THERAPY OF MYCOSIS FUNGOIDES WITH TOPICALLY APPLIED FLUOCINOLONE ACETONIDE UNDER OCCLUSIVE DRESSING

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The effects of topical fluocinolone therapy on the lesions of mycosis fungoides were evaluated in 6 patients. Concentrations of fluocinolone 0.01 to 0.2% beneath occlusive plastic film were used. Pre- and post-treatment histological studies were carried out. Treatment was effective in modifying lesions both clinically and microscopically. The degree of improvement appeared proportionately related to the concentration used. No serious side effects were observed. Improvement was noted for as long as 9 months when therapy was continued.

THE MANAGEMENT OF MYCOSIS FUNGOIDES has been difficult because the only types of treatment effective in controlling the lesions carry the threat of serious side effects or have limited applicability. Radiation therapy may resolve lesions and may even produce a total remission when used over the entire body surface in the form of the electron beam.[1, 11] However, recurrences are the rule and few cases of this persistent disease can be handled indefinitely with this therapeutic modality. Thus, there is need for additional control measures, particularly for patients who have received extensive irradiation.

During an investigation of possible means of reducing the skin reaction produced by electron-beam therapy in patients with mycosis fungoides, we noted that several patients treated topically with a concentrated preparation of fluocinolone acetonide exhibited an unusually rapid involution of lesions.

Following this lead, local treatment with fluocinolone has been given to 6 patients with mycosis fungoides and in all instances there has been pronounced regression of the treated lesions. Eczematous lesions and plaques have responded equally well. The influence of this form of therapy upon the tumor stage of the disease is a subject of continuing study.

Although resolution of some lymphomatous lesions has been reported after systemic steroid therapy[7] and involution of lesions of mycosis fungoides has resulted in some instances,[2, 9] it has been necessary to use large doses, with the danger of undesirable side effects. Three case reports[5, 6, 8] have suggested a specific beneficial effect upon lesions of mycosis fungoides induced by local injections of corticosteroid preparations. We have found one documented case report[3] of the successful use of topical steroid therapy in causing regression of the lesions of mycosis fungoides. Scholtz et al.[10] made the statement that such therapy is palliative in some stages. Marmelzat[8] reported a failure of this treatment.

MATERIALS AND METHODS

Fluocinolone acetonide cream in strengths varying from 0.01 to 0.2% was applied under plastic film occlusion from 12 to 24 hours daily. Where applicable, isolated areas were treated in this manner; occlusion of greater than 50% of body area was used in 3 cases. At first the cream was applied daily; the intervals between treatments were increased as improvement became apparent. There was no attempt selectively to choose one concentration of steroid over another. However, as improvement occurred with the use of the stronger concentrations, less concentrated preparations were substituted in several instances. A skin biopsy was performed in each case immediately before treatment and another from a comparable nearby area was performed after the treatment had produced gross changes in the skin.

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In 2 cases, after a treatment period, tissue specimens for comparison were obtained at the same time from treated and untreated areas.

CASE REPORTS

Case 1 (11-55-90). A 67-year-old Caucasian male had a 5-year history of a generalized scaling pruritic eruption. Mycosis fungoides first was diagnosed by cutaneous biopsy in April 1963. In May 1963 the patient received 1,200 rads (total body dose) by electron beam therapy. Erythema was reduced but pruritus and dryness persisted. He was hospitalized in July 1964 for 2 weeks because of an increase in pruritus, scaling and erythema. Generalized lymphadenopathy was present. Lymph node biopsy was interpreted as probable Hodgkin's paragranuloma. The patient's trunk and extremities were treated alternately at night with 0.025% fluocinolone acetonide cream beneath pliable plastic film. After 3 days of treatment considerable clinical improvement was noted. Upon discharge from the hospital, pruritus had disappeared; skin texture was smooth and erythema had resolved. During 4 months of observation the skin remained clinically normal with the use of 0.025% fluocinolone acetonide and occlusion once weekly. This regime was continued the last 2 months of 1964 but treatment was discontinued during January and February 1965, during which time the patient noticed new lesions. When seen on March 1, 1965, the patient exhibited recurrent erythema and scaling in the bathing trunk region. Biopsy showed a recurrence of mycosis fungoides. Therapy was renewed with 0.01% steroid cream 3 times weekly.

