enzyme is cytotoxic in vivo to leukaemic lymphoblasts and myeloblasts that are resistant to other drugs; it may also depress normal haemopoiesis. The pronounced antileukaemic activity of glutaminase in man demands further evaluation.

The short half life of glutaminase in the blood may be a disadvantage, as frequent injections or intravenous infusion may be necessary. The acinetobacter glutaminase has a half life of only one to two hours in mice but this can be extended to nine to 15 hours by succinylation or glycosylation of the molecule;[20] these manipulations might similarly affect the achromobacter enzyme. A prolonged blood half life may be unnecessary if tissue depletion of glutamine persists for long periods. Satisfactory tissue depletion occurred in mice given daily intraperitoneal glutaminase,[14] but in these animals the half life of the enzyme had been prolonged by infection with lactate dehydrogenase virus. Studies in uninfected mice would be more relevant to the treatment of patients. The optimum schedule for administering glutaminase in man may be deduced from the duration of glutamine depletion in the blood after single doses, but clinical trials to compare different schedules will be necessary.

Depletion of glutamine might be expected regularly to produce metabolic acidosis, since the kidney uses glutamine as a source of ammonia to excrete excess hydrogen ions. In mice, however, although glutaminase produces glutamine depletion in many tissues, its concentration in renal tissues rises, apparently because glutamine biosynthesis in the kidney is increased.[14] The metabolic acidosis in case 9 might have been attributable to the patient's age; also he received the largest absolute daily dose of glutaminase (40 000 IU) because of his size. Close monitoring of blood pH during glutaminase treatment is desirable until the frequency of metabolic acidosis is established and factors predisposing to it are identified. Lower doses of glutaminase, or prophylactic administration of alkali, might avert this complication.

The place of glutaminase in leukaemia treatment is open to conjecture. Its activity against asparaginase-resistant cells[12] and in our asparaginase-resistant patients suggests its use in such cases. Glutaminase might prove beneficial in patients who develop allergy to asparaginase and might replace asparaginase altogether since it removes asparagine as well as glutamine: simultaneous deprivation of two amino-acids, rather than of asparagine alone, might confer extra therapeutic advantage. Finally, glutaminase may have in its own right a place in leukaemia treatment. Its activity in vitro against chronic lymphocytic leukaemia[9] suggests its study in selected cases, as well as in prolymphocytic leukaemia,[21] which characteristically is refractory to treatment. Its activity in ALL and AML in the present study suggests that glutaminase should now be studied in patients with acute leukaemia who are at an earlier stage and in better general condition.

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Requests for reprints should be addressed to Professor A S D Spiers, Division of Medical Oncology, University Hospital, 75 East Newton Street, Boston, Massachusetts, 02118, USA.

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SHORT REPORTS

Bronchial reactions to aerosol inhalant vehicle

Freon-based aerosols are widely used for the delivery of both sympathomimetic drugs and, more recently, the corticosteroid agent beclomethasone diproprionate (Becotide). A fall in the specific airway conductance of both asymptomatic and asthmatic subjects after the inhalation of aerosol propellant vehicle has been reported, but these changes were not great enough to produce symptoms.[1] Patients sometimes report that the use of beclomethasone aerosol provokes mild wheezing, and they are usually advised to inhale a sympathomimetic bronchodilator aerosol first. We report here three asthmatic patients who had stopped using beclomethasone diproprionate because of such reactions. A possible causative role for the aerosol vehicle was therefore examined.

Patients, methods, and results

Three atopic patients (cases 1-3), aged 32, 48, and 54 years, were tested. Each had perennial asthma and had been using oral corticosteroids and a bronchodilator aerosol. In each case the bronchodilator aerosols were symptomatically beneficial and there were no obvious adverse effects. From the first inhalation of the beclomethasone aerosol all three experienced increased breathlessness and wheezing within minutes of using the inhaler. The following tests were made on different days in each of the patients: (1) the patient made two inhalations of the placebo aerosol which contained only the propellant vehicle (trichlorofluoromethane (propellant 11) and dichlorodifluoromethane (propellant 12)); (2) test 1 was repeated but was preceded by inhalation of 20 mg sodium cromoglycate (Intal); (3) test 1 was repeated and followed by the inhalation of two puffs of salbutamol aerosol (Ventolin) 20 minutes later; (4) the patient inhaled the propellant Freons (*a*) gaseous propellant 11, obtained by heating liquid propellant 11 to its boiling point, and, on another day, (*b*) gaseous propellant 12, obtained as a compressed gas; (5) the patient underwent bronchial provocation tests with histamine; (6) the capacity of gaseous propellant 12 to release histamine from the patients' white blood cells was tested.

