Medical Memoranda

Sustained Azathioprine-induced Remission in Wegener's Granulomatosis

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Malignant granulomatous disease of the respiratory tract has a relentless progressive course which as yet has not been greatly influenced by treatment.

In the case reported below azathioprine appears to have effected amelioration of this condition. Of particular significance is the continuance of this satisfactory state in the months following cessation of immunosuppressive therapy.

CASE REPORT

In 1962 the patient, a woman then aged 57, had been under investigation because of vitreous opacities. Special examinations showed negative x-ray films of the chest, sinuses, and jaws, and a normal blood urea. No significant features developed until the second half of 1967, when her general health and energy deteriorated. She had lost considerable weight and experienced severe headaches and pronounced nasal obstructive symptoms with discharges, which was not infrequently bloodstained.

On examination the essential abnormality was numerous scattered granulating areas in the nasal, pharyngeal, and subglottic zones. Again x-ray films of the chest, sinuses, and skull showed no changes. Biopsy specimens taken from various affected sites revealed a granuloma, showing dense infiltration with plasma cells, lymphocytes, eosinophils, and multinucleated giant cells, and a vasculitis, consistent with a diagnosis of Wegener's granulomatosis. The patient's general condition indicated considerable ill-health. There was no abnormality of the levels of haemoglobin, white cells (total and differential), platelets, blood urea, or serum proteins. X-rays showed no evidence of bone disease, and the E.S.R. (Westergren) was 106 mm. in the first hour.

Prednisone was prescribed in a dosage of 20 mg. q.d.s. No response in her local or general state resulted, and while under treatment she complained of numbness and paraesthesia of the distal parts of the lower limbs. Abnormal neurological findings were hypoalgesia to the level just above the ankles, with impairment of proprioceptive sensibility and an ataxic gait, but no motor phenomena were evident. In view of the progress of the disease in spite of corticosteroid treatment, this was gradually "tailed off," and azathioprine was prescribed at a daily dosage of 100 mg. Within a few days the patient had improved subjectively and objectively with the disappearance of the neurological signs of the polyneuropathy and the granuloma, so that after two months on azathioprine therapy no lesions were visible in the upper respiratory tract.

After one month's treatment the E.S.R. reading in the first hour fell to 36 mm. and subsequently was maintained in the region of 10 mm. The patient was discharged on a dosage of 50 mg. of azathioprine daily, but several weeks later anorexia and nausea appeared, as these effects were attributed to drug intolerance azathioprine was discontinued. To date the general well-being has been maintained, regular re-examinations have shown no indication of local recurrence of the granulomatous condition, and the E.S.R. level has not increased.

In summary, her prednisone therapy extended over three and a half weeks before it was progressively reduced; azathioprine was then prescribed at 100 mg. daily for two months and at 50 mg. daily for a further 10 weeks. All therapy has been discontinued over a 15-month period, with no indication of recrudescence of the disease process.

COMMENT

The concept that Wegener's granulomatosis represents an immunological reaction prompted the use of corticosteroid therapy. Reports of the results of such treatment have been somewhat contradictory, but in general it has proved of limited value and has been attended by multiple side-effects (Beidelman, 1963).
A logical extension was the use of drugs with immunosuppressive activity. Successful issues have been reported in lethal mid-line granuloma. In one case cyclophosphamide and steroids were combined (Greenspan, 1965), and in another intravascular infusion of methotrexate was used (von Leiden and Schiff, 1964). Dramatic improvement was obtained in a case of Wegener's granulomatosis treated with nitrogen mustard and chlorambucil (Holland and Manning, 1967). A pronounced beneficial response occurred after azathioprine therapy in a patient with Wegener's granulomatosis in whom biopsy had shown renal involvement, and after a year's therapy normal renal function had been preserved. A repeat renal biopsy had shown reduced activity of the lesions, the nasal and pulmonary affection had responded in large measure, the originally high serum level of gammaglobulin had been reduced, and there was a reversal of the direct Coombs test to negative (Bouronce, Smith, and Cuppage, 1967).