On April 1 previously erythematous areas had only residual scaling. The skin of the extremities appeared slightly atrophic.

Case 2 (14-56-34). A 52-year-old Caucasian female with a history of chronic dermatitis was found to have mycosis fungoides in 1948. Multiple forms of treatment, including Grenz and superficial x-ray, cyclophosphamide* and electronbeam therapy, produced remissions lasting several months. The patient developed extensive violacous papules and plaques in the summer of 1964. She was hospitalized for 10 days in August 1964, when nightly occlusion with 0.025% fluocinolone acetonide cream caused almost complete resolution of the lesions. Upon discharge the patient continued daily occlusive therapy with varying strengths of the steroid preparation (up to 0.1%) for 5 weeks, using an approximate total of 300 mg of fluocinolone to 30 to 60% body area. When seen again, all lesions had regressed except for a faint residual erythema of the arms. Increased fullness of the face was noted; blood pressure was normal and there was no change in weight. There was a recurrence of lesions within 2 weeks after substituting 0.025% fluocinolone cream. The patient was hospitalized again for 13 days in January 1965. A 2-hour postprandial blood sugar was normal. Occlusive therapy with 0.2% fluocinolone to an average of 60% body area again produced a remission. Lesions recurred when therapy was discontinued but remission recurred when .025% steroid was used. Blood pressure and weight remained stable. On April 12, 1965 there was only residual erythema at the sites of former plaques.

Case 3 (18-16-08). A 38-year-old Caucasian male presented with chronic exudative dermatitis of the face, ears, perineum, hands and chest of 5 years duration. He had received x-ray therapy to the hands with good results. Several courses of systemic steroids had improved the dermatitis. He was hospitalized for 11 days in September 1964 with 2 persistent dry lichenified plaques of dermatitis on the chest and right forearm. Biopsy of the forearm lesions showed mycosis fungoides.

Occlusive therapy with 0.025% fluocinolone acetonide cream was carriod out for 2 nightly periods. There was dramatic resolution of the lesions during a 3-day period of observation. The patient did not return for follow-up.

Case 4 (14-62-09). A 68-year-old Caucasian female had generalized exfoliative erythroderma for 2 years. Treatment with systemic steroids, methotrexate and nitrogen mustard was of limited benefit. When the patient was hospitalized in September 1964, exfoliative erythroderma, generalized lymphadenopathy and hepatomegaly were noted. White blood count was 18,000 with 78% mononuclear cells, many of which had folded nuclei and vacuolated cytoplasm (Sezary cells). Liver biopsy showed mild fatty infiltration. A diagnosis of mycosis fungoides was confirmed by skin biopsy.

Electron-beam therapy was begun late in September. Simultaneously occlusion with 0.01% fluocinolone acetonide beneath plastic film was carried out nightly to the arms. Three weeks later there was marked increase in pruritus, erythema and induration in all areas except the arms which were white and normal-appearing.

The patient was hospitalized again in late October, when 70% body occlusion with 0.1% fluocinolone acetonide (20 mg fluocinolone) led to dramatic overnight blanching of the skin and decreased induration. Immediate post-treatment 24-hour urine values for 17-keto

* Cytoxan, Mead Johnson and Laboratories, Evansville, Ind.

steroids and 17 hydroxycorticosteroids were 2.4 mg and 1.1 mg, respectively. No pretreatment values were obtained. WBC increased to 24,300, with 84% mononuclear cells. Therapy with 0.1% steroid cream with occlusion to 50 to 70% body area was continued until November 12 (a total of approximately 100 mg fluocinolone), with continued improvement of the skin. There was no weight gain or increase in blood pressure. Electron-beam therapy was completed on November 12, with a total dose of 1,200 rads. During the next 2 weeks erythema and telangiectasia increased despite continued occlusive therapy. Blistering of the feet developed. Some of the cutaneous changes were consistent with radiation injury but clinical evidence of recurrence of mycosis fungoides appeared within a few weeks. The patient continued a progressive downhill course, developing widespread tumors and plaques, despite continued occlusive therapy with weaker concentrations of topical steroids and the systemic administration of cytotoxic agents and corticosteroids.