The inhalation of the placebo aerosol caused the patients' forced expiratory volume in 1 second (FEV_1) to fall by 20% or more from the stable basal value (see table). This fall was maximal after five minutes, and the FEV_1 returned to normal over the next 45 to 60 minutes. The inhalation of sodium cromoglycate (test 2) blocked the reaction in two of the three patients, and the inhalation of salbutamol aerosol (test 3) resulted in return of the FEV_1 to pretest levels (see table). There was no reaction to the inhalation of gaseous propellant 11 or 12 (test 4), and bronchial reactivity to histamine was not especially marked (test 5). Only minimal amounts of histamine were released by gaseous propellant 12 from the leucocytes of both the patients and of control subjects, suggesting that Freons were not acting as a histamine releaser.

Four other patients (cases 4-7) with severe perennial asthma, who were

FEV_1 values (litres) in three patients after inhalation of Freon aerosol propellant

Case No:	1	2	3	4	5	6	7
Basal FEV_1	2·45	1·25	1·55	1·85	2·3	2·1	1·75
FEV_1 after Freon aerosol	1·65	0·9	0·95	1·85	2·3	2·1	1·75
FEV_1 after salbutamol aerosol	3·25	1·65	1·85	2·40	3·25	3·05	2·55

being treated with oral corticosteroids and beclomethasone diproprionate with no obvious adverse effects, did not react to inhalation of two puffs of placebo aerosol.

Discussion

Although the method of exposure was different, the absence of reaction to the gaseous Freons suggests that they were not the component responsible for the reactions to the aerosol propellant. The only other agents to which exposure may have occurred were the aluminium can and a range of extractives from rubber components of the metering valve.

There is no direct evidence that the asthmatic reactions were of an allergic nature, and some form of non-specific bronchial irritation seems a possible explanation. Such reactions to the aerosol vehicle may be obscured when it is being used for bronchodilator drugs that are effective. Investigation of adverse reactions of the sort described are indicated in patients presenting with such a history and possibly also in patients who fail to respond or who respond poorly to aerosol bronchodilators.

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Cardiothoracic Institute, London SW3 6HP
D H BRYANT, MD, FRACP, clinical assistant
J PEPYS, MD, FRCP, professor of clinical immunology

Miliary tuberculosis presenting with multifocal oral lesions

Extensive tuberculosis lesions of the oral cavity are rare and show few typical diagnostic clinical features.[1] A case recently seen in Kaduna, Nigeria, presented unusual oral features and resulted in the diagnosis of miliary tuberculosis.

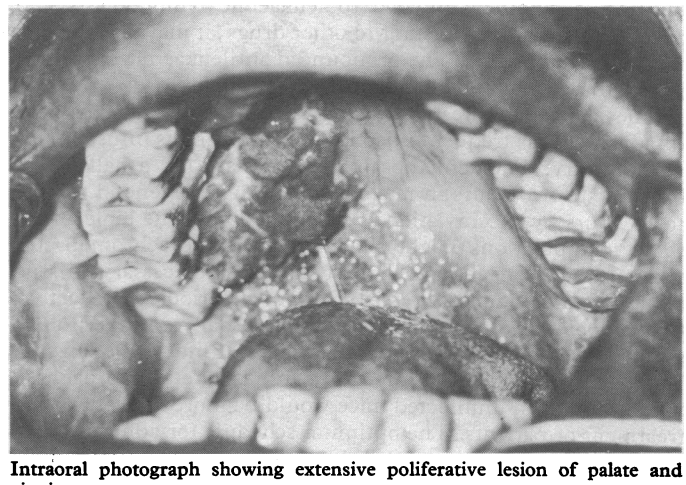
Case report

A 45-year-old Tiv farmer complained of discomfort around the gums in both his upper and lower jaws; he had had pain in the mouth but this interfered only slightly with his ability to chew hard foods. These symptoms had been present for about two years, and shortly before presentation he had noticed loss of appetite and loss of weight associated with cough, scanty sputum, and no haemoptysis. His presentation at the clinic, however, after a journey of over 300 miles, was because of his oral discomfort.

