Psoriasis—Treatment

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For dermatologists who see patients with chronic psoriasis week after week it is difficult not to be pessimistic about present methods of treatment. There has been no major therapeutic advance in recent years, and dithranol (anthralin), coal tar, ultraviolet irradiation, and topical corticosteroids still comprise the standard methods of treatment, though they fall far short of the ideal. Nevertheless, psoriasis remains one of the major foci for the attention of both clinicians and experimentalists in dermatology, and both have recently made important contributions. This article will not provide a comprehensive guide to the treatment of psoriasis but rather outline new work that has appeared over the last few years in this field. This work has included re-examination of some of the traditional therapeutic methods as well as a search for new ones.

Dithranol

The use of dithranol was first fully documented by Ingram²⁰ and its effectiveness has been confirmed by several other workers.^{21–23} Seville substantiated the original claim that to obtain the best results the dithranol paste must be of stiff consistency.²² He found that the maximum effectiveness was achieved by adding 15% hard paraffin to the standard zinc and salicylic acid (Lassar's) paste *B.N.F.* used as a vehicle for the dithranol. An investigation of the importance of the individual components of this paste (starch, zinc oxide, salicylic acid, and paraffin) showed that the only role of the starch was to increase the stiffness of the paste.²⁵ Under some circumstances zinc oxide can actually impair effectiveness since it may form a therapeutically inert complex with dithranol. This reaction is, however, prevented by salicylic acid. These findings almost certainly explain the differing therapeutic results achieved by different workers using pastes of different composition and illustrate once more the importance of the actual composition of the base in dermatological preparations. Moreover, this work clearly indicates that the standard dithranol paste *B.N.F.* could be greatly improved by modification along these lines.

The manufacture of dithranol pastes usually requires special milling machinery. Nevertheless, dithranol can be satisfactorily dispersed within the paste by using chloroform as a solvent. This procedure will allow suitable dithranol paste to be manufactured in small quantities when specialized equipment is not available.

Exolan (triacetoxyanthracene) has been introduced to try to overcome some of the disadvantages of dithranol.²⁶ The claims that it produces less staining and burning of the skin are certainly true, but unfortunately it is considerably less effective than dithranol.²⁷ Despite this, it is surprising that there has been so little systematic investigation of other compounds related to dithranol.

Topical Corticosteroids

Topical corticosteroid preparations are still the most frequently prescribed therapy in psoriasis. Certainly they are convenient to use, but often they are ineffective. The choice of product is bewildering. Numerous comparative trials have been carried

out between different preparations, but many trials have often ignored the most relevant clinical problems. Any assessment of effectiveness implies not only a measurement of the frequency and rapidity with which the lesions can be cleared, but also of the frequency and rapidity with which they relapse again after treatment. Considering this point when comparing the effect of fluocinolone acetonide cream under occlusion with tar, Knudsen found a higher immediate relapse rate in the group treated with steroids, though the initial response was more rapid.²⁸ Comparisons between different steroid preparations have not usually included such data. Clearly there is insufficient evidence to suggest that any one preparation is better than another, and thus the choice is best made on the basis of individual experience and cost.

Many patients are unaware of the long-term hazards of the indiscriminate use of topical steroids. Dermal atrophy, due to loss of collagen, is perhaps the most important of these and to the formation of striae, telangiectasia, ecchymoses, and poor healing. Patients with these chronic changes in the skin are being seen with increasing frequency in dermatological clinics. The steroid may be absorbed systemically, particularly when large quantities of ointment are applied or if occlusive dressings are used.²⁹ This is particularly important in children, who have a large skin surface area in relation to their mass and in whom stunting of growth may be produced. Depression of pituitary adrenal function occurs commonly, but it is rarely of clinical importance. A Cushingoid appearance is occasionally produced.

Staphylococcal folliculitis and infection with streptococci and Gram-negative bacteria may be very troublesome short-term side effects of topical steroids.

Occlusive Therapy

Occlusive therapy with plastic or polyethylene not only enhances the clinical effect and the absorption of steroids through the skin, but it also increases the incidence and severity of all the side effects mentioned above. It is generally felt that rapid relapse is particularly common after this form of treatment, which in some cases may possibly provoke episodes of pustular psoriasis. Nevertheless, convincing data on both these important points are lacking.

For all these reasons occlusive therapy has become less popular recently, though it is valuable for treating resistant psoriasis on the hands and feet. In an attempt to increase steroid absorption without using occlusion Groel used dimethyl sulphoxide as a vehicle for triamcinolone acetonide.³⁰ The therapeutic results, however, were disappointing.

The effect of vitamin A on the skin, particularly in conditions characterized by epidermal hyperplasia and hyperkeratosis, has received considerable attention in the last few years.³¹ One study, using the method of paired comparisons, found that 0.1–0.3% vitamin A acid produced a greater improvement than the base alone in 24 out of 26 patients with psoriasis.³² Confirming this effect both clinically and histologically, Fry and his colleagues were optimistic about its role in treatment.³³ Nevertheless, the place of vitamin A in routine therapy remains to be established.

