drugs mean pressures at entry to phase 2 were related to the mean pressures at entry to phase 1, so pressures before and during treatment were not independent of one another. As these values rose, so did the rate at which pressure rose on stopping bendrofluazide in men; the explanation of this effect is not clear, for it was much less pronounced after stopping propranolol and absent in women after the withdrawal of either drug. A similar effect, with the rate of increase in pressure assessed by return to a target value, has been reported after the withdrawal of treatment,[6,8] but to our knowledge the sex difference and the difference between the thiazide and the β blocker have not.

The results of phase 1 showed that there was no difference between the course of blood pressure in groups receiving placebo tablets compared with people under regular observation but taking no tablets.[3] The phase 2 results confirm that the placebo effect was negligible in men and only very small in women, re-emphasising that the decrease in pressure usually seen in control groups after admission to a trial or entry into a period of observation is likely to be due to the effects both of regression to the mean and of acclimatisation to personnel and procedures rather than to taking placebo tablets.

A period without drug treatment allows the return towards normal of biochemical values which have been disturbed by the drug but may have the disadvantage of increasing non-compliance and loss from follow up. Our results also suggest that pressure must be monitored to assess its return to possibly hazardous levels, since longlasting reduction cannot be expected after the withdrawal of antihypertensive medication.

Computing and statistical work were done by Mr P Brennan, Mr S G Thompson, Mr K Rennolls, and Mr M Singh.

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SHORT REPORTS

Zinc state in anorexia nervosa

Although anorexia nervosa causes appreciable protein energy malnutrition, evidence for deficiency of other nutrients is rare. The disease has several features common to zinc deficiency, including anorexia, impaired taste, and psychological abnormalities,[1,2] and one patient with refractory disease responded specifically to oral zinc supplementation.[3] Unfortunately, assessment of body zinc state is difficult. Low plasma and urinary concentrations with a normal hair zinc content have been found in anorexia nervosa,[1] but these are unreliable measures of body state. We have shown that peripheral blood leucocyte zinc content reflects the tissue state,[4] and we therefore measured neutrophil and plasma zinc concentrations in 14 patients with severe anorexia nervosa.

Subjects, methods, and results

We studied 14 women admitted for inpatient treatment of severe anorexia nervosa. Their weight as a percentage of ideal body weight was calculated from height and weight charts of the Metropolitan Life Insurance Company. Ten control subjects were drawn from normal female laboratory staff of similar ages. Fasting peripheral venous blood (30 ml) was taken from the patients on the morning after admission before refeeding had started. An aliquot was removed for measurement of plasma zinc and albumin concentrations, and then the polymorphonuclear leucocytes were isolated by density gradient sedimentation according to the method of Ferrante and Thong.[5] Contaminating red cells were removed by hypotonic lysis and the cells washed twice in phosphate buffered saline. An aliquot was removed for cell counting by light microscopy, and the remaining cells were digested in 5 ml 1·0M hydrochloric acid for 48 hours. The neutrophil and plasma zinc concentrations were measured by atomic absorption spectrophotometry. Statistical analysis was by Student's *t* test and linear regression.

The mean age of the patients was 21·7 years (controls 25·7 years), and the mean body weight was 71% of the ideal (controls 99%). There was a significant correlation between albumin and plasma zinc concentrations ($n=24$; $r=0·42$, $p<0·05$). Although overall plasma and neutrophil zinc concentrations were comparable in the patients and controls (table), three of the patients had low neutrophil zinc concentrations. Two of these (cases 1 and 11) also had low plasma zinc and albumin concentrations, but in the third (case 13) these two variables were normal. One patient (case 8) had a low plasma zinc concentration as an isolated abnormality, but the remaining eight patients and all the controls had normal plasma and neutrophil concentrations. None of the patients had clinical evidence of zinc deficiency.

Age, weight, and plasma albumin and plasma and neutrophil zinc concentrations in patients with anorexia nervosa

Case No	Age (years)	% Ideal body weight	Albumin (g/l)	Plasma zinc (μmol/l)	Neutrophil zinc (μmol/10^{10} cells)
1	18	72	32	11·5*	0·84*
2	19	65	40	16·4	1·50
3	19	74	35	16·5	1·41
4	19	67	37	13·6	1·46
5	19	79	38	19·0	1·13
6	20	73	33	12·8	1·09
7	20	69	38	15·3	1·21
8	23	71	45	11·6*	1·74
9	23	62	35	13·1	1·64
10	23	81	35	16·1	0·93
11	24	64	29*	9·2*	0·86*
12	25	62	39	17·4	1·22
13	26	79	43	17·7	0·86*
14	26	77	40	15·8	1·05
Mean (SD) in patients			37·1 (4·3)	14·7 (2·8)	1·21 (0·30)
Mean (SD) in controls			37·3 (4·0)	16·5 (1·1)	1·20 (0·19)
Normal laboratory range			31-40	12·4-19·1	0·91-1·71

*More than 2 SD below the mean in the normal population.
Conversion: SI to traditional units—Zinc: 1 μmol=65·4 μg.

Comment

We found a low tissue zinc state, as shown by neutrophil zinc depletion, in only three of our 14 patients. Two patients also had low plasma zinc concentrations, but these depend on the albumin concentration, which was low-normal and low, respectively, indicating coexistent visceral protein depletion rather than low zinc state. A third patient with a low plasma zinc concentration had a normal albumin concentration, but the neutrophil zinc concentration was high and she was thus tissue zinc replete. This is the first time that depletion of tissue zinc has been shown in anorexia nervosa, albeit in a minority of patients, but it may be incorrect to equate this with true deficiency. None of our patients had overt zinc deficiency, although they may possibly have had subclinical untoward effects. Further work is needed to resolve this.

