THE USE OF ANTIMETABOLITES IN THE TREATMENT OF PSORIASIS

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INTRODUCTION

Some of the recent trends in the therapy of psoriasis include the use of cytotoxic drugs, notably the antifolics (aminopterin amd methotrexate) and 6-mercaptopurine. The use of antifolics in the treatment of rheumatoid arthritis and psoriasis was introduced by Gubner et al in 1951 as a method of therapeutic suppression of tissue reactivity. In all the 9 cases of psoriasis treated marked improvement was noted. Various other workers have since provided evidence to support the efficiency of antimetabolites in the treatment of psoriasis. In 1964, Rees reviewed his 10 years' experience with aminopterin in the treatment of psoriasis, and in over 500 cases treated, no fatal or near-fatal reaction occurred. The same group of workers have also used methotrexate and have observed that it may be safer and more effective than aminopterin. For long-term therapy, aminopterin is given in the dosage of 0·5 mg. daily and methotrexate 2·5 mg. daily in courses. Lately, Ryan reported on 14 cases of psoriasis treated with antifolics and showed its effectiveness, but noted a high incidence of toxic side effects (including ulceration of the mouth, indigestion, intestinal bleeding. alopecia and impaired liver function) with a daily dose of more than 0·5 mg. of aminopterin or 2·5 mg. of methotrexate.

Recently, Cotton and Mier (1964) proposed a hypothesis that a genetic enzyme defect in the synthesis of hyaluronic acid exists in the psoriatic individual. This metabolic defect has been shown to result in an increased permeability from the capillaries to the epithelial cells, and a "wound reaction" in such skin results in a grossly exaggerated response in the mitotic rate, leading to parakeratosis. Hence, therapeutic agents which inhibit mitosis directly or indirectly may be used in the treatment of psoriasis. This has put the use of antimetabolites like methotrexate and 6-mercaptopurine as a rational therapy for psoriasis. The use of antimetabolites interfere directly with the synthesis of the essential constitutents of the cells: methotrexate in the production of folic acid and 6-mercaptopurine in the production of purines. Our own experience with the use of antimetabolites in severe cases of psoriasis is meagre but with the small number of cases treated we observed that methotrexate and 6-mercaptopurine have been able to produce clearance of the lesions considerably. However, there was a high incidence of toxic side effects, including a fatal case from severe marrow depression.

MATERIALS AND METHODS

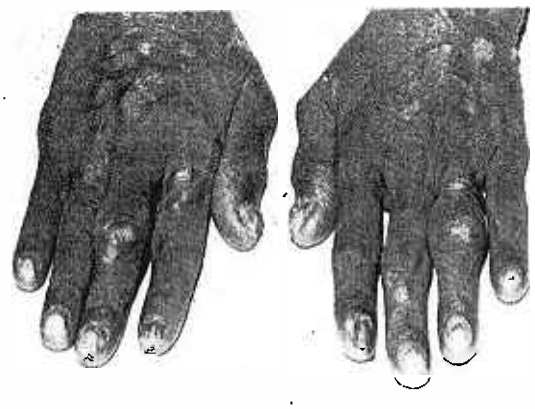
A total of 7 cases of generalised psoriasis, including 2 cases with psoriatic arthropathy have been treated with methotrexate or 6-mercaptopurine and followed up in Medical Unit II. All these cases have had local application of various preparations, including steroids and a combination of liq. picis carb. 6, salicylic acid 4, ung. H.A.D. to 100, for varying periods of time without much improvement. These cases were admitted to the wards for clinical and laboratory assessment, including urinary and hematologic examination, blood urea estimation and liver function testing. Two cases who had diabetes mellitus were deemed suitable for antibolite drug therapy.

The patients were warded throughout the course of the initial treatment and were started on methotrexate at 0·1 mg./kg. body weight or 6-mercaptopurine at 2 mg./kg. body weight. There was no particular preference for the two drugs, although we preferred 6-mercaptopurine owing to the lower incidence of side effects. Photographs of the patients were taken on admission and during the course of therapy, to show the degree of improvement. The total white blood cell count was checked every other day and a careful watch was kept daily on the onset of toxic side effects, commonly dyspepsia, nausea, ulceration of the oral mucosa, sore throat and alopecia. The patients were kept in the wards for varying periods of time usually