Systemic Treatment

The systemic approach to the treatment of psoriasis has taken several forms. Dietary therapy has its attraction in safety,

but this attraction is marred by its ineffectiveness to date. Investigators have often based their conclusions on the findings in only a few patients and have failed to take into account the unpredictable course of the untreated disease. Claims of a satisfactory response to a low-aurine diet³⁴ have been refuted,³⁵ while similar claims for a turkey meat diet—supposedly low in tryptophan³⁶—have not been substantiated. A low-protein diet³⁷ was found to be ineffective, as was also rapid weight reduction.³⁸ In our present state of ignorance dieting has nothing specific to offer the patient with psoriasis.

The occurrence of psoriasiform skin changes in zinc-deficient animals has led to an investigation of the role of zinc in patients with psoriasis. Greaves and Boyde³⁹ found diminished plasma zinc levels in patients with psoriasis, though this has been disputed.⁴⁰ Moreover, no improvement was noted when psoriatic patients were given oral zinc supplements.^{41 42}

SYSTEMIC CORTICOSTEROIDS

Systemic corticosteroids will suppress psoriasis. Unfortunately the effect is only temporary and the dose required is often comparatively high so that severe side effects frequently occur. The evidence of Ryan and Baker suggests that exacerbations may follow steroid withdrawal and episodes of generalized pustular psoriasis may be provoked.⁴³ However, the patients with whom they were concerned were initially a selected group of particularly severely affected psoriatics. Systemic steroids may have a small place in the treatment of erythrodermic or generalized pustular psoriasis, particularly in patients who have not responded to methotrexate. Apart from this, however, there are few—if any—other indications for their use in psoriasis.

FOLIC-ACID ANTAGONISTS

The rapid proliferation of the epidermis in psoriasis is somewhat analogous to cancer, and hence various drugs which were originally introduced for cancer chemotherapy have been tried in psoriasis. The folic-acid antagonists aminopterin and later methotrexate were the first of these agents and the latter has been extensively used. Undoubtedly, methotrexate is effective in suppressing psoriasis.⁴⁴ Many different dosage schedules have been evolved empirically. Weinstein and Frost have recently suggested a regimen of three doses at 12-hourly intervals which is repeated at weekly or longer intervals.⁴⁵ This schedule is based on evidence of the epidermal cell cycle time in psoriasis, and is claimed to have been effective in some patients who had not responded to more conventional methotrexate therapy.

Toxic effects of methotrexate such as leucopenia and oral ulceration have been recognized for many years. Unfortunately, liver damage (which is of insidious onset) has been reported with increasing frequency, while liver biopsy studies indicate that this may be a frequent complication of prolonged methotrexate therapy.^{46 47} In one study⁴⁴ the severity of liver damage was related to the duration of treatment. Nevertheless, most patients were treated by interrupted daily dosage—for example, 2.5 mg daily for five days each week—and there is evidence that larger single doses given at weekly or longer intervals are less toxic to the liver.

There are other important problems of renal and neurological toxicity as well as teratogenicity and immunosuppression when using methotrexate.⁴⁸ Patients should be most carefully selected and investigated (which includes a liver biopsy) before starting methotrexate. Careful follow-up is absolutely essential and periodical liver biopsy at intervals of six to twelve months has been suggested by many workers. An intermittent dosage schedule at weekly or longer intervals should be employed and the dose of drug used should be kept to a minimum. Every attempt should be made to discontinue treatment if possible.

OTHER ANTIMETABOLITES

Trials have been carried out with other antimetabolite drugs. Calabresi and Turner⁴⁹ used triacetyl azauridine, a pyrimidine antagonist, with favourable results, and their findings have recently been confirmed in a short-term double-blind trial.⁵⁰ Another drug used with some success was 6-mercaptopurine⁵¹ and there have been favourable reports on azathioprine.⁵²⁻⁵⁴ The alkylating agents cyclophosphamide⁵² and busulphan⁵⁵ have also been used in a few cases. The use of all these drugs, however, is likely to be limited by toxicity, the long-term effects of which are largely unknown.

Encouraging results have recently been claimed for the use of hydroxyurea in psoriasis.⁵⁶ This drug appears to be a specific inhibitor of DNA synthesis and it has been used for some years in the treatment of myeloid leukaemia. Toxic effects include depression of the bone marrow, teratogenicity, and impairment of renal function. Hepatotoxicity has not been reported, and the drug is claimed to be generally less toxic than methotrexate. Nevertheless, both its efficacy and its long-term safety in treating psoriasis remain to be confirmed.

Topical Antimetabolites

To avoid the systemic toxicity associated with all these antimetabolic drugs topical antimitotic therapy is a logical step and completes a full circle in the approach to treating psoriasis. The local interference with epidermal cell metabolism and mitosis which it is hoped to achieve with these agents is directly comparable to the effect of dithranol, which probably acts on nucleic acids.⁵⁷ The use of topical methotrexate has been investigated,^{58 59} but under the conditions used it was not found to be practical therapeutically. More encouraging are recent reports of the use of topical nitrogen mustard (mechlorethamine).^{60 61} This agent appears to have a definite beneficial effect in psoriasis but its use is at present limited by its instability in aqueous solution and by its liability to provoke allergic contact dermatitis.

Though chronic psoriasis is often a depressing condition for both patient and dermatologist, clearly therapeutic endeavour in this field is not stagnant. Inevitably, much work is unproductive, but it is reasonable to expect real progress soon. Perhaps at present topical cytotoxic drugs offer the most likely field of progress. More rational approaches to therapy await elucidation of the basic defects in the control of epidermal proliferation which characterize this condition.