Case 5 (02-68-58). A 38-year-old male developed dry skin in 1956. Gradually annular macular lesions with eczematization evolved on the anterior thighs. Biopsy in March 1961 was diagnostic of mycosis fungoides. Eight hundred rads of irradiation from the electron beam were given in April 1961 with gradual fading of lesions. Recurrence of scattered plaques on the back, anterior thighs and groin occurred in September 1963. An additional 400 rads were given in November 1964, with only minimal effect. Biopsy from the left inguinal region in January 1964 showed a lesion characteristic of mycosis fungoides.

Progression of the disease occurred, with development of thick indurated plaques in the groin and annular plaques on the buttocks. On November 23, 1964 0.1% fluocinolone acetonide with occlusion was initiated in both inguinal regions with striking flattening of the lesions after 2 weeks. Approximately 20 mg of fluocinolone was used. There was no change in weight. Therapy was continued intermittantly with varying concentrations of fluocinolone acetonide. When last seen in April 1965, the patient exhibited faint erythema and scaling in affected areas but no induration.

Case 6 (18-74-42). A 51-year-old Caucasian female had a one year history of a pruritic erythematous scaling eruption beginning on the thighs with gradual spread to the scalp, face, legs, arms and trunk. Previous therapy with the weaker concentrations of fluocinolone, without occlusion, was without benefit. There was improvement during the summer of 1964 in the light exposed areas (Fig. 1).

On January 7, 1965 there were indurated erythematous plaques with scaling on the trunk, buttocks, legs, arms and face. The second and third fingernails bilaterally showed distal onycholysis. Shotty cervical, submandibular and left inguinal nodes were palpable. The liver was palpable but not enlarged. Laboratory data included the following: WBC —9,000; PMN's—68; L—20; M—11; E—1; Hct—42; Hg—13.3 Gm; chest film—normal.

Biopsy findings were diagnostic of mycosis fungoides. For 12 days 0.2% fluocinolone acetonide beneath plastic film occlusion was applied to the abdomen and low back (18% body area), with dramatic resolution of plaques in the areas treated. A total of 60 mg fluocinolone was applied during this period. No change in blood pressure or weight was recorded. Generalized improvement was characterized by decrease in pruritus and fading of erythema in plaques outside the treatment area.

Following one week (January 26 to February 2, 1965) in which no therapy was used, no lesions reappeared in the previously treated area; there was an exacerbation characterized by erythema, induration and pruritus in the untreated areas.

Intermittent treatment with 0.2% fluocinolone acetonide and occlusion to the previously untreated regions was continued for 3 months, with improvement. Reduction of the concentration of fluocinolone acetonide to 0.025% was unsuccessful in controlling the disease; however, the originally treated area on the abdomen and back received no therapy after January 26, 1965, yet remained entirely clear during a 3-month observation period.

RESULTS

Clinical observations: All of the cases showed improvement with the use of fluocinolone therapy under occlusive dressings. While treatment with the stronger concentrations produced a quicker and more dramatic response, concentrations of 0.01% and 0.025% also had an effect in 4 cases. Fading of erythema and decrease in induration sometimes were noted after only one treatment. Improvement was sustained in the majority of cases for 6 weeks to 6 months of treatment. There is no follow-up on case 3. Case 1 remained improved with occlusive therapy used 3 times weekly; however, case 2 had prompt recurrence when this method of maintenance was attempted. Case 4 pursued a progressively down-hill course despite the continuation of therapy.