Measurement of the neutrophil zinc content is not a routine laboratory test; as other measures of zinc state are unreliable should zinc supplementa-

tion be part of the treatment of anorexia nervosa? Even though only some patients show depletion of tissue zinc, all patients require zinc as they regain weight. In extreme cases of weight loss, or when patients fail to gain weight, supplementation is probably indicated. Zinc supplementation of subjects who are not deficient, however, may cause copper deficiency with anaemia and may impair immunity. At present, therefore, widespread treatment of anorexia nervosa with zinc is not indicated.

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Subacute encephalopathy associated with human immunodeficiency virus in haemophilia A

Neurological complications associated with the acquired immune deficiency syndrome (AIDS) have been well described in homosexuals and drug abusers but not in haemophiliacs. We report on two haemophiliacs who suffered fatal subacute encephalopathy after seroconverting to human immunodeficiency virus (HIV). This is a new manifestation of the disease as seen in haemophilia and has important implications.

Case reports

Case 1—A 25 year old man receiving regular treatment with factor VIII concentrate for severe haemophilia A developed anti-HIV antibody in 1981. In October 1985 he developed axillary lymphadenopathy, a polyclonal increase in immunoglobulin, lymphopenia with a low T4:T8 ratio, and weight loss. The diagnosis was AIDS related complex. In November he was admitted with a *Streptococcus pneumoniae* chest infection. Subsequently he complained of lethargy, poor concentration, and difficulty with micturition. Examination disclosed diminished cognitive function and brisk reflexes. Computed tomography (CT) of the brain showed dilated lateral ventricles and widened sulci consistent with cerebral atrophy. By March 1986 he was incontinent and had difficulty walking and showed signs of a pyramidal tract lesion. A myelogram was normal and lumbar puncture yielded no evidence of infection with bacteria, fungus, toxoplasma, herpes simplex, herpes zoster, cytomegalovirus, or papovavirus. Serological findings were negative for syphilis, hepatitis B, herpes virus, and cytomegalovirus. He remained positive for HIV antibody. One month later he was admitted unable to walk and with paranoid delusions. Relentless neurological deterioration followed with painful spastic quadriparesis and convulsions. He died in July after four months in hospital. Permission for a necropsy was refused.

Case 2—A 48 year old haemophiliac who had been treated with factor VIII concentrate developed anti-HIV antibody in March 1983. In July 1984 he was noted to have axillary lymphadenopathy, thrombocytopenia, and lymphopenia with a low T4:T8 ratio. AIDS related complex was diagnosed. Additionally, he had chronic persistent hepatitis as a legacy of non-A, non-B hepatitis some years previously. He was admitted in August 1985 with weight loss, confusion, unilateral cerebellar dysfunction, and diplopia which was diagnosed clinically as an internuclear ophthalmoplegia. A cerebral CT scan showed low attenuation areas in the white matter of the frontal lobes and also in the right parietal lobe. Cerebrospinal fluid contained no evidence of infection by any of the agents sought in case 1. Similarly, serology and blood culture gave no evidence of infection with any agent other than HIV. He continued to deteriorate and, having progressed to coma, died in October 1985. Permission for necropsy was refused.

Comment

Several neurological syndromes associated with HIV infection have been described in patients with AIDS and also in patients with AIDS related complex.[1]

While an acute encephalopathy occurring as a reversible complication of primary HIV infection has been described in haemophilia A,[2] fatal subacute encephalopathy has not been recognised as a risk for these patients. The probability that the aetiological agent in our patients was HIV is increased by reports that the virus is neurotropic and replicates in brain cells.[3] Additionally, HIV is morphologically and genetically related to the visna virus, a neurotropic retrovirus affecting sheep and goats.[3] The occurrence of subacute encephalitis and other neurological syndromes associated with HIV infection in haemophilia A casts doubt on the recently expressed hope that viral pathogenicity may have been attenuated during preparation of factor VIII concentrate.[4]

Several practical difficulties arose during the investigation and subsequent management of these two patients. Firstly, we were unable to find a laboratory willing to test for HIV antigen in the cerebrospinal fluid of either patient at the time of lumbar puncture. Secondly, the patients required three to four months of barrier nursing and terminal care in facilities usually reserved for acute admissions. In view of the potential number of patients at risk[5] we suggest that consideration should be given to providing supra-regional laboratory and clinical facilities within the National Health Service for the diagnosis and management of syndromes associated with HIV.

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Hypothyroidism after treatment with ketoconazole

I report on two patients, a father and his son, who both developed hypothyroidism after treatment with ketoconazole.

Case 1

This patient, a 40 year old white man, had had severe chronic mucocutaneous candidiasis since the age of 5. The diagnosis had been confirmed by nail biopsy, and he had subsequently remained infected in the mouth, pharynx, larynx, oesophagus, and nails despite numerous and varied treatments, including treatment with vitamin B complex, dilute hydrochloric acid, and sodium thiosulphate in the 1950s; with dequalinium chloride paint, nystatin, amphotericin lotion and lozenges, and polynoxylin in the 1960s; and with intramuscular iron, clotrimazole, flucytosine, and miconazole in the 1970s. All of these treatments had been stopped because they were either ineffective or toxic.

In May 1982 he was given ketoconazole 200 mg orally twice daily, which