Azathioprine induced a prolonged remission in two patients with advanced Wegener's granulomatosis and renal insufficiency. Systemic symptoms responded, the pulmonary lesions regressed, the proteinuria was reduced, and progression of the renal failure was arrested, though the histological lesions were still evident on the examination of subsequent renal biopsy material (Kaplan, Hayeslett, and Calabresi, 1968). It is of considerable significance that chemotherapy was instituted only after high doses of corticosteroids had failed to control progress of the disease. Duazomycin A, a glutamid antagonist, was given in combination with azathioprine but was thought to have played a minor part, and small doses of prednisone were continued, as there is evidence that exogenous corticosteroids may have beneficial properties for those receiving antimetabolites as immunosuppressive therapy (Adams, Gordon, and Maxwell, 1967).

Two patients with Wegener's granulomatosis whose prognosis seemed extremely poor obtained clinical remission lasting 12 and 17 months respectively on a combined regimen of corticosteroid and azathioprine therapy (Norton, Suki, and Strunk, 1968). Serial measurements of the glomerular filtration rate showed significant improvement of renal function; it was not possible to assign a role of primary importance to either drug alone or in combination, but in both patients serious side-effects could be attributed to the use of high doses of corticosteroids. The extended period of survival of patients treated with antimitotic therapy is presented by Brown (1969); he considers that it is unjustifiable to withhold this form of treatment and that it is superior to corticosteroids alone.

The present patient showed a lack of response to corticosteroids, and, indeed, deterioration was obvious until azathioprine therapy was introduced. The beneficial effects on the patient's general condition, the total disappearance of the local lesions, and the response of the peripheral neuropathy all occurred soon after the start of azathioprine, and leave little doubt that this was the agent responsible for the remission. That this remission has endured for 15 months, even after discontinuance of this treatment, is striking. It may well be that this case represents a more benign example of this group of disorders; but the results afford encouragement for continued trials of this form of treatment and for combinations of various immunosuppressive agents in the more resistant varieties. The shortcomings of azathioprine alone are, however, evident in that inquiry regarding its current usage in Wegener's granulomatosis has revealed a beneficial effect in only one of three cases (B. Mornington, personal communication, 1968).

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REFERENCES

Accidental Poisoning in Children in Uganda

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The incidence and mortality of accidental poisoning in children are very high in Britain (Craig and Fraser, 1953; Swinscow, 1953; Sweetnam, 1968) and in the United States (Nelson, 1968; Beeson and McDermott, 1967), and in many countries are increasing (Craig and Fraser, 1953; McKenzie, 1960; McDonald, 1961; Ingle et al., 1966; Sweetnam, 1968). There is no published report from Uganda showing the nature and extent of accidental poisoning in childhood. This paper reports such findings from a retrospective study.

MATERIAL AND METHOD

The material for investigation was collected from the records of children admitted to the children's ward of New Mulago Hospital during a period of six years from January 1963 to December 1968. During this period 130 children were admitted with accidental poisoning; of these seven died. The total number of children admitted during the same period was 20,061. Thus children admitted for accidental poisoning accounted for 0·65% of the total admission of children. On all but one occasion (an accidental injection) the poison was ingested either as therapeutic overdosage or as a true accidental poisoning. Cases of suspected poisoning were excluded, as were the three cases of snake-bite, three of bee-sting, and nine of dog-bite. There were no repeaters.

Many types of poison were found to have caused the accidents, and an attempt was therefore made to classify the poisons into four broad groups similar to those of Swinscow (1953).

Household agents—meaning poisons used in homes and gardens
Food agents—meaning substances used as food or drink
Miscellaneous—those substances that cannot be grouped in any of the above categories.

FINDINGS

The groups of poisons and their incidence are shown in Table I.

Medicaments were the second largest cause of accidents, being involved in 36·9% of the total cases, which included 29 therapeutic accidents and 19 true accidental poisonings. These