PAPERS AND ORIGINALS

Treatment of Psoriasis with Azathioprine

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Summary

Azathioprine treatment benefited 19 (66%) out of 29 patients suffering from severe psoriasis. Haematological complications were not troublesome and results of biochemical liver function tests remained normal. Minimal cholestasis was seen in two cases and portal fibrosis of a reversible degree in eight. Liver biopsies should be undertaken at regular intervals if azathioprine therapy is continued so that structural liver damage may be detected at an early and reversible stage.

Introduction

Methotrexate has proved to be an effective treatment for intractable psoriasis since its use was first described by Gubner *et al.* (1951). Serious side effects from the drug are now being reported, however, in particular cirrhosis of the liver. Hepatic changes were noted in children who had been treated with methotrexate for acute leukaemia (Colsky *et al.*, 1955) and in a patient receiving it for psoriasis (O'Rourke and Eckert, 1964). Renal and central nervous system damage has also been described (Ryan and Vickers, 1966). We have therefore used azathioprine since 1969 as our drug of choice where systemic therapy for psoriasis was warranted.

Reports on the use of azathioprine in psoriasis are few. One patient who had seropositive rheumatoid arthritis and psoriasis was treated with azathioprine, and though the improvement in the arthritis was questionable it was definite in the psoriasis (Corley *et al.*, 1966). Hewitt *et al.* (1970) reported on 20 patients suffering from psoriasis who were given azathioprine with favourable results, but routine liver biopsies were not undertaken.

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On the basis of a favourable report on the use of 6-mercaptopurine in psoriasis (Kravetz and Balsam, 1964), azathioprine was tried in Britain (Greaves and Dawber, 1970). Ten patients with disabling psoriasis were given six weeks' inpatient treatment with azathioprine. Five of them showed reduction of their disease by 25% or more. The effects of methotrexate, corticosteroids, and azathioprine on fingernail growth in psoriasis were compared (Dawber, 1970), and though methotrexate was more effective than azathioprine in suppressing fingernail growth azathioprine was better than corticosteroids.

Pharmacology.—Azathioprine is absorbed from the gastrointestinal tract. Ten per cent. is excreted unchanged in the urine and 90% is broken down to 6-mercaptopurine, of which half is excreted in the urine within 24 hours. 6-Mercaptopurine is then converted into 6-mercaptopurine ribotide. This is the active agent which, because of similarities in structure to inosinic acid, competes for enzymes concerned in guanylic and adenylic acid synthesis. It also inhibits the synthesis of 5-phosphoribosylamine, a precursor of inosinic acid. Thus nucleic acid formation is inhibited.

Indications for Azathioprine.—Our psoriatic patients were considered for treatment with azathioprine if: (*a*) they needed frequent inpatient treatment with coal tar baths, ultraviolet light, and Lassar's paste with dithranol; (*b*) the inpatient regimen failed to clear their psoriasis; (*c*) they had previously suffered from the toxic effects of methotrexate or because they had failed to be controlled by it; (*d*) they were having systemic corticosteroids prescribed initially by other dermatologists; (*e*) they had exfoliative or pustular psoriasis; or (*f*) they were socially disabled by their disease.

Patients and Methods

When a patient was admitted to hospital a general medical examination was carried out, including full blood count, liver function tests (bilirubin, serum transaminase, alkaline phosphatase, total proteins, and serum albumin), chest radiography, and urine analysis. In addition a liver biopsy was performed before azathioprine treatment.

The patient was started on azathioprine 100 mg daily, and over two weeks the dose was increased to about 200 mg daily. This was maintained until the disease was in remission and the dose could be reduced. Occasionally we had patients on doses of 300 mg for up to six months; if remission did not occur on

300 mg the treatment was normally abandoned. The patients had a full blood count at monthly intervals, and a liver biopsy was performed initially after six months' therapy and then yearly.

Twenty-nine patients (16 men and 13 women) were treated with azathioprine of whom 21 had psoriasis vulgaris, seven had exfoliative psoriasis, and one had pustular psoriasis. Eleven had a family history of psoriasis, 12 had previously had systemic corticosteroids, 14 had been given methotrexate, and five acknowledged arsenic treatment in the past. Only 12 had never had any of these drugs. Thus in 59% of our patients the psoriasis had previously been severe enough to warrant systemic therapy before starting azathioprine.

The patients' ages ranged from 23 to 79 years, with six under 40 years. Women of childbearing age were advised to remain on an oral contraceptive throughout treatment.

