Blood lactate concentrations—The mean fasting blood lactate concentrations were higher in patients taking hypoglycaemic tablets (table II). None of the drugs produced any significant fall in fasting blood lactate concentrations. During hypoglycaemia the control mean blood lactate concentration rose by 76% at 90 minutes in diet-treated subjects and by 67% in tablet-treated subjects. Acebutolol impaired this blood lactate response in tablet-treated subjects ($P < 0.05$) with a rise of only 33% at 90 minutes. Propranolol slightly reduced the incremental area of blood lactate response in diet-treated subjects ($P < 0.05$). Atenolol had no significant effects on blood lactate concentrations in either group.

Blood NEFA concentrations—All drugs significantly lowered fasting blood NEFA concentrations in diet-treated subjects, and acebutolol also lowered them in drug-treated subjects (table III). After intravenous insulin administration the blood NEFA concentrations fell in all groups. The placebo blood NEFA concentration fell by 56% at 30 minutes in drug-treated subjects, and by 52% at 30 minutes in diet-treated subjects. The secondary rise of blood NEFA concentrations from adrenaline-mediated lipolysis was reduced in acebutolol- and propranolol-treated diet-controlled subjects. No significant effects on blood NEFA concentrations were observed in the tablet-treated subjects.

Discussion

The results show that these beta-adrenoreceptor blocking drugs differ in their effects on the metabolic responses during insulin-induced hypoglycaemia, and this probably reflects differences in pharmacological selectivity and ancillary properties. Propranolol delayed glucose recovery, as it does in normal subjects. Acebutolol potentiated the hypoglycaemic action of insulin in drug-treated diabetics in a manner similar to that found in normal subjects.³ Throughout the recovery phase the mean blood glucose concentration remained on average 0.7 mmol/l (12.6 mg/100 ml) lower when patients were taking acebutolol than when they were taking placebo, the incremental area being identical with that for control and atenolol curves. This implies that the magnitude of the adrenaline-induced glycogenolytic response was unaffected but that acebutolol impaired hepatic glucose output in some other way.

The beta-adrenoreceptors of the liver and skeletal muscle are thought to be predominantly of the beta₂ type. Hence the beta₂

adrenoreceptor blockade of the non-selective drugs might be expected to antagonise adrenaline-mediated glycogenolysis whereas the beta₁-blocking drugs should have no such effect. Hepatic glycogenolysis may, however, also be stimulated directly by a low blood glucose concentration. Studies on liver preparations and exercising normal subjects have shown that drugs with a membrane-stabilising action inhibit glucose release from the liver in response to a low blood glucose concentration.^{8, 9} Thus propranolol, possessing this action, impaired postexercise recovery of the blood glucose, whereas metoprolol, without membrane-stabilising activity had no such effect. Acebutolol also possesses membrane-stabilising activity, which probably accounts for its effect on the blood glucose concentration during induction of hypoglycaemia. Furthermore, it is not entirely devoid of beta₂-blocking activity and this may also contribute to the hypoglycaemic effect. In contrast, atenolol, being beta₁ specific and devoid of a membrane-stabilising action, does not affect the metabolic responses to insulin-induced hypoglycaemia.

These findings therefore support the hypothesis that beta-adrenoreceptor blocking drugs which are highly beta₁ specific and devoid of membrane-stabilising activity should be safer than non-selective drugs when used in diabetic patients at risk of hypoglycaemia.

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Photochemotherapy in mycosis fungoides

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Summary

Six patients with mycosis fungoides were treated with methoxsalen and long-wave ultraviolet light. They were assessed clinically and histologically before and after treatment. All six patients showed clinical improvement.

Histological clearing of both epidermis and dermis occurred in three patients, and epidermal clearing alone occurred in two.

Photochemotherapy may have a place in the treatment of the early and intermediate stages of mycosis fungoides, and it may also be useful as an adjunct to other forms of treatment in the more advanced stages.

Introduction

Mycosis fungoides is a malignancy of T lymphocytes that predominantly affects the skin. Visceral involvement is not commonly recognised even in later stages, and many patients die of their disease without evidence of systemic disease.

Gilchrest *et al*¹ reported the efficacy of photochemotherapy with systemic psoralens and long-wave ultraviolet A light (PUVA) in nine patients with mycosis fungoides but confirmed this histologically in only one. Hjortshøj and Schmidt² reported

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two patients with tumid mycosis fungoides assessed histologically before and after PUVA treatment; one patient achieved complete remission. We report here our initial experience with six patients who were assessed both clinically and histologically.

