and irregular mottled opacities showed in the chest *x*-ray.

Treatment was started with oxygen and bronchotracheal lavage, followed immediately by intermittent positive pressure ventilation with oxygen-enriched air via an oral cuffed Flotex tube. This was followed by antibiotics, bronchodilator drugs, and steroids; the patient was controlled by relaxants and sedatives. Intravenous Intralipid and Aminosol-Fructose-Ethanol was given. On the ninth day of continuous intermittent positive pressure ventilation she developed pitting oedema of the face and extremities. Ascites was present with typical signs of everted umbilicus, shifting dullness, and fluid thrill. Biochemical findings revealed that her serum protein, serum electrolytes, and serum osmolarity were within normal limits. She had a normal electrocardiograph.

The peripheral oedema and ascites were thought to be due to continuous intermittent positive pressure ventilation, as in the case of Dr. J. T. Styles and others (29 August, p. 522) and she was, therefore, subsequently ventilated with a subatmospheric expiratory phase down to -5 cm. H_2O. The treatment was combined with intravenous frusemide. Steroid therapy was stopped as it causes sodium retention. This treatment led to a disappearance of peripheral oedema and ascites. A gross diuresis of two litres of urine was achieved in 24 hours.

The interesting feature of this case lies in the fact that peripheral oedema and ascites developed so rapidly while the child was having intermittent positive pressure ventilation. This treatment has been employed in adult patients with poliomyelitis over much longer periods of time in our special care unit. Peripheral oedema and ascites have not been seen there.—I am, etc.,

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Nocturia during Steroid Therapy

SIR,—Your recent leading article entitled Nocturia during Steroid Therapy (24 October, p. 193) prompts me to record some findings in three recent cases of hypertrophic osteoarthropathy associated with lung cancer. All three noted nocturia. None was receiving any therapy. There were no restrictions in diet. All were up and about for 14 to 15 hours each day.

Case 1.—Male aged 57 years with squamous cell carcinoma of right lung. Plasma sodium 135 mEq/1., and plasma potassium 4·2 mEq/1.

Case 2.—Man aged 63 with inoperable squamous cell carcinoma of right lung.

	8a.m. to 8p.m.	8p.m. to 8a.m.
Urine volume (ml.) av. over 6 days ..	580 (545)	1120 (580)
Total Sodium (mEq.)	61 (58)	139 (84)
Total Potassium (mEq.)	31 (24)	34 (27)
S.G.8	1·017 (1·015)	1·012 (1·016)

The figures in parentheses are the values found five weeks after lobectomy for removal of the tumour. Further assessment will be carried out six months after operation.

Plasma sodium 135 mEq/1., and plasma potassium 4·3 mEq/1.

Case 3.—Male aged 63 with squamous cell carcinoma of right lower lobe. Lobectomy performed, 6 November 1970. Plasma sodium 138 mEq/1., and plasma potassium 3·3 mEq/1.

	8a.m. to 8p.m.	8p.m. to 8a.m.
Urine Volume (ml.) av. over 6 days ..	425	1260
Total Sodium (mEq.)	24	117
Total Potassium (mEq.)	22	33
S.G.	1·017	1·009

	7a.m. to 3p.m.	3p.m. to 11p.m.	11p.m. to 7a.m.
Urine Volume (ml.) av. over 5 days ..	340	520	900
Total Sodium (mEq.)	16·5	35	65
Total Potassium (mEq.)	10	15	17
S.G.	1·013	1·013	1·010

It has been suggested that the oedema and increase in blood flow in hypertrophic osteoarthropathy might be the result of inappropriate stimulation of extra-renal volume receptors (7 March, p. 630). Thus, by day when the patients are up and about, this inappropriate stimulation results in an increase in extracellular fluid volume, with the passing of urine low in volume and low in total sodium. At night a counter to this daytime imbalance might be the naturesis and increased water excretion which follows the overdistension of the atria when excess fluid shifts to the thorax in the supine position.

The cause of new periosteal bone formation in osteoarthropathy is obscure. An increased exchangeable calcium pool with high bone accretion rate has been found in a case of osteoarthropathy.[1] Bone contains a significant amount of exchangeable sodium. Could an increased amount of exchangeable sodium in bone be a prime factor in the calcium disturbance?—I am, etc.,

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Phenytoin, Folate, Vitamin B_{12}, and Cyanide

SIR,—There is evidence that folates lower phenytoin serum levels and enhance its metabolism.[1-3] Thus the improvement in mental state and the increase in fit frequency produced by folic acid might be partly mediated through a decrease in tissue levels of phenytoin.[4]

The part played by vitamin B_{12} seems to be similar. Cytochrome P450 has a crucial role in the oxidative detoxication of a drug, but it is competitively inhibited by other drugs and powerfully by cyanide. There is a small metabolically active pool of cyanide present normally, and this is probably formed from the action of thiocyanate oxidase present in red cells on thiocyanate in plasma. There is a reciprocal relationship between the concentration of plasma cyanide and vitamin B_{12}.[5] Hydroxocobalamin is a powerful cyanide antagonist, with the formation of cyanocobalamin. Consequently phenytoin can impair the detoxication of cyanide and vice versa. It is possible that plasma cyanide concentration may tend to rise excessively in vitamin B_{12}-deficient subjects, and some of the neuropsychiatric complications may result from the neuropathic effects of cyanide.[5] However, with deficiency of vitamin B_{12}, N^5 methyl tetrahydrofolic acid cannot be converted back to tetrahydrofolic acid via the vitamin B_{12}-dependent pathway and therefore accumulates in the plasma. This reduces the amounts of folate available for other metabolic pathways and so results in a functional folate deficiency.

It would also be expected that the rate of accumulation of cyanide is a function of thiocyanate oxidase concentration (and therefore red cell mass).[5] The hypothesis fits in with clinical observations. Patients with uncomplicated pernicious anaemia have a lower serum folate concentration than patients with subacute combined degeneration. Severe anaemia conferred "protection" from neurological complications, and it is usually accepted that the adverse neurological effects of treating pernicious anaemia with folic acid occur after the haematological remission.[5] Administration of folic acid lowered serum-vitamin-B_{12} levels in patients on anticonvulsants.[6] Leber's hereditary optic atrophy may result from a defect in the detoxication of cyanide as well as retrobulbar neuritis of vitamin-B_{12} deficiency and tobacco amblyopia.[7] Hydroxocobalamin has been superior to cyanocobalamin in the treatment of these cases[7 8] Remarkably, toxic amblyopia has also been reported from phenytoin.[9] Phenytoin-induced neuropathy has been unresponsive to folic acid supplements. Thus an interference with the cyanide metabolism can be postulated to play a part in the neuropsychiatric side effects of phenytoin in some patients. It is important that treatment with hydroxocobalamin rather than cyanocobalamin is given with folic acid, since cyanocobalamin may be potentially harmful.[8]

Phenytoin has also a direct neurotoxic action. Since the toxic signs of phenytoin include drowsiness, ataxia, giddiness, blurred vision, nystagmus, confusion, and fits—quite like those of bromide, digitalis, and lithium—it is conceivable that they are due to their interference with the action of adenosine triphosphatase-sodium pump and ion fluxes in nerve cells.[4]—I am, etc.,

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