hydroxy-β-methyl glutaryl CoA. If the greatly raised cholesterol levels in hyperosmolar non-ketotic diabetic coma are due to accelerated formation rather than decreased degradation or excretion, then any block in ketone production should occur beyond the initial stage of synthesis.

Further explanations for the lack of ketosis in this condition would be increased urinary excretion of ketones or an increase in their utilization. The lack of significant ketonuria does not support the former suggestion, and there are no reports that the turnover of ketone bodies is increased.

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Preliminary Communications

Azathioprine in Pemphigus Vulgaris

British Medical Journal, 1970, **3**, 84–86

INTRODUCTION

Pemphigus vulgaris is almost invariably fatal if untreated. Systemic corticosteroids in high doses will usually suppress the disease, but in most cases maintenance therapy must be continued indefinitely (Lever and White, 1963), and many patients develop side-effects from this treatment. The disease may be due to an immunological disorder (Beutner *et al.*, 1968), and immunosuppressive drugs therefore offer a rational alternative to corticosteroid therapy. Though immunosuppressive drugs are now widely used in a variety of conditions, there have been few direct comparisons of their therapeutic efficacy relative to their toxicity in man. Lever and Goldberg (1969) used methotrexate to control pemphigus vulgaris but found fairly high doses were required. In view of the increasing evidence of hepatic damage due to long-term methotrexate therapy (O'Rourke and Eckert, 1964; Coe and Bull, 1968; Muller *et al.*, 1969) we have sought an alternative immunosuppressant. Possibly azathioprine (Imuran) has a high therapeutic index relative to other immunosuppressive drugs (Corley *et al.*, 1966; *New England Journal of Medicine*, 1968; Bach *et al.*, 1969), and we report here our experience with azathioprine in the treatment of four cases of pemphigus vulgaris.

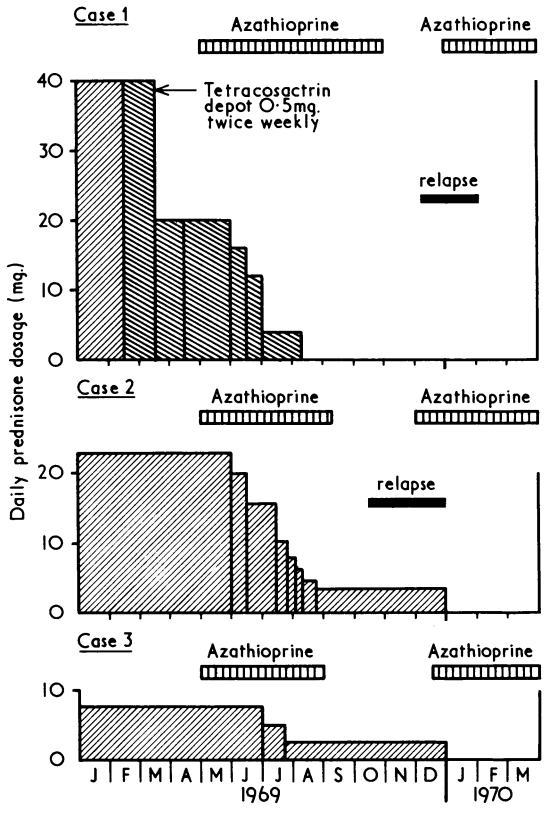
METHODS

In all four cases the diagnosis of pemphigus vulgaris was confirmed histologically by finding intraepidermal bullae with acantholytic cells. The patients had received systemic corticosteroid therapy for four to seven years before azathioprine was started, and regular attempts to reduce their maintenance dose of corticosteroids had enabled a reasonably accurate estimate of their steroid requirements to be made. All had mildly active pemphigus lesions at the start of the trial. Azathioprine was added, in a daily divided dose of 2·5 mg./kg. body weight, to the maintenance dose of corticosteroid, and after four weeks the steroid was gradually reduced. When levels of up to 3 mg. prednisone daily were reached the azathioprine was withdrawn, and was restarted when definite evidence of relapse was obtained. Steroid reduction was then continued to zero.