The presence of moon facies in case 2 sug-

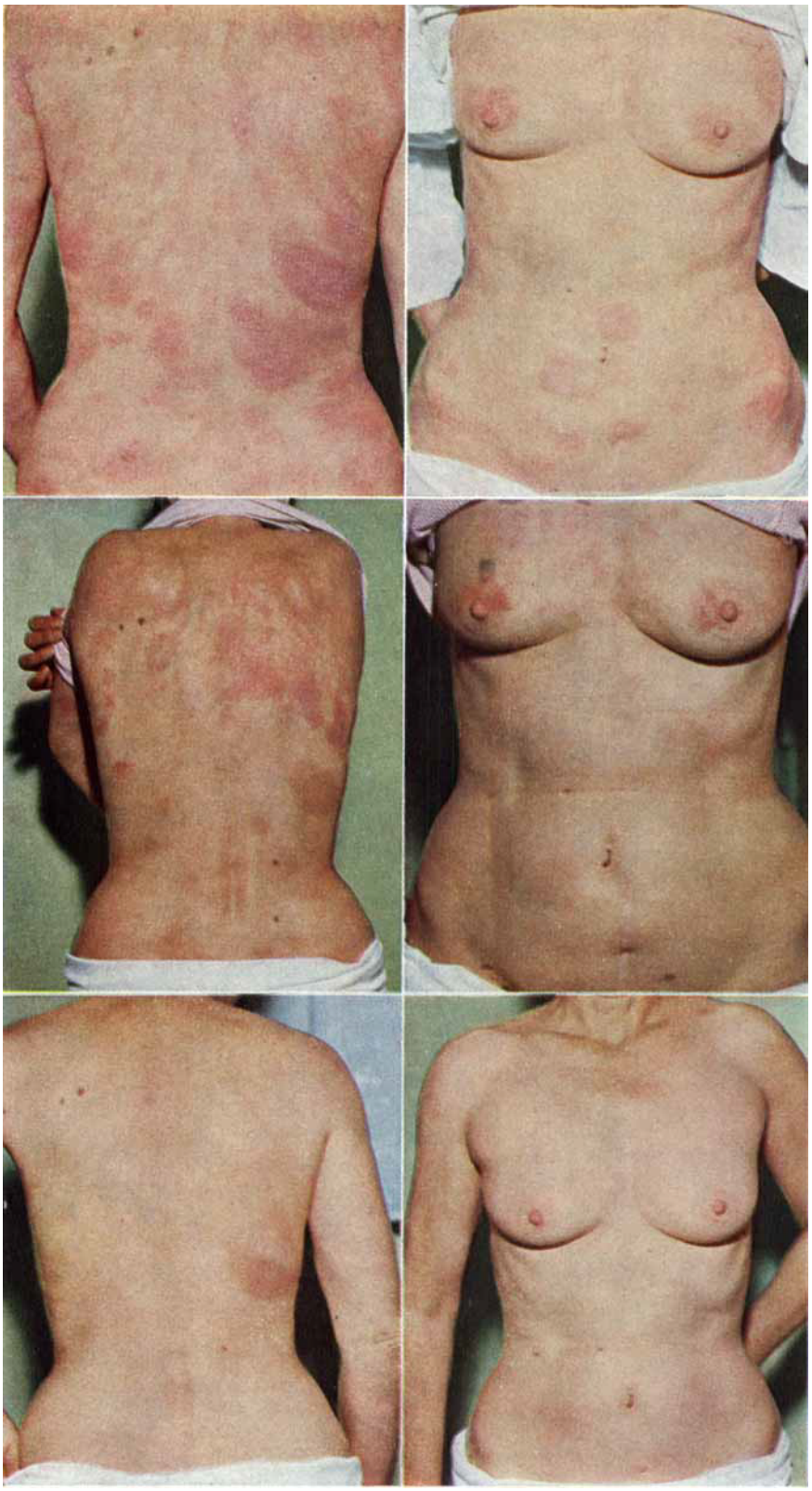


FIG. 1. Clinical photographs of case 6. A and B, pretreatment photographs of back and anterior trunk. Plaques are easily seen. C and D, 2½ weeks following initiation of daily occlusive therapy with 0.2% fluocinolone acetonide to the lower trunk. There is complete clearing of the treated areas, with some improvement of untreated areas. E and F, 3 months following commencement of therapy. All areas received intermittent occlusion with 0.2% fluocinolone acetonide except the lower trunk, which remained untreated for 2½ months.

gested fluocinolone induced hypercorticism although blood pressure and weight remained stable and a subsequent 2-hour postprandial blood sugar was normal. She had applied approximately 300 mg of fluocinolone topically during 5 weeks to 30 to 60% body area. Uncontrolled isolated 24-hour urine determinations of 17-keto and hydroxycorticosteroids were depressed in case 4, following the topical application of 30 mg of fluocinolone to 70% of the body area; there was no clinical evidence of hypercorticism. Following 12 days of application of a total of 60 mg of fluocinolone to 18% body area in case 6, there was improvement of untreated control areas. In case 4, a patient who received whole-body electron-beam irradiation during the period of steroid therapy, improvement was restricted only to the chemically treated and occluded areas, suggesting that the steroid cream and not the electron beam alone was responsible for the change.