Patients and methods

Six patients with histologically proved mycosis fungoides were studied (see table I). Previous treatment had included topical steroids in all cases, electron beam treatment in five, local x-ray treatment in four, oral corticosteroids in three (with azathioprine in one), and topical nitrogen mustard in one. Topical steroids alone had been used for three or more months before PUVA treatment.

TABLE I—Clinical data and clinical response to treatment

Case No	Sex	Age (years)	Duration of disease (years)	Stage before PUVA	Total exposure dose (J/cm ²)	Stage after PUVA
1	F	76	17	2	14.5	0
2	F	79	4	3	124	3
3	M	49	2	3	80	0
4	F	68	11	2	73	0
5	M	27	14	2	123	0
6	F	71	5	3	27.5	0

Treatment and investigation—Methoxsalen, 30–50 mg according to body weight, was given two hours before exposure to high-intensity long-wave ultraviolet light from a Waldmann PUVA 4000 apparatus using 40 Sylvania Lifeline FR90T12/PUVA/HO tubes for five patients; the sixth patient received ultraviolet light from a Dermatron unit. The patients were treated three times a week, with increasing exposure times as treatment progressed. A skin biopsy was performed immediately before the start of PUVA treatment, and another was performed when the lesions had disappeared clinically or when the clinical state appeared stable. On each occasion the size and site of the lesion were noted, and the second specimen was taken from within the same lesion as the first and adjacent to it. Treatment before the second biopsy lasted from two to six weeks.

Clinical staging—The staging of mycosis fungoides was based on clinical examination of the skin, lymph nodes, liver, and spleen. One patient (case 2) underwent liver biopsy, which gave negative findings; another (case 6) underwent lymphangiography, liver and spleen scan, and a sternal marrow biopsy before treatment, and again the findings were normal or negative. The stages were: stage 0—poikiloderma atrophicum vasculare; stage 1—plaque lesions; stage 2—infiltrated plaques; stage 3—nodular tumours; stage 4—histological lymph node involvement; stage 5—hepatic or splenic disease.

Histological assessment was performed independently by two observers who had no knowledge of the clinical state of the patient and whose findings were collated. "Mycosis fungoides cells" were recognised as atypical lymphoid cells with large, hyperchromatic nuclei; a crenated nuclear outline was not invariably discernible. An arbitrary scale was used to grade epidermal mycosis fungoides cell involvement, ranging from 0 (no cells) to ++++ (virtual replacement of epidermis by mycosis fungoides cells). The polymorphous dermal infiltrate was graded as 0 (no infiltrate), + (scattered focal infiltrate), ++ (loose band of infiltrate), +++ (dense band of infiltrate). Mycosis fungoides cells were recorded as present or absent from the dermal infiltrate.

Results

Clinical assessment—All patients showed improvement on treatment as judged by resolution of lesions or healing of ulcerated lesions, or both. Lesions in four patients apparently cleared completely, but this was confirmed histologically in only two of these four. Ulcerated lesions persisted on the soles of the feet in a fifth patient who was otherwise cleared clinically and who cleared histologically in the lesion examined. Nodular lesions persisted at six weeks in the final patient, although overlying ulceration healed. Therapeutic response judged by clinical staging is shown in table I.

Histological assessment—Histologically five of the six patients showed complete clearance of mycosis fungoides cells from the epidermis

(table II), while the remaining patient showed considerable improvement after three weeks' treatment. A similar but less pronounced trend was evident in the dermis: three patients showed complete clearance of mycosis fungoides cells, and in two of these the reticular dermis was affected before treatment (fig 1). Two of the remaining three patients showed some reduction in papillary infiltrate without clearance of the infiltrate containing mycosis fungoides cells (fig 2).

TABLE II—Presence of mycosis fungoides cells and density of polymorphous infiltrate before and after treatment

Case No	Epidermal mycosis fungoides cells		Dermal mycosis fungoides cells		Papillary dermal infiltrate		Reticular dermal infiltrate	
	Before	After	Before	After	Before	After	Before	After
1	+++	0	Yes	No	++	+	+	0
2	+++	0	Yes	Yes	+++	++	+++	+++
3	+++	0	Yes	No	+++	0	++	0
4	++	+	Yes	Yes	++	++	+	+
5	+++	0	Yes	No	+++	0	0	0
6	+++	0	Yes	Yes	+++	++	+	+

FIG 1—Case 3. Reticular dermis (a) before and (b) after PUVA. (Haematoxylin and Eosin. $\times 200$.)

There was no discernible reduction of infiltrate containing mycosis fungoides cells in case 4, while case 1 showed a minimal infiltrate in which mycosis fungoides cells were not detected. The reticular dermal infiltrate was abolished in three patients in whom the papillary infiltrate was abolished or diminished; in none of these three patients were mycosis fungoides cells detected in their biopsy specimens after treatment. Subcutaneous fat was infiltrated in one patient (case 2), and this was unaffected by treatment.

