MEDICAL GRAND ROUNDS
September 18, 1969

Parkland Memorial Hospital

PSORIATIC ARTHRITIS

I. Psoriatic Arthropathy - The following clinical classification of Wright (3) consists of three types, all of which lack rheumatoid factor and subcutaneous nodules (4, 5).

A. Mild Arthritis of DIP Joints-- Males predominate, skin lesions usually sparse, fingernail changes almost always present (6), other joints often involved, 50% assymetrical onset often acute resembling gout, and less painful than most rheumatoid arthritis (RA)--.

Patient [redacted] (Private patient of Drs. Hurd and Jacobson). This 27 WM [redacted] developed psoriasis at age 17 which gradually spread to involve patches of skin over the lower back, gluteal area, the scalp, thighs, palms, soles and finger- and toenails. Although somewhat variable, the extent and severity of the skin involvement has worsened each year. At age 24 he began having DIP joint pain of the fingers and toes. At age 25 he developed a bilateral plantar faciitis which was treated surgically and with phenylbutazone. During the past 2½ years, some improvement in the skin lesions has resulted from occlusive steroid ointment applications with triamcinolone and Saran wrap, but recurrences followed each decrease in therapy. In 1968 a two month trial on Methotrexate (dosage unknown) was without benefit. About this same time, he had an episode of slight conjunctivitis, but denied ever having urethral discharge or other joint involvement.

On [redacted], 1969, he was first seen by Dr. Hurd who observed minimal DIP joint arthritis of hands and feet, ? of tenderness of PIP joint of right little finger and extensive nummular plaques of classical psoriasis. Routine laboratory tests were normal including FBS, WBC, platelets and urinalysis. He was begun on 75 mg of 6-MP per day and followed at weekly intervals. Slow, but continuous improvement in the psoriasis and arthritis has been observed during the past month, and WBC's have remained in the normal range with no detectible drug toxicity to 6-MP.

B. Severe Deforming Polyarthritis--Younger males predominate; associated psoriasis often severe, extensive and uncontrollable, and is frequently of the pustular, exfoliative or unstable form; malaise or fever frequent; skin and joint symptoms usually synchronous in remissions and exacerbations; spinal involvement frequent; there is a close resemblance to Reiter's disease. This form is chronically disabling, often with a fatal outcome--. >50% onset similar to

Patient II. [redacted]. This 29 WM developed a Reiter's disease triad of urethritis, conjunctivitis and arthritis of the right knee and hip at the age of 21. After two months, the urethritis and conjunctivitis disappeared, but the arthritis persisted, and he developed balanitis and a generalized psoriatic rash which included the face and keratodermia blenorrhagica of the soles. Hand joints, wrists, elbows, knees and ankles were severely involved and by 5 months after the onset of symptoms,

he was confined to a wheelchair. Aspirin and steroid therapy had little demonstrable effect. ESR 69, slide latex fixation test negative, SSCA, ANF neg.

Age 23, he was hospitalized at [redacted] and given intravenous Methotrexate on three different occasions. Initially, significant improvement without complete clearing of the psoriasis and arthritis occurred, but subsequently, although made severely anemic by his disease and its therapy (Hgb 7.0), he gained little improvement in his arthritis. ESR ranged from 94 to 146 mm/hr. He appeared moribund and openly discussed suicide.

In [redacted] 1964 (age 24) he had developed severe flexion deformities of the fingers, elbows, and knees, the nails were thickened, yellowed and pitted, and he was covered by total body psoriasis. 6-Mercaptopurine, 75 mg/day, was begun, and within two weeks, significant decrease in skin erythema and joint pain had occurred. Within 9 weeks, no active arthritis was present and he had gained 10 to 15 degrees of additional extension of the elbows and knees. The 6-MP was gradually reduced to 50 mg/day because of a decrease in WBC from 9,750 to 3,500 during this time. The WBC returned to a normal range although the patient continued to steadily improve. The drug was continued for 16 months during which time he began to walk with the aid of crutches, grew new finger and toenails, and became free of both psoriasis and active arthritis. The drug was then stopped, and one month later anterior uveitis was noted of his right eye. This was treated topically. Nine months later, the psoriasis recurred in a patch on the groin and in the fingerwebs, and he noted return of mild urethritis. 6-MP was again begun 50 mg alternating with 25 mg/day with good results. The patient then began to regulate his own intake of the drug, often omitting it for 3 weeks at a time during symptom-free intervals. With weight gain, reconstructive surgery, and supreme confidence in the miracle of modern medicine, this young patient has returned to the realm of the living. No objective clinical or laboratory evidence of toxicity to 6-MP have been observed in this patient at the dosage range of 25 to 50 mg/day.