The patients were assessed at two-weekly intervals and haemoglobin concentration, white cell count, platelet count, liver function tests, and blood urea concentration were determined before starting azathioprine and at each subsequent attendance. Before beginning azathioprine, autoantibodies to intercellular material were estimated by the indirect immunofluorescent technique of Beutner and Jordon (1964).

CASE HISTORIES AND RESULTS

The results of azathioprine therapy are shown diagrammatically in the Chart.



Effect of azathioprine therapy in three cases of pemphigus vulgaris.

CASE 1

A 54-year-old man presented in 1962 with widespread crusted lesions of the face and groins which were initially treated with topical steroid. The diagnosis of pemphigus vulgaris was made in 1963, when he developed widespread suprabasal bullae, and prednisone in high dosage was started. Maintenance corticosteroid therapy had been required ever since, the usual dose being of the order of 40 mg. prednisone daily; he had relapsed on four occasions on doses of 10-30 mg. daily. For three months before azathioprine therapy he had received tetracosactrin (Synacthen) depot 0·5 mg. intramuscularly twice weekly instead of prednisone. Despite this treatment he had continual erythema and crusting of the face and groins. He had Cushingoid facies and bilateral ischaemic necrosis of the femoral heads presumed to be due to prolonged corticosteroid therapy. Autoantibodies to intercellular material were present in the serum in a titre of 1/320.

He improved slightly while taking azathioprine despite gradual reduction of the tetracosactrin depot injections to zero. He remained well on azathioprine without steroid therapy for two months, but within six weeks of stopping azathioprine his skin deteriorated and he gradually developed extensive crusting and erythema of the face, limbs, and trunk. Azathioprine was then restarted and his skin cleared over a period of six weeks. He has remained well for three months on azathioprine alone.

CASE 2

A 38-year-old man presented in 1964 with widespread bullae and oral ulceration which initially required prednisone 80 mg. daily for suppression. His average maintenance dose following a relapse in 1967 had been 20 mg. prednisone daily. He had taken prednisone 22·5 mg. daily for five months before starting azathioprine, and despite this treatment a shallow ulcer formed on the hard palate. He had ischaemic necrosis of the right femoral head. Autoantibodies to intercellular material were not detected in the serum.

He remained well while taking azathioprine despite reduction of prednisone to 3 mg. daily. Six weeks after stopping azathioprine he developed widespread skin irritation with no visible lesions but with several new mouth ulcers, biopsy of which revealed the changes of pemphigus vulgaris. Azathioprine was therefore restarted; the irritation and mouth lesions then slowly improved over a period of two months. Prednisone was then stopped and he has remained well for four months on azathioprine alone.

CASE 3

A 77-year-old woman presented in 1963 with widespread bullous pemphigus which initially required prednisone 50 mg. daily and corticotrophin 20 units intramuscularly daily for suppression. She had never taken less than 7·5 mg. of prednisone daily, and despite this she still had active pemphigus of the umbilicus at the time azathioprine was started. Autoantibodies to intercellular material were not detected in the serum.

No change was observed following reduction of prednisone to 2·5 mg. daily while she was taking azathioprine. The azathioprine was then stopped for three months, and since there was no sign of relapse at the end of this time azathioprine was restarted, prednisone being withdrawn completely. She has remained well for four months on azathioprine alone.

CASE 4

A 63-year-old woman presented in 1966 with widespread pemphigus vulgaris which initially required prednisone 60 mg. daily for suppression. Her maintenance dose was 15 mg. prednisone daily, and, while taking this dose, she had chronic oral and umbilical lesions. Autoantibodies to intercellular material were present in the serum in a titre of 1/80.