Results

Nineteen (66%) of the 29 patients benefited from azathioprine, and of these 19 we were able to wean three off the drug completely. The first, who had previously been exfoliating, was completely clear six months after stopping the drug and had psoriasis only on his elbows and knees a year later. The second, who had very severe exfoliative psoriasis, had been on systemic steroids for so long and in such doses that her adrenal glands no longer responded to corticotrophin stimulation. She is now completely free of psoriasis six months after stopping azathioprine and only requires 50 mg cortisone acetate daily to replace endogenous cortisol. The third patient had severe psoriasis, was given the drug for one month only, and was completely free of the disease when last seen nine months later.

Thirteen patients had from 75 to 100% clearing of their psoriasis and remained well on doses of azathioprine varying from 75 to 200 mg daily. Three of these had previously had exfoliative psoriasis. One patient had only a 50% reduction in his disease. Two still have extensive psoriasis and are on doses of 200 mg azathioprine daily but are much improved in that neither are exfoliating or pustulating as they were before (table I).

TABLE I—*Analysis of Results of Treatment with Azathioprine in 29 Psoriatic Patients*

No. of Patients		Improvement		Reason for Discontinuance	
Men	Women	50%-75%	75%-100%	Side Effects	No Benefit
16	13	3	16	3	7

SIDE EFFECTS

Alimentary symptoms which included nausea, diarrhoea, or abdominal pain occurred in 12 patients (41%). In most cases the symptoms ceased within a few weeks of starting treatment. We found it useful to reduce the dose of azathioprine, and then gradually increase it, if these symptoms occurred. The high incidence of gastrointestinal complaints was interesting because patients with renal transplants or rheumatoid arthritis who were being treated with azathioprine and systemic corticosteroids, did not appear to be similarly affected. Two patients reported abnormalities of taste in that they no longer enjoyed drinking alcohol.

Macrocytosis and raised indices (mean corpuscular volume and mean haemoglobin concentration) occurred in 12 patients (41%). Anaemia itself occurred in only one patient who had a mixed iron deficiency and macrocytic anaemia, and it was rectified by iron therapy and a reduction in the dose of azathioprine.

Leucopenia below 3,500/mm³ occurred at some stage during treatment in 10 patients. This was treated by stopping or reducing the dosage of the drug until the white blood count returned to normal, which it did rapidly. In one patient the white blood count fell to 1,600/mm³, but this was due to concurrent treatment with allopurinol 400 mg daily because of an asymptomatic uric acid level of 10·6 mg/100 ml. Allopurinol is a xanthine oxidase inhibitor and it therefore interfered in the metabolism of azathioprine and produced higher levels of the drug than we had realized.

Thrombocytopenia occurred in only one patient. He was known to have cirrhosis (probably secondary to treatment with methotrexate) but his only complaint was his psoriasis. Topical treatment was of no avail so azathioprine therapy was begun. It was abandoned 10 days later when his platelet count fell to 40,000/mm³.

No deterioration in the results of biochemical liver function tests was noted during treatment, though some patients had minimal pretreatment abnormalities which remained unaltered. Satisfactory liver biopsy samples were obtained from 20 patients in whom therapy was fully established. The biopsy slides were coded and randomized before being examined by an independent authority for evidence of portal inflammation, bile duct damage, ductular proliferation, viral and alcoholic hepatitis, fatty change, nuclear variability and vacuolation, mitoses, cholestasis, Kupffer cell proliferation, piecemeal necrosis, focal necrosis, diffuse lobular inflammation, fibrosis, and cirrhosis. Changes were graded on a slight, moderate, and severe scale. Details of whether the patient had previously received methotrexate and azathioprine, or azathioprine alone, were then correlated with the pathological changes. There was no severe damage that could be attributed to azathioprine, all the changes present being of a reversible nature.

Two features in which there was a difference between biopsies performed before azathioprine and those done after were very slight cholestasis and portal fibrosis. Cholestasis was never seen before treatment, but two patients had it afterwards, one of whom had taken methotrexate in the past. Portal fibrosis, again of very mild degree, was seen in eight out of 20 posttreatment cases (see table II). Reticulin-stained sections of the liver biopsy from case 3 (table III) at 12 months are shown in the figure. The degree of fibrosis is minimal, and the follow-up biopsy carried out at 24 months showed nothing abnormal despite continuation of the drug.

