

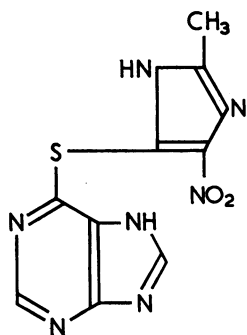
SYMPATHETIC OPHTHALMITIS TREATED WITH AZATHIOPRINE*†

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THIS drug with the chemical name 6-(1-methyl-4-nitro-5-imidazolyl) thiopurine‡ (Figure) was developed as part of a programme designed to present the thiopurines in a masked, but metabolically active form, in order to treat adenocarcinoma in rodents (Elion, Callahan, Bieber, Hitchings, and Rundles, 1961; Elion, Bieber and Hitchings, 1960; Hitchings and Elion, 1959) and chronic granulocytic and acute leukaemia in man (Rundles, Laszlo, Itoga, Hobson, and Garrison, 1961).



In the course of studies with azathioprine further interesting biological properties were revealed. In the suppression of the development of haemagglutinins to sheep cells in mice (Nathan, Bieber, Elion, and Hitchings, 1961) and in the suppression of the homograft reaction to renal transplants in dogs (Calne, 1961) it showed a therapeutic index superior to that of 6-mercaptopurine.

In the prolongation of survival of skin homotransplants, azathioprine is much less effective than for prolonging survival of kidney transplants (Hechtman, Blumenstock, Thomas, and Ferrebee, 1962). Of interest is the finding that the use of azathioprine enables lung homografts to survive longer (Hardy, Eraslan, Dalton, Alican, and Turner, 1963).

Dosage.—In man the dose is 1.5 to 3 mg./kg./day by mouth.

Toxicity.—Anorexia, nausea, vomiting, and weakness.

HAEMATOPOIETIC TISSUES: As with other active thiopurines (6-mercaptopurine, thioguanine) there occurs suppression of proliferation of normal and leukaemic granulocytes, and possibly suppression of primitive lymphoid elements in patients with acute leukaemia. The platelets are scarcely affected. With prolonged dosage a mild degree of anaemia without accelerated red cell haemolysis can occur. Cytopenias produced by azathioprine have always subsided quickly with reduction in dose or suspension of therapy.

Azathioprine has been used in association with other drugs (azaserine, actinomycin C, prednisolone) to prevent rejection of renal homografts in man (Murray, Merrill, Harrison, Wilson, and Dammin, 1963). Radiation therapy to the spleen and local graft sites has also been used (Hume, Magee, Kauffman, Rittenbury, and Prout, 1963; as well as thymectomy and splenectomy (American College of Physicians, 1963).

The effectiveness of azathioprine in the suppression of the immune response suggested that it might be useful in the treatment of diseases of the “autoimmune” or hypersen-

* Received for publication August 28, 1967.

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‡ Other common names are B.W. 57-322 and “Imuran”.

sitivity type. It has been used in treatment of acquired haemolytic anaemia and disseminated lupus erythematosus.

The exact aetiology of sympathetic ophthalmitis is still unknown. Duke-Elder (1966) discussed the two most likely theories of causation, the first being that of direct infection of the contralateral eye, and the second that of hypersensitivity or autoimmune response. In the latter, absorption of the uveal pigment from the damaged eye into the circulation is thought to lead to antibody formation and reaction with the newly foreign antigen in the contralateral eye.

Case Report

A boy aged 3 years 9 months was referred on April 28, 1967, with a perforating injury to the left eye, caused by a fish-hook when his father cast a fishing line.

Examination.—There was a 15 mm. perforating corneal wound extending from the limbus at 10 o'clock into the sclera at 2.30 o'clock. Iris and vitreous had prolapsed.

Treatment.—The prolapsed tissues were abscised and the wound closed with nine silk sutures. Hyalase was used to debride the scleral wound. Air was injected and retained *via* a separate corneal paracentesis at 5 o'clock. 500 mg. soframycin were injected subconjunctivally and atropine drops and terramycin ointment were instilled.

Progress.—Slit-lamp examination was impossible postoperatively because of lack of co-operation, so each week the eye was examined under general anaesthesia using a loupe. The eye progressively became quieter. The anterior chamber was well formed, with moderate flare, and clear fundus details could be seen except on the last examination, when the fundus details were blurred. No steroids were used at this stage either locally or generally.

