1963. The mean serum urate concentration during an acute attack was 0·49 mmol/l (8·2 mg/100 ml), but there were 10 men, additional to those described here, whose levels ranged from 0·24 to 0·38 mmol/l (4·0 to 6·4 mg/100 ml) and who were taking no drugs. A further three patients, including one woman, had concentrations of 0·22, 0·24, and 0·25 mmol/l (3·7, 4·0, and 4·2 mg/100 ml) respectively but were taking phenylbutazone or probenecid.

A normal serum urate concentration in acute gout may be misleading diagnostically. Polarising microscopy is simple and specific, and the value of a therapeutic test with colchicine should not be forgotten.

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Response of patients offered influenza vaccination by injection and by nasal insufflation

Vaccination against influenza has been advocated particularly in those who are at risk from complications of infection. In the present study "at risk" patients in a general practice with 5400 patients in a residential area in the suburbs of Glasgow were identified using a feature card retrieval system[1 2] and offered vaccination either subcutaneously or intranasally. Patients included were those in the 70 years and over age group, those with chronic chest or heart disease, and patients taking steroids. Four hundred and thirty-four such patients were identified. The aim was to determine the number of patients at risk; the number who accepted the offer of influenza immunisation; whether the form of immunisation affected the response rate; and to compare the response in the "at risk" patients with those in a "healthy" group.

The study

"At risk" patients were randomly allocated to one of two groups, those from the same family being allocated to the same group. The 228 patients in group A were sent a letter which invited them to attend the surgery without an appointment for immunisation by nasal insufflation, using a killed virus vaccine insufflation manufactured by Duphar Laboratories. The 206 patients in group B were invited to telephone to arrange an appointment for influenza vaccination by injection. Overall, about one-third of the patients accepted the offer of immunization (table). In the group of patients with disease about one-half responded, compared with just over a quarter in the 70 and over age group. There was no significant difference in the response rate between those offered immunisation by injection and those offered immunisation by insufflation.

A further 310 "healthy" patients in the age group 50-69 were selected from the practice. This group was subdivided randomly into two groups, one group being offered immunisation by injection and the other immunisation by insufflation. As with the "at risk" group, overall about one-third of the patients responded. Nevertheless, in this group more patients responded to the offer of immunisation by insufflation (37%) than to immunisation by injection (23%)—a significant difference ($P < 0.01$).

Number of "at risk" patients responding when offered influenza vaccination

	Patients with chronic respiratory or cardiac disease or on steroids		Patients aged 70 years and over		Total	
	No offered	No (%) accepting	No offered	No (%) accepting	No offered	No (%) accepting
Nasal insufflation..	44	22 (50)	184	52 (28)	228	74 (32)
Injection ..	33	16 (48)	173	48 (28)	206	64 (31)
Total ..	77	38 (49)	357	100 (28)	434	138 (32)

Discussion

While immunisation of patients at risk from influenza (estimated in this study to be about 8% of the practice) is widely advocated, this advice is not always followed in practice and only a small proportion of such patients are in fact protected. In this study, only one-third of patients responded to the offer of immunisation, although a higher proportion of patients with disease responded than patients in the 70 years and over age group. This difference could not be accounted for by difficulty in attending the surgery as domiciliary immunisation was also offered to this group. Possibly patients in the older age group are less willing to accept medical intervention unless they consider it necessary. Many patients in this group may have felt well and indeed the response rate was similar to the overall response rate in the 50-60-year-old control group.

We felt that the fear of an injection might deter patients from accepting immunisation. While this might be a factor in the "healthy" group of patients, there was no evidence for this in the "at risk" group. Thus, if a maximum response rate is wished for in "healthy" patients immunisation intranasally is more likely to achieve this than subcutaneous administration of the vaccine.

We are grateful to Duphar Laboratories Limited, Southampton, for help and provision of vaccine and to Drs Thorburn, Prentice, Kiernan, and Budge for their co-operation.

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Cushing's disease: failure of treatment with cyproheptadine

The successful treatment of three patients with pituitary-dependent Cushing's disease with cyproheptadine has recently been reported.[1] We have studied pituitary and adrenal function in a 13-year-old boy with Cushing's disease and found cyproheptadine to be ineffective.