After taking azathioprine for 14 days she developed fever, with malaise, generalized aches and pains, nausea, vomiting, and a follicular maculopapular rash on the trunk. The symptoms subsided when azathioprine was discontinued and prednisone alone was continued in the same dosage as before. Nine months later she sustained collapse fractures of the lumbar vertebrae due to steroid therapy, necessitating admission to hospital. A single oral dose of 50 mg. azathioprine was given and she again had a severe reaction, with prostration, vomiting, and a widespread skin eruption. The white cell count and liver function tests were normal during the reaction, and skin biopsy showed only non-specific perivascular inflammatory changes with dermal oedema. When the reaction had subsided patch tests to azathioprine (powder and 10 mg./ml. solution) were negative at 48 and 72 hours, but an intradermal injection of azathioprine (0·05 ml. of a 10 mg./ml. solution) produced a positive reaction with erythema and induration maximal at 36 hours. The same solution produced no reaction in three control subjects, and probably the patient had become hypersensitive to azathioprine.

DISCUSSION

Our experience of the use of azathioprine in treating pemphigus vulgaris previously controlled with corticosteroids suggests that the drug effectively controls the disease and enables steroids to be withdrawn completely. In one of our cases the effect of azathioprine on the disease could not be assessed owing to the development of a severe systemic reaction to its use, but the other three patients have now been well without steroids for several months. In two of these relapse followed withdrawal of the drug, and the condition was again controlled when it was reintroduced. The third did not relapse when azathioprine was withdrawn for 12 weeks, and this suggests either that the initial maintenance dose of prednisone had been too high or that azathioprine had had a sustained beneficial effect on the course of the disease. Autoantibodies to intercellular material were not found in two of the cases. This is compatible with previous reports of cases, reviewed by Beutner *et al.* (1968), in which autoantibodies were not found in about 20% of cases.

There have been few reports of the use of immunosuppressive drugs in pemphigus vulgaris. Wolff and Schreiner (1969) reported the use of azathioprine (in a dose of 3 mg./kg. body weight) in four patients and though they achieved a substantial reduction in steroid dosage, they could not maintain patients on azathioprine alone. Krakowski *et al.* (1969), however, were able to wean a patient off steroids for four months while giving a maintenance dose of azathioprine 75 mg. on alternate days. Other cytotoxic drugs believed to have an immunosuppressive effect have been used. Lever and Goldberg (1969) treated five cases of pemphigus vulgaris with methotrexate with good results in four. Ebringer and Mackay (1969) gave repeated courses of cyclophosphamide to a patient with pemphigus vulgaris and induced remissions for periods up to 11 months.

The time required for azathioprine to have a therapeutic effect in pemphigus vulgaris and the duration of this effect following withdrawal of therapy, are uncertain, but probably both these effects are likely to be measured in weeks rather than days. The sustained remission following cyclophosphamide described by Ebringer and Mackay (1969) suggests that other immunosuppressive drugs may have a similar prolonged effect.

We feel that the present results are sufficiently encouraging to warrant further trials of azathioprine in the treatment of pemphigus vulgaris.

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Medical Memoranda

Case of Ergot Poisoning

British Medical Journal, 1970, **3**, 86–87

Ergotamine tartrate is often prescribed in the treatment of migraine. Complications from the drug are rare but potentially serious, as is illustrated by the following case, where severe lower limb arterial spasm resulted from its use. This provided an opportunity to study the reversible vasoconstrictor effect by means of plethysmography, ultrasound, thermography, and arteriography.

CASE REPORT

A 28-year-old woman complained of intermittent claudication in the left calf of 18 months' duration. The distance at which calf pain occurred varied from 100 yards to 1 mile (90 to 1,600 m.). One month before her admission this distance had on occasions been as short as 25 yards (23 m.), and both calves were affected. On admission she had severe paraesthesiae in the toes and soles of both feet. Her legs felt "icy cold and dead." On direct questioning she admitted to suffering from headaches for several years. These had been previously diagnosed as migraine and became more frequent under stress. They were characterized by pains in the back of the neck radiating over the left temple. There was occasional blurring of vision and vomiting but no warning aura. She was given Migril and Cafergot suppositories to be self-regulated during the attacks. The attacks had been more severe during the preceding few months with the result that two or three times the prescribed dose was taken. She admitted that the claudication was exacerbated by taking ergotamine preparations. Her health was otherwise good.