C. <u>"Indistinguishable" from Rheumatoid Arthritis (except absence of RF).</u> --Females predominate (66%), relatively mild erosive arthritis with rare ulnar deviation or interosseous muscle wasting. Psoriasis may be of any severity, but usually varies with the arthritis--.

<u>Patient III</u>. [redacted]. This 59 WF has an 8-year history of polyarthritis involving ankles, knees, elbows, neck and shoulders. The onset of arthritis preceded the initial observation of psoriasis by 3 months, and the latter has remained restricted to the edge of the scalp with no finger or toenail involvement. Two years ago (1967) because of the severity of the joint complaints, 6-MP 75 mg/day was begun. After 3 weeks of treatment, arthritis became so severe in the left ankle that intra-articular steroid was given, and effusions persisted in both knees. After 3 months of therapy, the psoriasis was spreading involving the scalp, left elbow and left knee. 6-MP was

increased to 100 mg/day (1.5 mg/kg). After two months, it was felt that little improvement in either arthritis or psoriasis had occurred, and the drug was gradually tapered to 25 mg/day, over the next two months. Methotrexate in a dosage of 7.5 mg/day was then started. Over the next two weeks, there was worsening of the patient's arthritis, and persistence of her psoriasis. In addition, she developed nausea, vomiting and diarrhea. Both drugs were then stopped and rapid disappearance of the gastrointestinal symptoms occurred. Laboratory work-up on this patient showed ESR 43 mm/hr, latex fixation test neg, SSCA 1/7 neg and antinuclear neg undiluted.

II. Differential Diagnosis

A. Coincidental Rheumatoid Arthritis and ?Unrelated Psoriasis--Lack finger and toenail involvement, and rarely have DIP joint involvement. Have rheumatoid factor (>80%) and may have subcutaneous nodules. Psoriasis often trivial and follows a clinical course unrelated to the arthritis.

Patient IV. [redacted] This 67 WF developed a patch of psoriasis about the size of her hand over the extensor surface of her right knee at age 43. The severity of this lesion varied with the season of the year being paradoxically worse during the summer months. She denied having any arthritis or morning stiffness prior to or during the first 15 years of her rash. The rash remained localized to the one patch, did not involve the nailbeds, and was ignored by the patient. However, at age 58, she developed the abrupt onset of pain in most of the finger joints, both wrists and both knees, and after a trial of aspirin from her private physician, she was referred to the PMH Arthritis clinic. Initial workup showed ESR 80 and latex fixation test, SSCA, and L.E. prep were negative. Multiple MCP, PIP and two DIP joints were swollen and painful to motion or pressure. The patch of psoriasis over the right knee was erythematous with silvery, mica-like scales at the margins. Particularly painful was the left knee which was tapped and 40 mg of prednisolone TBA instilled into the joint. Her arthritis responded dramatically, but transiently, to the steroid not only in the injected joint, but also in the hands. Because of the absent rheumatoid factor, the two DIP joints with arthritis, and the patch of psoriasis, she was diagnosed as having psoriatic arthropathy.

However, her arthritis became progressively more incapacitating, the DIP joint involvement disappeared although the psoriasis remained, and during the next year she showed the following SSCA titers for rheumatoid factor (Negative, 1:7 neg, 1:14 neg, 1:28 pos and 1:56 pos) and latex fixation tests went from negative to 2+. The arthritis was symmetrical in distribution, produced interosseous atrophy and was shown by x-ray to have erosions and osteoporosis characteristic of rheumatoid arthritis. She ultimately required 4 to 10 mg of prednisolone, 12 aspirin, 4 Darvon, and 300 mg of phenylbutazone/day to obtain minimal control of her arthritis. She has had progressive fading of the patch of psoriasis over the past few years so that it is now barely visible.