On examination there was an extensive proliferative granulomatous lesion affecting the gingivae, the buccal mucosa, and the palatal tissues in the upper right molar region (see fig); a separate but similar lesion was present in the lower left premolar region which extended buccally to the inner aspect of the lower lip and lingually to the floor of the mouth. He was afebrile. Enlarged lymph nodes were felt in the right anterior triangle of the neck. His liver was palpable 4 cm below the costal margin and was not tender. Choroida tubercules were not seen. Chest *x*-ray examination showed miliary mottling throughout both lung fields.

Biopsy of the oral lesions showed acid-fast bacilli, epithelioid cells, Langhans's giant cells, and early caseation. The liver biopsy specimen contained many epithelioid cell granulomas with giant cells and slight central necrosis. The Mantoux test initially gave negative results; the haemoglobin concentration was 10·9 g/dl, and the white blood count 3·9 × 10^9/l (3900/mm^3) with 7% myeloblasts. Total protein was 85 g/l and albumin 5 g/l.

Mycobacterium tuberculosis was cultured from both the oral lesion and the sputum. He was treated with streptomycin 1·0 g intramucularly, sodium para-aminosalicylic acid (PAS) 6 g, and isoniazid 300 mg daily. Within three months of starting chemotherapy the oral lesions had fully healed and the miliary mottling had cleared. While taking PAS and isoniazid his weight increased from 45 kg to 51 kg, his condition improved, haemoglobin rose to 14·2 g/dl, and the white blood count was 9 × 10^9/l (9000/mm^3) with a normal differential count. His Mantoux reaction became strongly positive when his nutritional state improved.[2]



Intraoral photograph showing extensive poliferative lesion of palate and gingivae.

Discussion

Tuberculosis remains an important disease in developing countries and among immigrants to developed countries.[3] The oral lesion is usually described as an irregular ulcer with undermined edges that slowly increases in size and is painful. Any site in the oral cavity may be affected, particularly areas of trauma, and the important differential diagnoses include simple traumatic ulceration and squamous cell carcinoma. A more diffuse granular proliferation of gingival tissues may occur, and extensive multifocal and proliferative lesions were seen in this case.

The oral lesion is usually secondary to pulmonary infection as a result of direct inoculation or, rarely, as a result of haematogenous spread from sites in the pulmonary, gastrointestinal, or genitourinary tracts.[4] In this case the two-year history of oral symptoms leading to the diagnosis of miliary tuberculosis seems to indicate the primary nature of the oral lesion. Nevertheless, the presence of a multifocal oral lesion supports the hypothesis of secondary implantation or haemotogenous spread in a case of disseminated disease. We feel, however, that this oral lesion was primary and preceded the symptoms of miliary tuberculosis by several months, and indeed remained the chief complaint throughout.

Any lesion presenting in the oral cavity must be fully investigated, and assessment should include full physical examination, biopsy, and chest *x*-ray examination. We have confirmed the value of liver biopsy in miliary tuberculosis, and the identification of *Mycobacterium tuberculosis* on culture, although essential, must not delay the use of antituberculosis drugs as a therapeutic trial when tuberculosis is strongly suspected.[2 5]

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St George's Hospital, London, SW17 0QT
P G McANDREW, MB, FDS, senior registrar in oral surgery
Maxillofacial Unit, Ahmadu Bello University Hospital, Kaduna, Nigeria
E O ADEKEYE, FDS, senior registrar in maxillofacial surgery
Department of Medicine, Ahmadu Bello University Hospital, Kaduna, Nigeria
A B AJDUKIEWICZ, BSC, MRCP, senior lecturer in medicine