On June 16, 1967, 7 weeks after the injury, the parents noticed a red, watery right eye, of 24 hours' duration. By this time the boy was more co-operative and the slit lamp showed two plus cells and flare in each anterior chamber. Exudate was present in the right pupil, with posterior synechia formation. No keratic precipitates were seen in either eye. A diagnosis of sympathetic ophthalmitis was made and the injured left eye was excised immediately, on the basis that removal of auto-antigen would ameliorate the course of the disorder.

Pathological Report (Dr. C. H. Greer, Department of Pathology, Royal Victorian Eye and Ear Hospital)

MACROSCOPY.—The globe is rather soft and there is a linear almost horizontal corneal scar extending from 10 to 2 o'clock. The retina is in place and the vitreous partly watery. The lens is thin but clear and there is a knot of scar tissue behind the wound where part of the iris is missing.

MICROSCOPY.—Sections show a large area of scarring in the upper cornea near the limbus whence granulation tissue passes back to incarcerate iris remains and spread out behind the lens. There is diffuse uveitis, most marked in the ciliary body where the foci of inflammatory cells contain epithelioid cells in addition to lymphocytes and eosinophils. Early Dalen-Fuchs nodules are evident. There is haemorrhage in the suprachoroidal space anteriorly where the choroid is detached. The retina at the inferior ora serrata is probably torn. Brightly eosinophilic serous exudate is present in the outer plexiform layer of the retina around the disc. The appearances are consistent with early sympathetic ophthalmitis.

Diagnosis.—Perforating corneal injury (fish hook); retinal tear; early sympathetic ophthalmitis.

Postoperative Management

- (1) Intramuscular hydrocortisone 30 mg. 6-hrly for 3 days, followed by prednisolone 10 mg. four times a day by mouth.
- (2) Azathioprine 50 mg. daily.

Intensive treatment was given to the right eye at the time of enucleation with subconjunctival depomedrol 0.50 ml. and mydracaine min. V. This was followed by 1 per cent. hydrocortisone

drops hrly, 1 per cent. hydrocortisone ointment hrly, 1 per cent. atropine drops 4-hrly, and 0.5 per cent. atropine ointment at night.

Blood estimations, performed initially three times weekly, were normal.

Result.—The right eye quietened rapidly on this regime, and after one week only an occasional cell was evident with the slit lamp. The posterior synechiae pulled off the anterior lens capsule allowing wide pupillary dilatation.

On July 21, 1967, the visual acuity in the right eye was 6/6 (E test) and the eye was white, with no cells evident on biomicroscopy. No fundus abnormality was seen.

Present Management.—This consists of prednisolone 2.5 mg. daily, azathioprine 50 mg. daily, atropine 1 per cent. 1 drop twice daily and 1 per cent. hydrocortisone ointment three times daily, night (to the right eye).

Comment

It is intended to maintain the present dosage of azathioprine for several months, with blood counts at regular intervals. The systemic prednisolone will be carefully reduced, using slit-lamp control.

The rapid improvement seen in this patient may well have occurred because of prompt excision of the exciting eye with removal of the source of antibody stimulation. Local and systemic steroid treatment have helped to prevent destructive sequelae during the acute phase of the inflammation. However, because of the normally grave visual prognosis in sympathetic ophthalmitis, one considers that the use of the immuno-suppressive agent azathioprine could well have dampened the inflammatory reaction in the sympathizing eye. The management of perforating injuries in children should, of necessity, be more radical when accurate slit-lamp assessment is not possible.

I am grateful to Dr. D. O. Crompton, for suggesting the use of azathioprine, to Mr. Peter Knight, surgeon for advice in its administration, to Dr. C. H. Greer, for the pathology report, and to Messrs. Burroughs Wellcome for supplying the drug.

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ADDENDUM

Twelve months after the diagnosis of sympathetic ophthalmitis, azathioprine treatment was discontinued. There has been no recrudescence of the inflammation in the 3 weeks since then. At present the treatment is prednisolone 2.5 mg. on alternate days, 1 per cent. atropine 1 drop twice daily, and 1 per cent. hydrocortisone ointment thrice daily, both to the right eye.

If autoantibodies do occur in this disorder and if they disappear over a period, then the above treatment would appear to be logical. If, as in certain other instances, antibody persists for life, then azathioprine would need to be given indefinitely.