Comment: This patient emphasizes that occasionally in rheumatoid arthritis initially rheumatoid factor is negative, there is rare transient DIP joint arthritis, and there may be coincidental psoriasis.

B. Reiter's Disease--As illustrated by patient II, at certain stages in the clinical course of psoriatic arthropathy, the differentiation from Reiter's may be impossible. Indeed, several published reports suggest that there may be some common relationship between these two forms of arthritis of unknown etiology (7, 8). However, the two entities usually differ clinically from one another in the following ways.

1. Family History. 25 to 50% of patients with psoriatic arthropathy have a close relative who has had psoriasis.(3). Reiter's patients resemble the general population, 1% (9).

2. Joint Involvement. Reiter's favors lower extremity joints while psoriatic arthritis occurs preferentially in small joints of the hands although both can involve other joints (10).

3. Ocular Involvement. Conjunctivitis, at least transiently is seen in over 50% of Reiter's, and iritis is present in 30 to 50% of severely involved patients. Both are very unusual in patients with psoriatic arthritis (10).

4. Synchronous Flares of Arthritis and Skin Lesions are more characteristic of psoriatic arthropathy than Reiter's (10).

5. Keratodermia Blenorrhagica of the soles of the feet in Reiter's may appear identical to pustular or rupioid psoriasis early, but the massive hyperkeratosis which ultimately develops in the 8-10% of Reiter's showing this lesion is both grossly and microscopically different from the lesion of psoriatic arthritis (10).

C. Gout--36 to 40% of patients with psoriasis manifest hyperuricemia compared to 10 to 12% of the general population (11, 12). For this reason, acute, large joint arthritis, or podagra in a patient with extensive psoriasis should raise the question of gout as the etiology of the arthritis.

D. Behçet's--Balanitis, arthritis, uveitis and mucous membrane lesions of the mouth, rectum and/or vagina may be confused with Reiter's and much less frequently with psoriatic arthropathy. The penile lesions are painful as are the mucous membrane lesions, whereas psoriasis may only itch slightly (13).

E. Systemic Lupus Erythematosus--The rash of SLE usually involves the face which is usually spared in psoriasis. Renal disease is unlikely in psoriasis except as terminal amyloidosis (14) in the pustular form. Both may cause DIP joint arthritis (1).

III. Incidence

A. Table I. PREVALENCE OF PSORIASIS IN PATIENTS WITH POLYARTHRITIS AND CONTROLS (From Baker, Ref. 15)

Group			Number	Number with Psoriasis	
				Present	Past & Pres.
Arthritics	Sero-positive*		246	3 (1.22%)	5 (2.03%)
	Sero-negative*	(a) Whole group	96	32 (33%)	33 (34.38%)
		(b) "Indistinguishable" from rheumatoid subgroup	73	13 (17.81%)	14 (19.18%)
Controls			738	9 (1.22%)	11 (1.49%)

*For rheumatoid factor.

B. Arthritis in Patients who have Psoriasis (16)

Psoriasis occurs in the general population in an incidence which varies from 0.2 to 3.0% with most series suggesting about 1% of Caucasians affected. Negroes (17), Japanese (18) and American Indians (19) have psoriasis much less frequently than other races, and Egyptians have an incidence of 3%.

The incidence of polyarthritis in patients with psoriasis varies from 7 to 15%. Since the random incidence of rheumatoid arthritis in the general population is 3 to 5% (20), this suggests that 60 to 70% of the arthritis in the psoriasis patient group is not a mere chance association of the two diseases, or that psoriasis predisposes the patient in some way to rheumatoid arthritis.