Histological studies: A clear identification of highly atypical large mononuclear cells has been required as a prerequisite for the initial diagnosis of mycosis fungoides. The most distinctive feature of such cells is their presence within the epidermis in clusters, the so-called Pautrier microabscesses. All of the cases exhibited this sign, as well as patches of more diffuse infiltration of the epidermis by atypical large mononuclear cells. Other features of mycosis fungoides that were encountered in all of the cases were scattered abnormally large mononuclear cells in the upper dermis, a polymorphous inflammatory infiltrate concentrated near the epidermis but always penetrating at some point to the mid-dermis or deeper, epidermal stimulation resulting in acanthosis. The histological diagnosis of mycosis fungoides was considered unequivocal in each case.

In 4 of the cases a post-treatment biopsy specimen was removed from the same region as the first specimen. In 2 cases 2 specimens were obtained in the post-treatment period, one from an untreated plaque and the other from a treated lesion that initially had the same gross appearance as its control.

The appearance of the treated lesions, examined from 3 days to 3 months after the onset of steroid therapy, was clearly improved in every case. The amount of cellular infiltrate was much reduced and not only were inflammatory cells less numerous but the abnormal presumably neoplastic mononuclear cells also were decreased greatly (Fig. 2–7). Pautrier abscesses were no longer present and other intraepidermal tumor cells were not visible. The epidermis was reduced in thickness, and in 2 cases it was abnormally thin, with almost absent rete projections (Fig. 7). Mycosis fungoides could not be recognized in any of the post-treatment biopsy specimens. Although a few mononuclear cells were present, appearance was that of mild chronic inflammation.

COMMENT

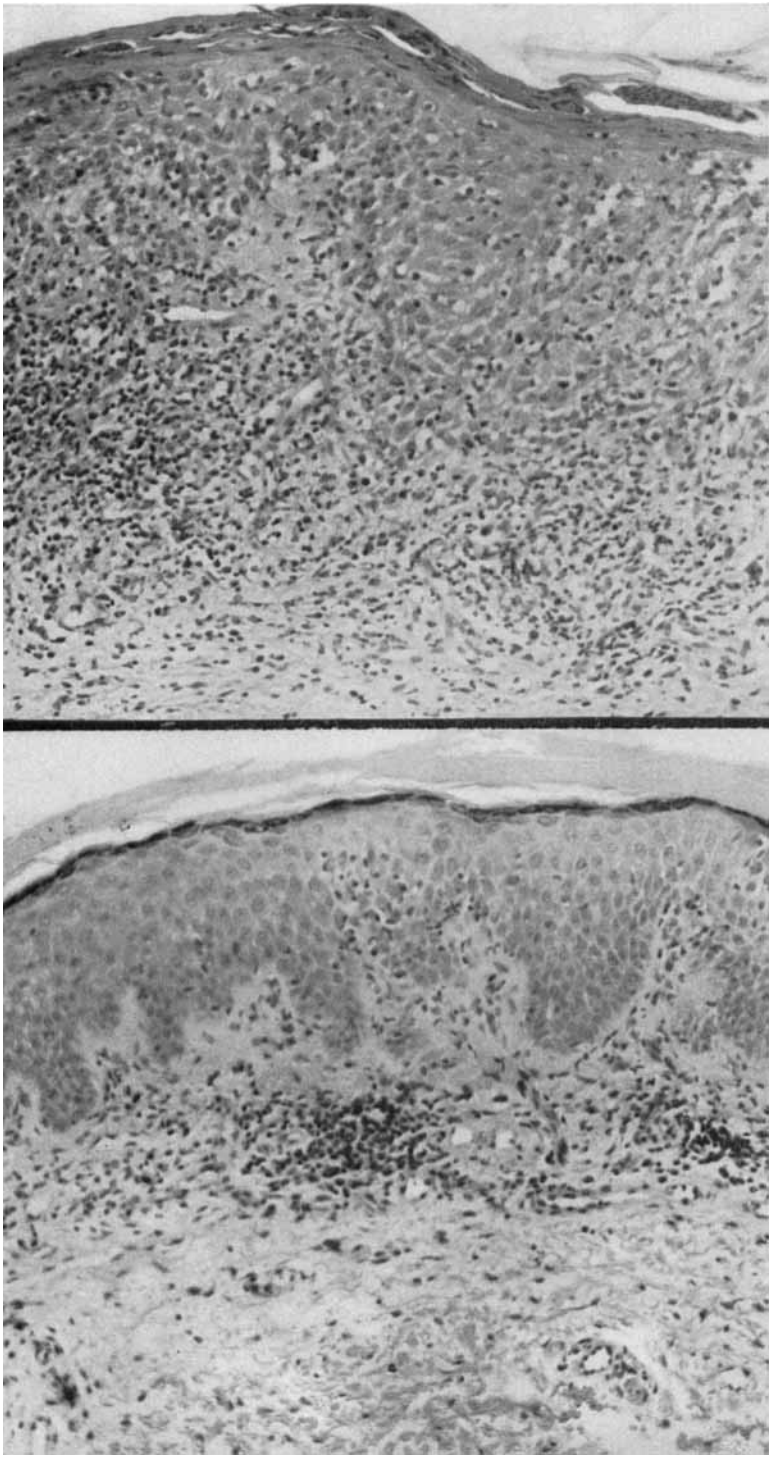
The mechanism of action of the fluocinolone acetonide in inducing regression of the lesions of mycosis fungoides is unknown. The almost immediate reduction of erythema might be accounted for by a vasoconstrictor effect of the drug. However, the decrease in induration and "melting away" of the plaques was clearly more than a vascular effect. The disappearance of the inflammatory infiltrate may correspond to the anti-inflammatory effect of steroids under other conditions. The decrease in abnormal mononuclear cells suggests an additional cytotoxic influence. It appears that in 5 of the 6 cases the effect was local and not mediated through systemic steroid absorption since the treated areas improved while untreated areas remained unchanged.