Case report

A 13-year-old boy presented in November 1975 with obesity and short stature. He had always been plump but had not grown for three years. He had become an extremely light sleeper and emotionally labile but had had no headaches, visual disturbance, or weakness. His weight was above the 75th centile and height below the 3rd centile. He had a plethoric facies, a moderate "buffalo" hump, profuse axillary hair, pubic hair stage 4, external genitalia stage 3, and testicular volumes of 8 and 6 ml. Blood pressure, fundi, and visual fields were normal. Bone age was 12·3 years.[2] Skull *x*-ray picture was normal. Pituitary and adrenal function tests (table) confirmed the diagnosis of Cushing's disease. The plasma cortisol rose from a rather high resting concentration of 402 nmol/l to 520 nmol/l (14·6 μg/

100 ml to 18·8 μg/100 ml) at 90 minutes in response to an insulin-induced hypoglycaemia of 2·2 mmol/l (40 mg/100 ml) at 30 minutes, while the growth hormone concentration fell paradoxically from a resting value of 14 mU/l to 0·8 mU/l at 60 minutes. There was loss of diurnal variation in the concentrations of growth hormone and prolactin. Hypothalamus-pituitary-thyroid function and gonadotrophin values were normal. A sleep electroencephalogram (EEG) showed no appreciable decrease in slow-wave (stages 3 and 4) sleep.

He was treated with cyproheptadine 8 mg/day, increasing to 24 mg/day over two months. He immediately became less irritable and emotionally labile, and his sleep pattern improved so that he no longer woke at the slightest sound. There was no increase in height. His adrenal function was unaltered (table), and after six months bilateral adrenalectomy was performed (Professor L P LeQuesne). Two rounded, fleshy adrenal glands were removed, histological examination of which confirmed diffuse hyperplasia of the cortex of both glands.

Results of pituitary and adrenal function tests

Date	Treatment status	Plasma cortisol (nmol/l)		Urinary free cortisol (nmol/24 h)	ACTH (ng/l)	
		9 am	Midnight		9 am	Midnight
12 Jan '76	Baseline	557	380	330	56	50
13 Jan '76	Baseline	460	467	365	27	50
14 Jan '76	Baseline	555	350	386	27	30
27 Feb '76	Cyproheptadine 8 mg/day	365	340	605		
30 April '76	Cyproheptadine 16 mg/day	440	410	405		
11 June '76	Cyproheptadine 24 mg/day	440	410	570		

Conversion: SI to traditional units—Plasma cortisol: 1 nmol/l ≈ 0·04 μg/100 ml. Urinary free cortisol: 1 nmol/24 h ≈ 0·4 μg/24 h.

Comment

ACTH release is controlled by the hypothalamus, and serotonin may act as a transmitter. In Cushing's disease the underlying fault is in hypothalamic regulation, and other abnormalities of hypothalamic function, such as loss of diurnal variation in growth hormone and prolactin concentrations, abnormal growth hormone responsiveness to hypoglycaemia, and an abnormal sleep EEG, may be found.[3]

Cyproheptadine is a centrally acting serotonin antagonist that blocks hypoglycaemia-induced cortisol secretion.[4] Its use in hypothalamo-pituitary-mediated Cushing's disease seems logical and theoretically provides a treatment of Cushing's disease that avoids bilateral adrenalectomy and reduces the risk of Nelson's syndrome. Its use was unsuccessful in our patient. Krieger recently reported[5] that out of 40 patients with pituitary-dependent Cushing's disease, some 60% were successfully treated with cyproheptadine; she also reported successful treatment of three out of four patients with Nelson's syndrome. One of her patients, however, who had a normal proportion of slow-wave sleep failed to respond to cyproheptadine. This was also the case in our patient. Perhaps the sleep EEG will be useful in predicting which patients will respond to cyproheptadine.

We thank Dr Lesley Rees, of St Bartholomew's Hospital, for measurements of plasma ACTH, and Professor R W Gilliatt, of the National Hospital, Queen Square, for recording the sleep EEG.

Requests for reprints should be addressed to Dr C G D Brook.