IV. Etiology

A. Possibility of Genetic basis--Table II. (From Wright, Ref. 3)

PERCENTAGE FAMILY HISTORY OF RHEUMATIC COMPLAINTS AND PSORIASIS

Group	No. of Patients	Percentage of Family History			
		Psoriasis	Rheumatoid Arthritis	Muscular Rheumatism	Psoriatic Arthritis
Distal Joint	22	50	14	45	4
Deformed	10	40	0	10	30
Indistinguishable	66	24	12	27	6
Coincidental rheumatoid	20	35	10	50	5
Uncomplicated rheumatoid	95	2	24	29	0
Uncomplicated psoriasis	85	33	6	20	2

The high population frequency of psoriasis, and the lower first-degree relative frequency do not accord with a simple genetic explanation, or even one involving two recessive genes (21). It is possible that two or more forms of inheritance exist (22). In selected large family studies, an autosomal dominant inheritance has been inferred (23), but comparison of the large number of good studies by competent geneticists would suggest that "genetically speaking, psoriasis may show as much variety as (p)sin" (24).

B. Inciting Factors--The Koebner ('isomorphic') phenomenon--

Psoriasis is one of a limited number of diseases exhibiting the developmentof the 'type reaction' at the site of irritation, injury, operation wound, sunburn, vaccination or pre-existing disease (2, 25). Not present at all times in an individual patient, this phenomenon occurs in 47% of patients with psoriasis at some time during the course of their disease (26), usually appearing 8-10 days after injury, but occasionally as soon as 3 days or as long as 18 days. The psoriatic 'lesion' is preceded by capillary dilatation at the site. Therapeutic procedures overzealously undertaken (27) auto or industrial accidents (26) a variety of unrelated drugs (28, 29) or rarely just scratching may flare or initiate psoriasis in a susceptible individual. This phenomenon has considerable medico-legal implications for obvious reasons.

The important question which may be raised in psoriatic arthropathy is whether the Koebner phenomenon occurs in the synovium, and thus precipitates an inflammatory response in a joint minimally irritated by trauma, mild rheumatoid arthritis or Reiter's disease.

C. Histological and Biochemical Studies--Studies of DNA (30) and protein synthesis (31) rates by psoriatic skin compared to that of skin from normal subjects has shown up to 7-fold greater turnover in psoriasis. The granular layer of the skinis not established and more immature epidermal cells are thrust into the keratin layer. The significant differences in enzyme content of psoriatic skin compared to normal are probably related to this acceleration of epidermal synthesis although an etiologic significance may ultimately be established for these changes (32, 33).

Placing patients with psoriasis on a low-protein diet (34), especially one low in tryptophan (35, 36) may produce marked improvement, especially in mildly involved patients. Rapidly dividing skin cells are probably more sensitive to selective amino acid deprivation than non-dividing cells elsewhere in the body.

Diets high in taurine cause worsening of skin lesions, and taurine is concentrated by psoriatic skin and excreted less rapidly in the urine in psoriatic patients than in normal (37).

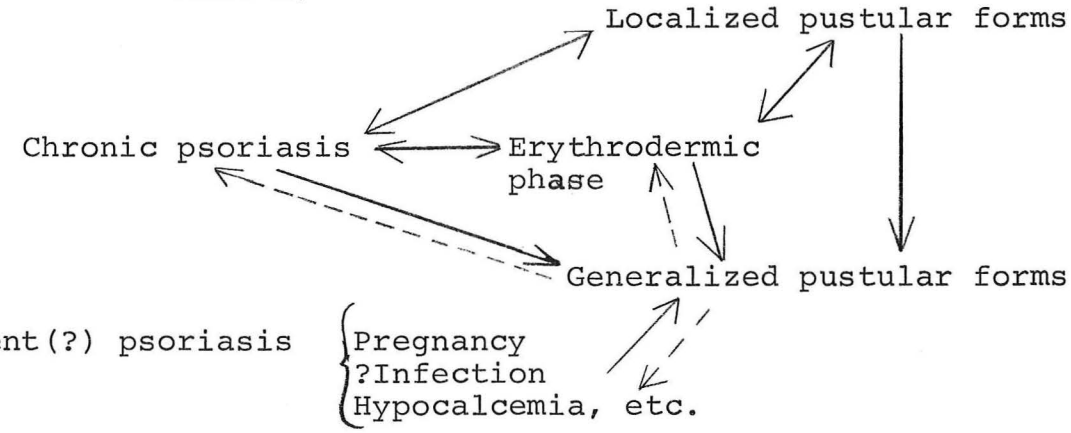
D. Associated Conditions Worsening or Improving Psoriasis--The following make psoriasis worse: post partum state (2), hypoparathyroidism (38). Hypocalcemia is occasionally seen in pustular psoriasis. The following make it better: Pregnancy (2), measles (2), ultraviolet light exposure in moderate amounts (27).