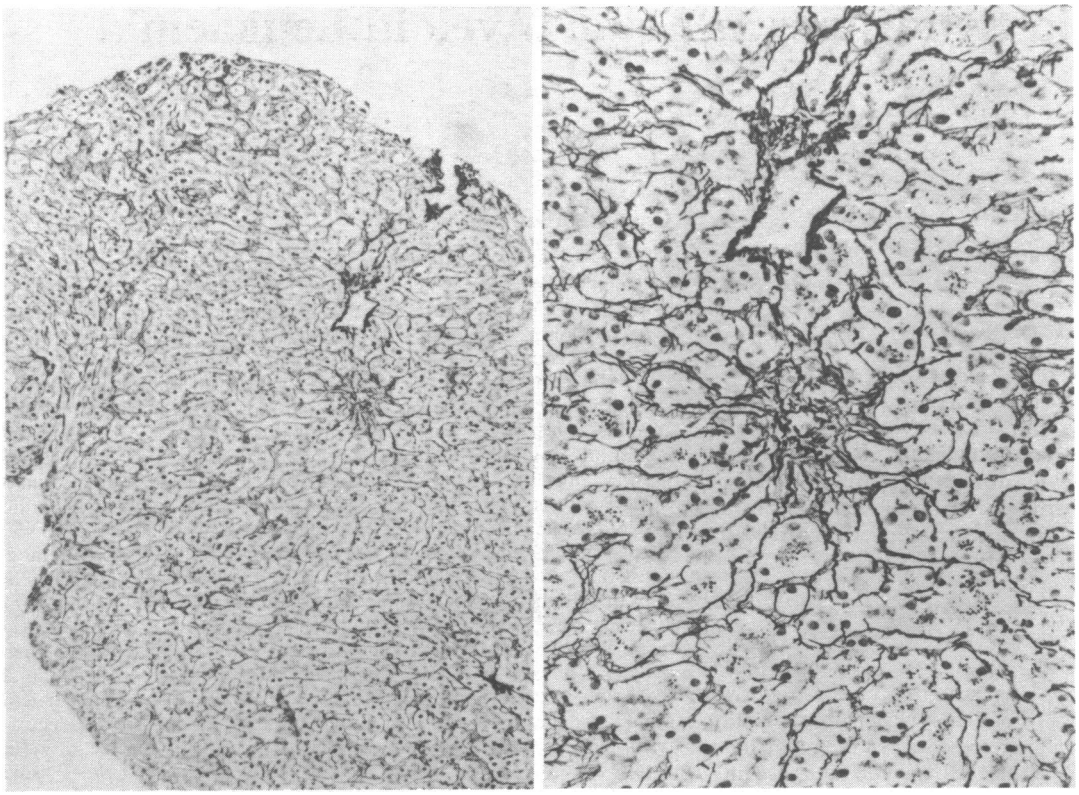
TABLE II—*Analysis of Eight Patients with Portal Fibrosis*

	Months of Treatment		Comment and Medical History
	Azathioprine	Methotrexate	
Patients who received methotrexate and azathioprine before liver biopsy*			
Case 1	1	48	Had restarted methotrexate before biopsy
„ 2	3	12	Had restarted methotrexate before biopsy
„ 3	12	25 mg only	Follow-up biopsy after 24 months, normal
„ 4	23	1	Follow-up biopsy after 31 months, normal
„ 5	15	15	Biopsy before starting azathioprine showed more pronounced changes
„ 6	28	60	
Patients who received only azathioprine before liver biopsy†			
Case 7	9		Alcoholic
„ 8	12		Congestive cardiac failure

*Six out of 11 had portal fibrosis.
†Two out of nine had portal fibrosis.

Comment

Patients showed poorer tolerance and clinical response to azathioprine than to methotrexate, and the drug will therefore represent an advance in therapy only if the long-term complications are significantly less. Over 10 years passed before cirrhosis was reported as a result of treating psoriasis with methotrexate,



Liver biopsy specimen after 12 months on azathioprine showing minimal fibrosis as demonstrated by reticulin stain. (Low power magnification X99: high power X243.)

and this length of time will be needed before similar complications of azathioprine can be assessed. The portal fibrosis changes which were detected in the present study were minimal and apparently of reversible degree but they represent a worrying feature in a group of patients who received relatively short-term therapy. Cholestasis has previously been described after azathioprine treatment and is a second feature seen in these patients.

We conclude that while azathioprine may be a useful drug in the management of chronic psoriasis there is a need for hepatic function to be monitored regularly throughout the treatment period by liver biopsies. A reassuring feature of the drug is the absence of change in results of biochemical liver function tests, which was noted early in the cases treated with methotrexate. Furthermore, if azathioprine is to be used in the management of psoriasis, it has to be realized that it is usually a long-term therapy and though some patients may be weaned off it completely when their disease has gone into temporary remission, it is likely that they will require it again in the future.

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