The significance of the epidermal atrophy in 2 treated lesions is uncertain inasmuch as both of these patients had received electron-beam therapy prior to the application of the steroid preparation. Although a control specimen in one of the cases from an area treated by irradiation alone showed no atrophy, there is a possibility that the epidermal changes reflected some synergistic effect of the 2 agents. The influence of the steroid upon the infiltrated cells occurred equally in irradiated and nonirradiated cases so this clearly did not require associated irradiation. Case 6 had never had any irradiation therapy.

While it is unlikely that any cases of mycosis fungoides will be cured with local steroid application, there is an important place for this method of therapy in the palliation of this disease in the erythematous, eczematous or plaque forms. Areas of relapse after electron-beam therapy may be treated in this manner.

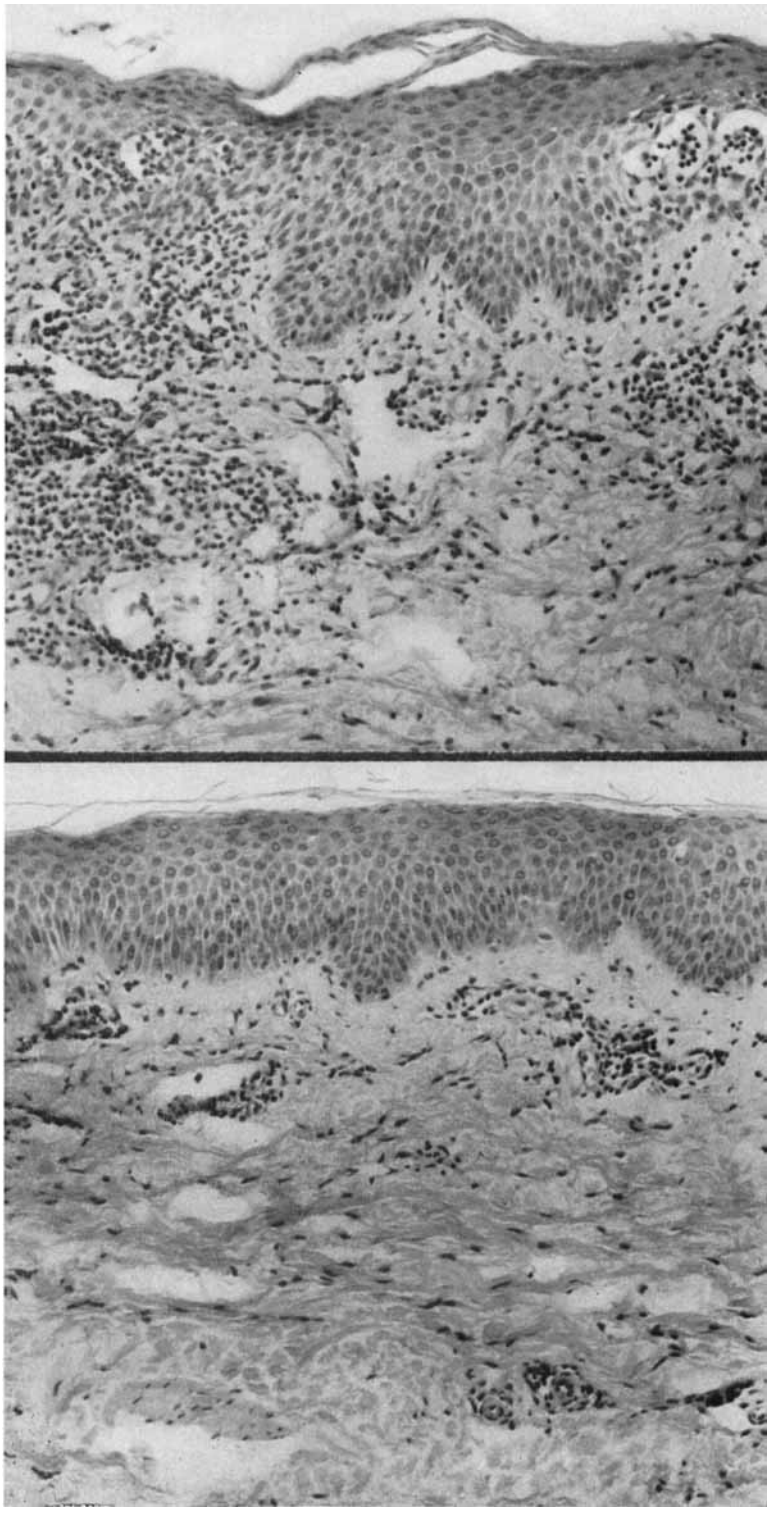
Application of fluocinolone acetonide with occlusion over large body areas in patients with psoriasis has been shown to depress urinary 17-keto and 17 hydroxycorticosteroids temporarily.[4] Our uncontrolled observation in

case 4 suggests this might also be the case in patients with mycosis fungoides. The clinical suggestion of hypercorticism in case 2 following an average daily use of 8.6 mg fluocinolone topically was not supported by blood pressure elevation, weight gain or subsequent 2-hour postprandial blood sugar determination. Case 6 did show evidence of systemic absorption while using an average of 5 mg of fluocinolone daily to 18% of the body area. The full