Malabsorption occurs in psoriasis? 20 intestinal lesion

V. Pathology

A. Skin Changes. Depending upon the relative proportion of microabscess formation and keratinization, and the deeper, erythematous changes which are present, psoriasis may be termed "chronic," "pustular" or "erythrodermic." The latter two forms are transitional phases which are usually more widespread and potentially dangerous to the patient, and are more frequently associated with deforming arthritis (2).

Fig. 1. Relationship between Varieties of Psoriasis (from Wilkinson, Ref. 2)



Histopathologically, all of these forms share the characteristic changes of closely-set micropustules in the upper part of the epidermis, elongation and clubbing of the rete ridges, acanthosis, a reduced or absent granular layer and (usually, but not always) hyper- and parakeratosis of the keratin layer. Lymphocytic infiltration and significant edema of the papillae are believed to be secondary changes which are usually seen (39, 40).

The twisting of the capillary loops in the dermis has been compared to the curled filament of an Edison electric bulb. The cutaneous neural elements show invasion of the epidermis by axons, Schwann cells and perineural cells. These capillary and neural element changes are said to be present in clinically normal appearing skin from psoriatics and absent from the skin of normal control subjects (41, 42, 43).

B. Synovial Changes in Psoriatic Arthritis (44, 45). In most instances, the chronic synovitis seen in psoriatic arthritis is no different from that of rheumatoid arthritis with thickened synovial lining layer cells, villous proliferation of deeper vessels and dense infiltration of perivascular areas with lymphocytes and plasma cells. However, in occasional patients with DIP joint involvement, dense acellular fibrous tissue with few inflammatory changes replaces the joint space, and adjacent bone may show increased calcification rather than the atrophic osteoporosis usually noted in rheumatoid arthritis. In addition, some patients show extensive destruction of adjacent bone accounting for the "gnawing or whittling away" of the bone shaft seen in x-rays of these patients, and the "opera glass" deformity of the fingers seen in late stages of uncontrolled disease.

C. Radiographic Signs--Early radiographic changes in psoriatic arthritis resemble those of rheumatoid arthritis with cortical bony erosions, narrowing of the joint space and adjacent osteoporosis around involved joints.

Distinguishing characteristics may ultimately appear (46, 47):

1. DIP joint involvement with resorption of terminal phalanges (whittling), bony ankylosis of the interphalangeal joints, or severe osteolysis progressing to extensive disability.

2. Bony proliferation at the base of the phalanges at the site of tendon insertions with sharply demarcated bone erosions of the interphalangeal joints of the hallux. Destruction of bone of the interphalangeal joints of the hands and feet may eventually produce wide joint spaces.

3. Extensive bone resorption include the shafts of the hand bones may give rise to the opera-glass hand with shortening of the fingers almost to the base of the wrist.

4. Sacro-iliac erosions, sclerosis and ankylosis may occur in 10 to 30% of patients with psoriatic arthritis, and are seen in more than half of the patients with the deforming type of disease.

5. Cervical apophyseal sclerosis, erosions and spinal ligamentous calcifications are seen in psoriatic arthritis and form a "variant" form of ankylosing spondylitis.

VI. Treatment

A. Conventional, Conservative Management--Because the skin and joints usually flare and subside synchronously, and measures which improve the skin suppress the arthritis, attention should be given to control of the skin lesions. Once completely free of rash, the patient may go many months or years without a recurrence (27), and require no therapy.