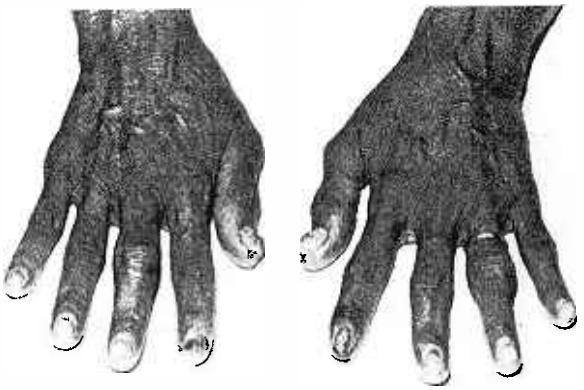
TABLE I

	Age	Sex	Race	Diseases & Duration	Local application	Antimetabolites used	Results & Follow up	Side effects
1.	41	M	Mal.	Generalised psoriasis 9 years	Psoriasis lotion: (liq. pis. carb 6 salicylic acid 4 ung H.A.D. to 100) Betnovate ointment	Methotrexate 5 mg. daily 4 weeks 6-mercaptopurine 75 mg. daily 2 weeks	Improved. Maintained on 6-mercaptopurine 50 mg. daily in intermittent weekly courses	Nil
2.	54	M	Ch.	Generalised psorisis 9 years Diabetes mellitus 5 years	"Psoriasis lotion" (above)	Methotrexate 5 mg. daily 2 weeks	Skin lesions improved remarkably. Followed up with Betnovate ointment to residual lesions	Nil
3.	40	M	In.	Generalised psoriasis 2 years Psoriatic arthropathy 1 year	"Psoriasis lotion" Hydrocortisone cream	Methotrexate 5 mg. daily 2 weeks	Out-patient follow up with hydrocortisone cream	Developed jaundice after 2 weeks and methotrexate withdrawn
4.	43	M	In.	Generalised psoriasis 5 years	Hydrocortisone cream Betnovate ointment (Bethamethasone 17-velarate)	6-mercaptopurine 100 mg. daily 4 weeks	Skin lesions cleared up after 3 weeks Followed up with hydrocortisone cream	Indigestion Nausea Ulceration of mouth Alopecia Leucopenia
5.	51	F	In.	Generalised psoriasis 4 years Psoriatic arthropathy 6 months Diabetes mellitus 4 months	Ung H.A.D. only	6-mercaptopurine 75 mg. daily 4 weeks	Improvement noted after 1 week. Followed up with Hydrocortisone cream to residual lesions	Ulceration of mouth Anorexia Leucopenia
6.	49	M	Ch.	Generalised psoriasis 6 months	"Psoriasis lotion" Betnovate ointment	6-mercaptopurine 100 mg. daily 5 weeks	Skin lesions show improvement after 2 weeks	Severe marrow depression after 5 weeks. Fatal termination from agranulocytosis and sepsis.
7.	40	M	Mal.	Generalised psoriasis	"Psoriasis lotion" Betnovate ointment	Methotrexate 5 mg. daily 2 weeks	Improved after 2 weeks Followed up with Betnovate ointment	Nil

A case of generalised psoriasis (4 years) with psoriatic arthropathy, and diabetes mellitus is now presented, together with the clinical progress chart



Before treatment.