On physical examination she was fit but anxious. The upper limb pulses were present and equal. There were no ischaemic changes in the fingers and the blood pressure was 120/80 mm.Hg in both arms. There were no pulses palpable below the femorals in either of the lower limbs and there were no bruits. The feet and legs were cold and pale. The capillary return was slow and there was reduced sensation to pin-prick, touch, and vibration over the soles. All the reflexes were present and equal.

She was treated with bed rest. The limbs were kept at room temperature. An intravenous infusion of low molecular dextran (Rheomacrodex), 500 ml. eight-hourly, containing heparin 5,000 i.u. was begun and a total of 2 litres was given. The legs became warmer but she experienced severe burning pain, requiring large doses of analgesics. The cutaneous sensitivity improved and the toes showed reactive hyperaemia. The foot pulses returned on the fifth day. She was discharged on the nineteenth day, when the foot pulses were present and the capillary return was normal, but she still experienced some hyperaesthesia of the soles, aggravated by walking. One month later these symptoms persisted but had diminished.

INVESTIGATIONS

Arteriography.—Bilateral femoral arteriograms were performed on admission and showed severe narrowing of both superficial femoral arteries which extended throughout their lengths. The calf vessels were very narrow and difficult to identify. Smoothness of the arterial wall was seen at all levels (Fig. 1, right thigh). On the tenth day bilateral femoral arteriograms were repeated and showed good filling of the femoral and popliteal arteries in both limbs (Fig. 2, right thigh). No atheroma or occlusion was demonstrated.

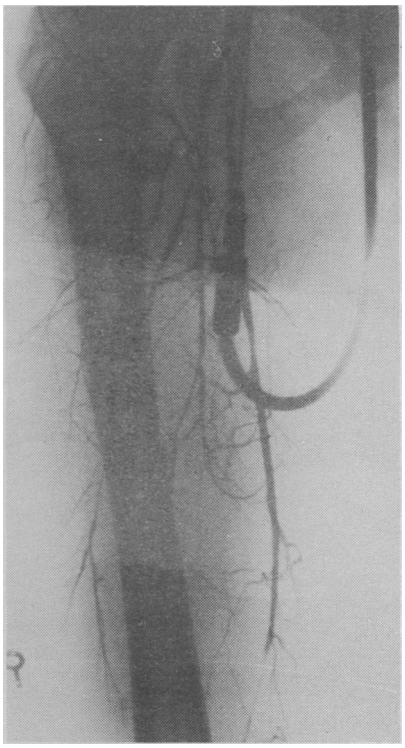

FIG. 1.

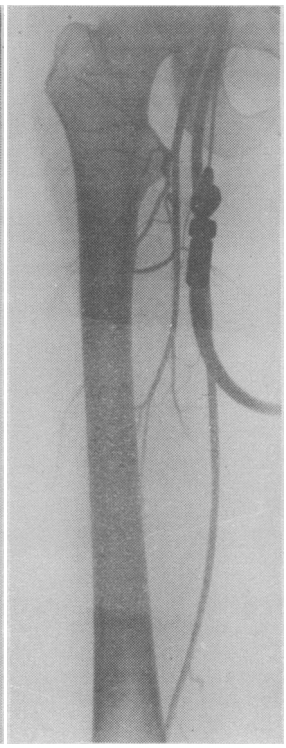

FIG. 2.

Plethysmography.—Serial studies were made of blood flow in the calf and foot of both legs by strain-gauge plethysmography. Measurements were made of resting flow and perfusion pressure (the difference between arterial systolic and venous pressure). The peripheral resistance was calculated from the ratio of perfusion pressure to the resting flow.

Ultrasound.—Daily examination of the posterior tibial and dorsalis pedis pulses and indirect ankle systolic pressure measurements were made by means of a Doppler flow velocity meter (Yao *et al.*, 1968, 1969) until the pulses were clinically palpable. Improvement was seen in the change of configuration of the flow velocity patterns, together with gradually increasing ankle systolic pressure.