1. Goeckerman Regimen (Tar and UV light [48]). This is believed to be the safest, dirtiest, most effective treatment for extensive psoriasis. An ointment is applied to the skin surface morning and night containing 5% coal or wood tar, 25% starch and a washable ointment base. Each morning, the patient is de-tarred with mineral oil and bathed carefully to remove the oil and any residual scale. Then sufficient UV light exposure with the eyes shielded is given to produce mild erythema, more tar is applied and the whole procedure repeated until the psoriasis gives up and goes away. Thick plaques are given extra exposure to UV light and the patient continues to seek sun or sunlamp exposure at home. Tar is renewed if new lesions appear. If arthritis is present, analgesics such as aspirin and Darvon may be given (1). Chloroquin or related compounds should be avoided (28), and gold thiomalate has been of little value, and may cause a skin rash due to drug sensitivity (1).

2. Anthralin and Related Compounds. Colorless derivatives of coal tar believed to contain the essential active ingredient have replaced crude tar and may be equally beneficial although there is some disagreement on the latter point among dermatologists (49, 50, 51). It should be used with UV light applications as above.

3. Topical, Intradermal and Parenteral Triamcinolone. For more localized lesions this steroid appears to have a selective advantage over other steroids, and may give dramatic clearing when initially used. However, a two-year trial in 17 patients with psoriasis and arthritis (52) concluded that improvement was only transient in spite of continued therapy, and that cessation of the drug often produced a more extensive relapse.

B. Antimetabolic Drugs for Refractory Psoriasis and/or Psoriatic Arthritis

1. Methotrexate in oral dosage of 25 mg every 7 to 10 days (53, 54) or parenteral dosage of 0.5 to 3 mg/kg of body weight (55, 56) have produced impressive improvement in both skin lesions and arthritis in very severely involved, refractory psoriasis and/or psoriatic arthropathy in more than 60% of patients. The effect is present in 2 to 3 weeks after initiation of therapy, and when remission has occurred lasts from 2 weeks to 17 months (55). All potential recipients should be screened in advance for hepatic or renal abnormalities, incipient infection or peptic ulcer disease. The mechanism of action of this drug (57) and its immunological effects (58, 59) are well known.

2. 6-Mercaptopurine in oral daily dosage of 0.3 to 1.5 mg/kg of body weight also produces remissions in refractory psoriasis. Our own results (60) and that of others (61) suggest that about 70% of patients respond dramatically within a few days to therapy. Advance screening for liver disease,

incipient infection or peptic ulcer disease should be done before beginning therapy.

Table III. THERAPY OF PSORIATIC ARTHRITIS WITH 6-MP (From Baum et al, Ref. 60)

Patient	Onset of Improvement After Starting 6-MP (Days)	Duration of Improvement After Stopping 6-MP (Months)
[redacted]	14 20 14	2
[redacted]	14 7 5	2
[redacted]	5	9
[redacted]	21	2
[redacted]	11	-
[redacted]	5	-
[redacted]	7	-

3. Comparison of the Two Drugs. Of the two agents, methotrexate appears to be the more toxic at the dosage range necessary to achieve a therapeutic effect. Both 6-MP (62) and methotrexate (63) produce or activate liver injury, and BSP and SGOT determinations should be done before and during their use. Patients with psoriasis appear to be more susceptible to immunologic suppression by cytotoxic drug therapy than normals (64), and in the case of methotrexate about 1% of patients died of systemic infections within a few weeks of beginning therapy (54). Both drugs decrease cellular proliferation, but probably not sufficiently to produce major impairment of antibody production in most patients. Recent work by Hurd and Ziff (65, 66) suggest that the effect of 6-MP, when given in the above dosage range, is more anti-inflammatory than immunosuppressive.

4. Observed Toxicity to Methotrexate and 6-MP

Methotrexate

- Infections, often fatal pneumonia (54)
- Fetal malformation (67)
- Renal toxicity (68)
- Megaloblastic anemia (69)
- Leukopenia, thrombocytopenia and anemia (54)
- Gout (70)
- Liver toxicity followed by cirrhosis (63)
- Peptic ulcer (54)

6-MP

- Leukopenia, thrombocytopenia and anemia (60)
- Liver toxicity (62)

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