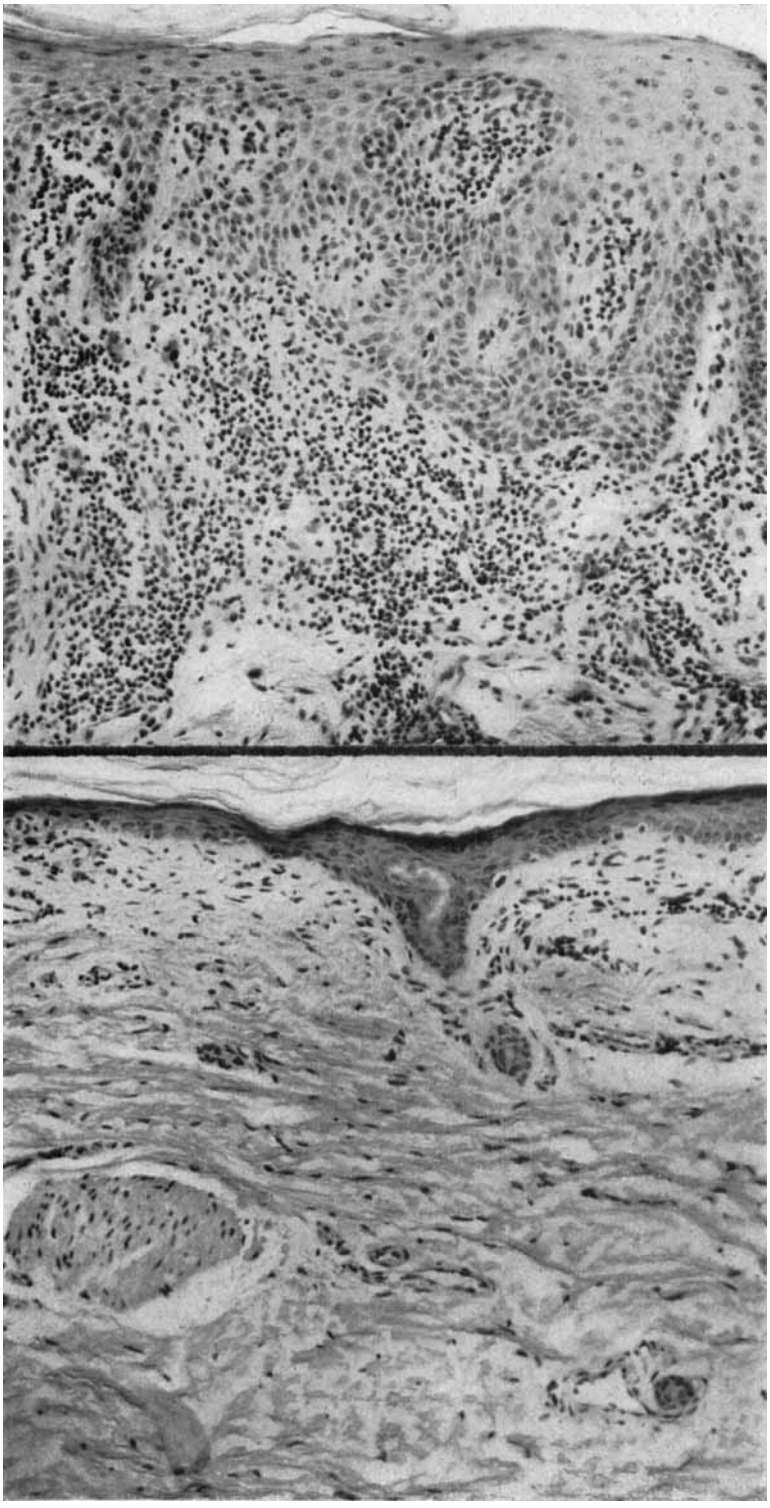
FIGS. 2 and 3. Case 2 before and after therapy. Extensive epidermal infiltrate before treatment (top) had disappeared prior to the post-treatment biopsy (bottom). Some mononuclear infiltration of the corium remained but this no longer contained atypical cells (H. and E., ×150).

clinical significance of side effects from systemically absorbed topical fluocinolone has yet to be determined as does the development of local cutaneous atrophy. Careful control and follow-up of patients undergoing this therapy are necessary when the dose of fluocinolone approaches 5 mg per day. The management of each patient will be an individual problem.



FIGS. 4 and 5. Case 3 before and after therapy. Prominent Pautrier microabscesses (top) were not seen in the specimen removed 5 days later from the same region (bottom). The dermal infiltrate was much reduced following therapy (H. and E., ×150).

Some patients may require highly concentrated fluocinolone preparations. Others may respond to weaker concentrations. After an initial response is obtained, occlusion of selected areas once or twice weekly may suffice for the maintenance of improvement.



FIGS. 6 and 7. Case 4 before and after therapy. In addition to pronounced diminution in the cutaneous infiltrate after therapy (bottom), there was marked epidermal atrophy (H. and E., ×150).

CONCLUSIONS

Topical fluocinolone acetonide in varying concentrations beneath occlusive plastic film dressings was effective in modifying the eczematous and plaque-like lesions of mycosis fungoides in 6 patients. Stronger concentrations appeared to give a more pronounced response. This effect has been observed to last up to 9 months when treatment was continued; longer follow-up studies have not yet been made.

Histologically, this therapy brought about dissolution of the inflammatory infiltrate in the lesions but also led to disappearance of large neoplastic cells from the lesions. This suggests a cytotoxic effect upon the tumor cells. Systemic effects from absorption of topically applied fluocinolone have been observed with doses of 5 mg per day or above.

There is an important place for this type of therapy in selected patients with mycosis fungoides.

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Symposium on Osteosarcoma

A 2-day Symposium on Osteosarcoma will be presented at the Ohio State University College of Medicine under the direction of the Division of Orthopaedics, on April 15-16, 1966. The faculty will consist of authorities in this field, among whom are Sir Stanford Cade, Dr. H. A. Sissons, Dr. David Dahlin, Dr. Harold Jacox, Dr. Kenneth Francis and Dr. Jonathan Cohen.

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