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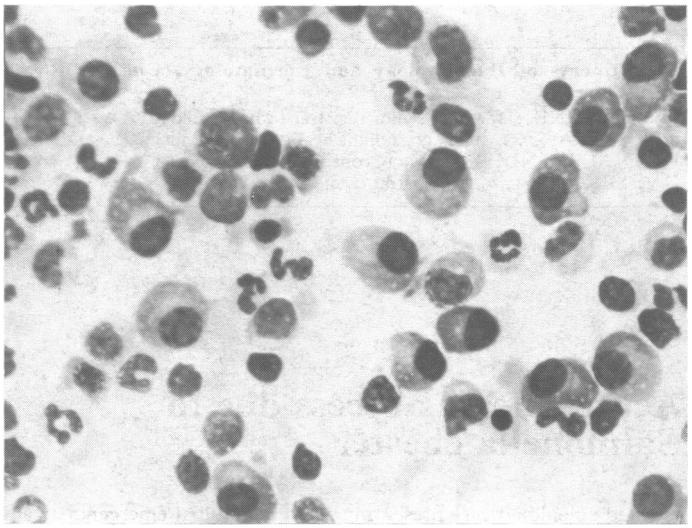
Pruritus as a presentation of myelomatosis

Cutaneous manifestations of plasma cell dyscrasia are uncommon but have been the subject of several reports.[1 2] We report two patients who presented with generalised pruritus in whom diagnoses of myelomatosis were unequivocally established. To our knowledge, this association is unreported.

Case reports

Case 1—A 74-year-old retired factory inspector presented with a widespread itchy infected rash which was initially thought to be infected eczema with sensitisation. Treatment was started with topical steroids and antihistamines to relieve the itch. Investigation showed no evidence of any systemic disease. During the next eighteen months the rash improved and severe generalised pruritus became the dominant complaint. Physical examination now showed small eczematous patches on both ankles and slight axillary lymphadenopathy. Investigation showed a raised ESR (58 mm in 1 h, Westergren) but otherwise normal peripheral blood values. Total serum proteins were 92 g/l with a globulin concentration of 51 g/l. A paraprotein band in the beta-2 position was shown on electrophoresis and immunoglobulin measurement showed an IgG level of 49 g/l (IgA and IgM levels were both reduced). Bence Jones protein was absent. Bone marrow examination showed a plasmacytosis with pleomorphism and clumps of atypical primitive cells (see figure). Skeletal survey showed moderate osteoporosis, but no evidence of osteolytic lesions.



Bone marrow appearances in case 1 showing plasma cell infiltrate. (H and E × 560.)

The diagnostic criteria for myelomatosis were therefore fulfilled. Treatment was initiated with intermittent melphelan (0·25 mg/kg/day) and prednisolone (60 mg/day) for four consecutive days at six-week intervals. Pruritus cleared rapidly after chemotherapy but recurred some ten days before the second pulse became due. A similar sequence of events followed this pulse of chemotherapy but subsequently the patient remained free from pruritus. Biochemical evidence of response was also obtained, with the IgG concentration falling to 20 g/l and other immunoglobulins rising to normal. Eighteen months after starting treatment the patient remains in good health without further pruritus.

Case 2—An 87-year-old retired engineer presented with a one-year history of generalised pruritus and occasional night sweats. He had varicose eczema and mild oedema of both legs, areas of lichenification, and generalised excoriation. Investigation showed a raised ESR (110 mm in 1 h, Westergren), a mild normochromic normocytic anaemia (Hb 11 g/dl), and slight thrombocytopenia of 76·0 × 10^9/l. Serum globulins were increased at 41 g/l. Electrophoresis showed a paraprotein band and immunoglobulin quantitation showed a raised IgA level of 20·1 g/l. Bence Jones protein was absent and skeletal survey negative. Bone marrow examination showed a definite infiltrate of immature and atypical plasma cells, confirming the diagnosis. The results of all other investigations to establish the presence of an underlying systemic disease were negative. A similar chemotherapeutic regimen of melphelan and prednisolone was started and within four months pruritus had cleared completely. Insufficient time has elapsed to assess fully the response to treatment.