All patients showed an increase in both epidermal pigmentation and dermal pigmentary incontinence. Epidermal lichenification was present before, but not after, treatment in two patients. The remaining patients showed mild epidermal atrophy after treatment.

The main side effects were pruritus and cutaneous irritation. One or both of these occurred in the initial three patients, one of whom developed small blisters over tumid lesions. The affected skin in patients with mycosis fungoides seems to be less tolerant of PUVA than is the skin of patients with psoriasis, and the initial dose of ultraviolet light based on skin type was reduced in later patients. One patient suffered nausea after taking the tablets.

Discussion

The hallmark of mycosis fungoides is the mycosis fungoides cell, best defined on electron microscopy by its cerebriform nucleus; large and small cell variants exist. On light microscopy mycosis fungoides cells lack reliable histochemical or cytological

FIG 2—Case 2. Papillary dermal infiltrate (a) before and (b) after PUVA. (Haematoxylin and Eosin. $\times 580$.)

markers, and the classification of individual mononuclear cells within the pleomorphic infiltrate of mycosis fungoides may be difficult.

Mycosis fungoides commonly runs an indolent course over many years. Current treatments may achieve satisfactory long term palliation, although none has been shown to prolong life. Topical corticosteroids provide symptomatic relief for earlier lesions. Topical nitrogen mustard applications are effective but patients tend to develop contact dermatitis and attempts to overcome this by inducing tolerance before such treatment have not been entirely successful.³ Local x-ray therapy treats only the

site exposed, but whole-body electron beam therapy⁴ overcomes that limitation. Nevertheless, relapse occurs after both treatments, and dosage considerations preclude their regular use as maintenance therapy. Systemic chemotherapy with one or more cytotoxic drugs has been used, usually in more advanced disease, with limited success.⁵

The rationale for the use of PUVA in proliferative and neoplastic disorders is based on the cytotoxic capability of photoexcited psoralens binding with the pyrimidine bases of nucleic acids to inhibit DNA synthesis.⁶ PUVA treatment has been successfully used to treat psoriasis.⁷ We have confirmed histologically that PUVA treatment can clear the epidermis of mycosis fungoides cells. Reliable data on dermal penetration of intact skin by ultraviolet A light are not available, but extrapolation from available evidence⁸ suggests that PUVA might not always be an effective means of treating mycosis fungoides when there is a considerable reticular dermal component. Moreover, hyperpigmentation inevitably accompanies PUVA treatment, and darkly pigmented epidermis transmits ultraviolet A light poorly.⁸ In this study the reticular dermal infiltrate was cleared only when the overlying infiltrate was completely or substantially abolished. The most dense dermal nodules responded least well, as shown in one patient (case 2) who also developed deep pigmentation. Whether advanced nodular lesions could be expected to clear with long-term treatment seems doubtful but is not answered by this study.

We conclude that PUVA treatment may have a use in the management of mycosis fungoides, particularly in early and pretumid disease and perhaps in more advanced, tumid cases in association with electron beam therapy or radiotherapy. We are currently conducting a more extensive study of the role of PUVA in mycosis fungoides.

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SHORT REPORTS

Congenital hepatic fibrosis and choledochus cyst

Kerr *et al*¹ described 13 patients with congenital hepatic fibrosis, one of whom had a choledochus cyst. We report another patient with a choledochus cyst and associated congenital hepatic fibrosis, and suggest that this is more than a chance association.

Case report

A 30-year-old housewife first became ill at the age of 4, when she developed jaundice for six weeks. No definite diagnosis was made. At 7 years she was found to have an enlarged liver, and the next year developed jaundice,

abdominal pain, and fever. She continued in ill health until the age of 10, when she was readmitted for investigation. At laparotomy a choledochus cyst was found, extending from the junction of the cystic duct with the common bile duct to behind the first part of the duodenum. A choledochocystoduodenostomy was performed. The histological appearances in a liver biopsy specimen were those of congenital hepatic fibrosis. She remained well afterwards until the age of 18, when she developed recurrent attacks of epigastric pain, jaundice, and fever.

Further investigations were performed at the age of 22, when a barium meal showed gas in the biliary tree, with reflux of barium into the cyst from its junction with the duodenum. A diagnosis of recurrent attacks of ascending cholangitis was made. Antibiotic treatment caused temporary improvement, but the attacks of pain increased in frequency, until by the age of 29 they were occurring every three months.

She was then readmitted for further investigation. A barium meal again showed reflux into the choledochal cyst, with considerable narrowing of the anastomosis with the duodenum. Oesophageal varices were also seen. Liver