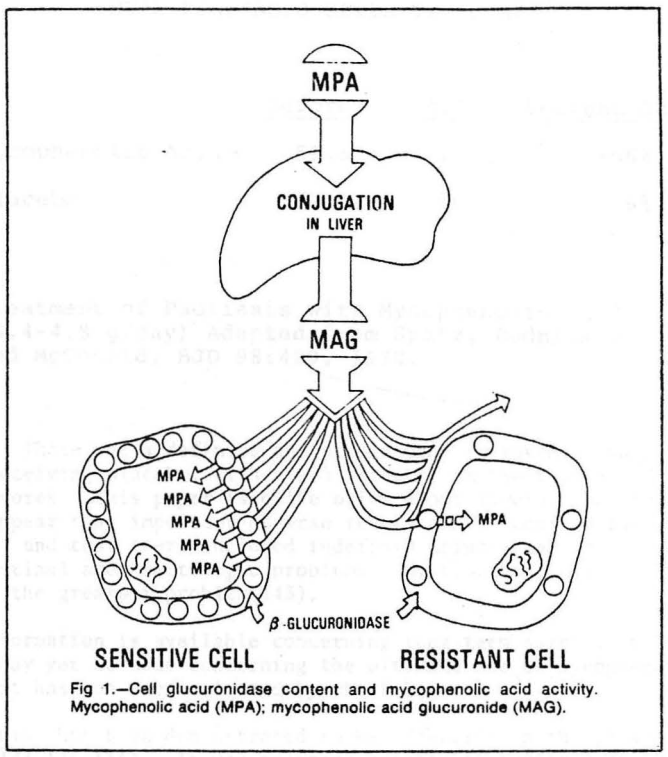


Fig 1.—Cell glucuronidase content and mycophenolic acid activity. Mycophenolic acid (MPA); mycophenolic acid glucuronide (MAG).

which the cell is then sensitive. Since many solid tumors have relatively high levels of β-glucuronidase activity it was postulated that these tumors would be relatively sensitive to the drug. Likewise, keratinocytes have high β-glucuronidase activity so that it was postulated and hoped that the accelerated proliferation which occurs in psoriasis would be relatively sensitive to the drug(140).

In a preliminary trial in 29 psoriasis patients complete or almost complete clearing occurred in more than half. Significant toxicity was low but there was a significant frequency of gastrointestinal symptoms, particularly diarrhea(141). Subsequently Spatz, Rudnicka, and McDonald reported 28 patients with severe psoriasis treated with mycophenolic

MEAN PSORIASIS SEVERITY SCORE

	Before	After	Percent Change
Mycophenolic Acid	59.5	26.1	-56%
Placebo	62.1	56.5	- 9%

Treatment of Psoriasis with Mycophenolic Acid (3.4-4.8 g/day) Adapted from Spatz, Rudnicka, and McDonald, BJD 98:429, 1978.

acid(142). There was a definite and significant improvement when compared to those receiving placebo, with a 56% relative in their standardized severity scores. This paper is quite brief about adverse reactions but it would appear that important adverse reaction did occur in the majority of patients and that there included indefined urinary and hepatic, gastrointestinal and hemotologic problems. Gastrointestinal problems constitute the greatest problem(143).

No information is available concerning long-term safety. No statement may yet be made concerning the ultimate use of mycophenolic acid, and it has not been released by the F.D.A.

Azaribine has been demonstrated to be effective in the treatment of psoriasis(144,145,146). It was released briefly in 1976-1977 for use in psoriasis but was withdrawn because of an unacceptable increase in thromboembolic complications.

Psoriatic arthritis will respond to a variety of treatments(144). There is a good correlation between improved skin lesions and improved joint symptoms. For this reason skin clearing should be thought of first. For those patients with severe cutaneous disease who therefore require systemic chemotherapy or agressive treatment with the Goeckerman regimen or with PUVA, there is a clear association between improvement in cutaneous lesions and in joint lesions. This in itself is consistent with the possibility that joint disease is a direct result of skin disease as is the observation that skin disease almost invariably preceeds joint disease. The most effective treatment of severe psoriatic arthritis is systemic methotrexate, given as is done for skin involvement.

Once skin treatment has been instituted, residual arthritis should be started with aspirin, or by other non-steroidal anti-inflammatory agents. Each drug should be taken to a full therapeutic dose or to toxicity. A recent report indicates that systemic gold therapy as it used in rheumatoid arthritis is even more effective in psoriatic arthritis(145). Failing in this, psoriatic arthritis will usually respond to systemic methotrexate(46,147) or azathioprene (6-mercapto-purine)(148).

It is reported that crysotherapy is less effective in patients with psoriatic arthritis compared with patients with rheumatoid arthritis(149,150 Dorwant, et al. both rheumatoid arthritis and psoriatic arthritis patients all of whom received gold sodium thiomalate or amrothioglucose(151) Remission rates, total improvement rates and relapse rates were all more favorable in the psoriatic arthritis group. Ten of 14 or 71% of patients with psoriasis improved or went into remission. On the basis of this data one should attempt cryotherapy in all patients with moderate to severe psoriatic arthritis who fail on more conservative therapy. It is of note that none had improvement in their skin lesions.

An important clinical administrative and financial advances in psoriasis treatment has been the Psoriasis Day Care Center(152,153,154). Such centers have been developed, usually in association with a university program for the intensive in-hospital treatment of patients with extensive psoriasis which is resistent to out-patient treatment. By far the best treatment for such patients has been the program developed by Goeckerman more than 50 years ago. This involves the topical application of tar several times daily and one or two exposures daily to UVB. Because of mess and logistics patients must be hospitalized for this treatment.

The important advance of 10 years ago was the realization and capacity to act on the realization that patients need not be hospitalized 24 hours a day for such treatment and that a lower intensity of nursing support and the absence of stamp would decrease the inconvenience immeasurably and the expense by more than 50%. In such centers, the therapeutic results are equivalent.

In order to define correctly what it is that happens in a Day Care Center strict guidelines are generally utilized. For the University of California, San Francisco, Day Care Center the following five items make up the criteria(155):

I. Medical Need: Physician availability and the presence of nursing personnel comparable to that present in the usual hospital inpatient system must be required.

II. Patient Selection: Only patients who normally would be admitted to the hospital will be accepted, and all must be physician referred.

III. Organization: Treatment is provided in a manner similar to that received by hospital inpatients.

IV. Physical Plant: Physical facilities are equal to those normally used for the same purpose in an inpatient setting.

V. Records: Comprehensive medical records are kept. These guidelines have ensured third-party coverage for patient admissions.

A flow diagram for the Goeckerman routine illustrates how time is spent in the day care center.

	Routine Center Therapy (Six Days a Week)
9:00 a.m.	Begin UVL treatment Apply ointments Shampoo scalp and apply liquor carbonis detergens in Nivea® oil
10:30 a.m.	Patient group discussion
12:00 noon	Lunch provided Doctor examines patients Reapply ointments
2:00 p.m.	Rest, recreation Therapeutic group sessions
3:00 p.m.	Remove excess tar Repeat UVL Tub bath Shampoo scalp Apply decolorized tar for discharge
4:00 p.m.	Instructions in home medications Discharge

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