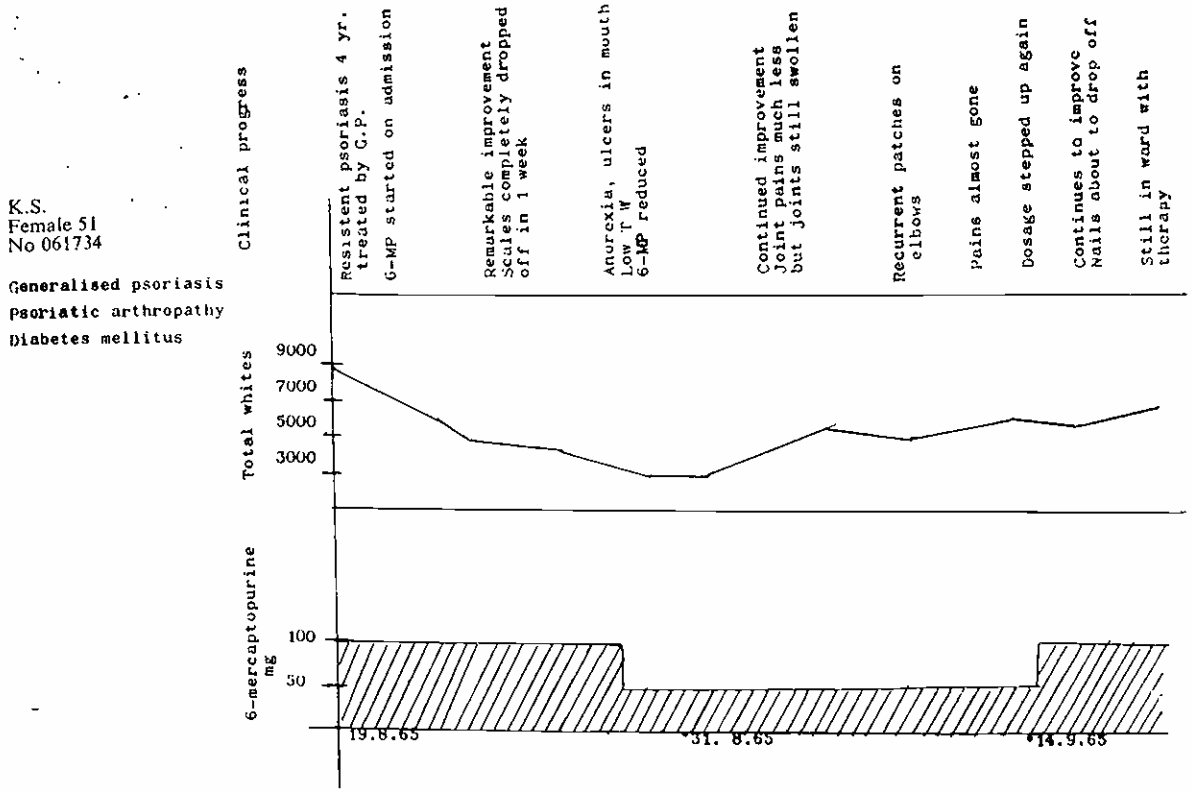
Three weeks later.

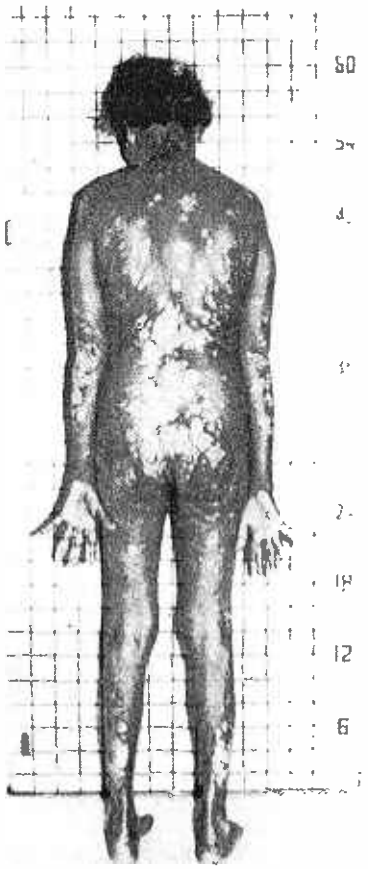
NOTE:

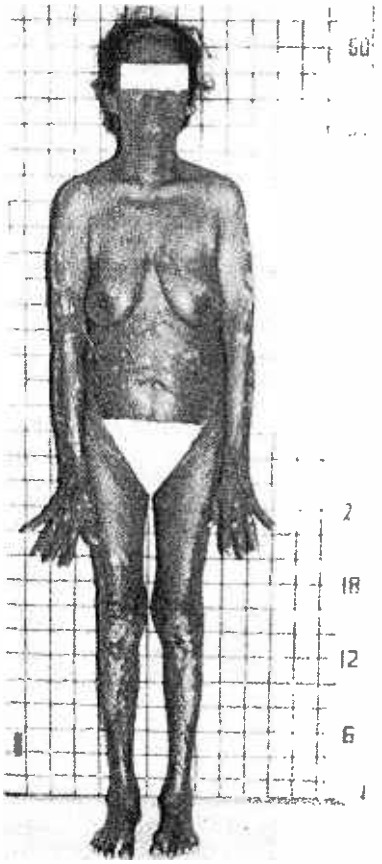
1. Striking improvement of skin lesions
2. Decrease in joint swellings (the patient also had less arthralgia).
3. Gradual dropping off of involved nails.

CHART II

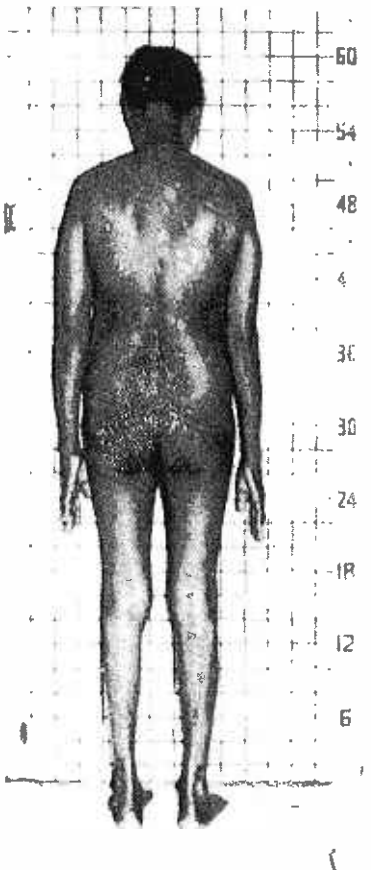
CLINICAL PROGRESS CHART TOGETHER WITH DRUG DOSAGE AND TOTAL WHITE COUNT.

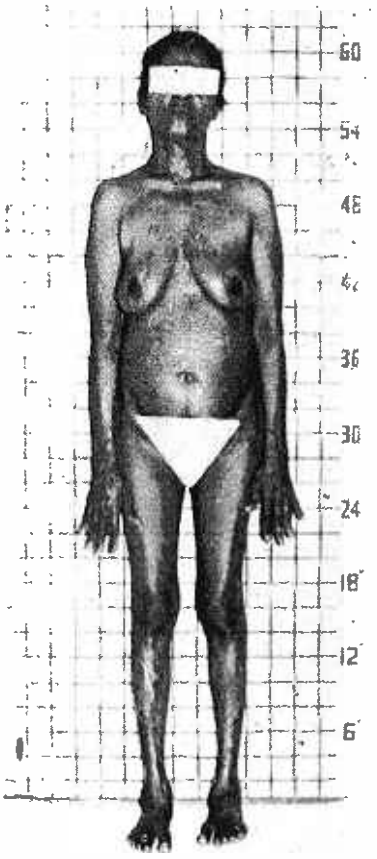






Before treatment with 6-Mercaptopurine.





Three weeks later.

between 2 to 6 weeks, until the skin lesions were almost completely cleared. Meanwhile, local applications were continued. The patients were then discharged for follow up at the skin clinic, with local applications to any residual lesions or with short weekly courses of antimetabolites in those cases with flareups. One case has been on intermittent courses of antimetabolites for about one and a half years.

RESULTS

A summary of the 7 cases treated with methotrexate or 6-mercaptopurine is given below.

In all the cases improvement of the skin lesions were noted, usually within the first week of therapy. However, a high incidence of side effects were noted.

a) **Ulceration of the mouth** was noted in 2 cases. These ulcers healed rapidly with decreased dosage of the antimetabolites together with the use of Vitamin C and dequadin paint.

b) **Anorexia and indigestion** in 2 cases were transient.

c) **Alopecia** was noted in one case with methotrexate therapy but when the drug was changed to 6-mercaptopurine the symptom disappeared.

d) **Liver function** was impaired in one case who developed jaundice two weeks after methotrexate therapy, but this rapidly returned to normal on discontinuing treatment.

e) **Leucopenia** of less than 4,000 was noticed in three cases, two with methotrexate and one with 6-mercaptopurine.

   i) in the two cases with methotrexate, the counts returned to normal on lowered dosage of the drug.

   ii) in the third case with 6-mercaptopurine marrow depression continued despite withdrawal of the drug, and the patient died five days after complete withdrawal of the drug, from sepsis and agranulocytosis.

COMMENTS

Although many dermatologists have shown the effectiveness and relative safety of antifolics and 6-mercaptopurine in the treatment of psoraisis, the results we have obtained in our cases have led us to be somewhat cautious. The use of these agents are not free of side effects, but with careful clinical and laboratory control, including reduction of dosage or discontinuing the drug at the first sign of side effects, they need not be dangerous. Each case should be carefully assessed to make certain that there are no contraindications to anti metabolites therapy. Such contraindications include:

1. renal disease
2. pregnancy, because of possible foetal malformations.
3. hepatic disease
4. old age, probably because of an occult decline in renal or hepatic function.

SUMMARY

A brief review of the use of antimitotic agents in the treatment of psoriasis is made.

Of the 7 cases of generalised psoriasis treated with methotrexate or 6-mercaptopurine in Medical Unit II, improvement of the skin lesions is noted in every case. However, there was a high incidence of toxic side-effects including a fatal case.

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