morbidity survey and found that more deaths were assigned to chronic bronchitis and chronic obstructive airways disease than to asthma.[28]

For every patient with a diagnosis of chronic bronchitis we found another two unlabelled patients with similar symptoms, and for every patient with the diagnosis of asthma we found two or three with wheeze and no diagnosis. This proportion of undiagnosed asthma has also been shown in children.[29,30] Moreover, if the threshold for the diagnosis of asthma was lowered to include any patients who had suffered an episode of wheezing in the past 12 months then up to a third of this population would be eligible for the label of asthma. This large reservoir of patients suggests that substantial shifts in "asthmatic" patients' rates of using hospitals and general practitioners could easily result from changes in diagnostic fashion alone.

The apparent lack of criteria on which the diagnosis of chronic bronchitis can be distinguished from asthma in adults together with the shift away from the label of chronic bronchitis suggests that a diagnostic transfer from chronic bronchitis to asthma has occurred. The increasing morbidity and mortality that is attributed to chronic obstructive airways disease also suggests that a new diagnostic fashion is emerging.[6] Until we have universally agreed clinical and epidemiological diagnoses for asthma, chronic bronchitis, and chronic obstructive airways disease we should be cautious in postulating changes in the epidemiology of respiratory disease only on the basis of trends in drug prescriptions and service utilisation statistics.[31,32]

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Hypophosphataemic rickets after ifosfamide treatment in children

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Ifosfamide is being increasingly used to treat solid tumours in children. Adverse effects include nausea, vomiting, alopecia, myelosuppression, and haemorrhagic cystitis. Nephrotoxicity has been reported in adults, with both glomerular disease[1] and tubular damage, which led to Fanconi's syndrome in two patients.[2,3] Studies in children, however, have not found any appreciable nephrotoxicity.[4] We describe three children with previously normal renal function and bone biochemistry who developed hypophosphataemic rickets due to urinary loss of phosphate after high dose ifosfamide treatment for malignancy.

Case reports

Case 1—A 23 month old boy with embryonal rhabdomyosarcoma of the prostate received local radiotherapy and chemotherapy over 18 months. The chemotherapy comprised ifosfamide (total dose 177 g/m^2), cisplatin (90 mg/m^2 per course with mannitol and hydration, total dose 359 mg/m^2), cyclophosphamide, vincristine, adriamycin, actinomycin D, and etoposide. He remained well with no evidence of recurrence of the tumour, but nine months after chemotherapy ended he developed difficulty in walking due to knock knees. Radiographs of his knees showed signs of rickets and secondary hyperparathyroidism. Further investigations showed a low glomerular filtration rate and renal tubular damage, with an adult type Fanconi's syndrome, comprising hypokalaemia, phosphaturia, hypophosphataemia, glycosuria, acidosis, and impaired urinary acidification and concentration (table). Serum alkaline phosphatase activity was raised. After treatment with oral phosphate his serum phosphate concentration rose to normal and his gait improved.

Case 2—A 4 year old girl with embryonal rhabdomyosarcoma of the left middle ear received radiotherapy and chemotherapy consisting of ifosfamide (total dose 132 g/m^2), actinomycin D, adriamycin, vincristine, and etoposide. After receiving ifosfamide for eight months (108 g/m^2) she developed a painful limp; investigation showed hypophosphataemia, phosphaturia, glycosuria, and raised serum alkaline

Renal function and bone biochemistry in three children after ifosfamide treatment

	Plasma phosphate (mmol/l)	Plasma alkaline phosphatase (U/l)	Plasma potassium (mmol/l)	Plasma calcium (mmol/l)	Plasma magnesium (mmol/l)	Fractional excretion of phosphate* (%)	Fractional excretion of glucose (%)	Glomerular filtration rate† (ml/min/1·73 m²)
Case 1‡	0·39	475	2·3	2·66	0·71	90·7	41·6	66
Case 2	0·49	536	3·4	2·29	0·87	12·2	16·1	162
Case 3§	0·34	439	2·4	2·43	0·96	32·6	50·3	76
Approximate normal range	1·00-1·75	71-212	3·3-4·7	2·13-2·62	0·7-1·0			89-165

*Fractional excretion of a substance (s) in urine calculated by $U_s/P_s \times P_{cr}/U_{cr} \times 100$, where U=urine concentration, P=plasma concentration, Cr=creatinine.
†Glomerular filtration rate measured by clearance of edetic acid labelled with chromium-51.
‡Plasma bicarbonate concentration 14·0 mmol/l; urine pH 6·1; osmolality of early morning urine sample 329 mmol/kg.
§Osmolality of random urine sample 275 mmol/kg; plasma osmolality 283 mmol/kg.

phosphatase activity (table). She continued to receive ifosfamide for a further three months, but the limp persisted and radiographs of her wrists and knees two months later showed signs of rickets.

Case 3—A 3 year old girl with a malignant epithelial schwannoma of the nose received ifosfamide (total dose 124 g/m²), adriamycin, vincristine, and etoposide. Nine months after diagnosis she developed severe nephrogenic diabetes insipidus and the ifosfamide was stopped. She also had more generalised renal tubular damage, and investigation two months later showed phosphaturia, hypophosphataemia, hypokalaemia, glycosuria, and a diminished glomerular filtration rate; serum alkaline phosphatase activity was high (table). Four months later she developed a limp, and radiographs of her wrists and knees confirmed rickets.

Other cases—Investigation of renal function in a further 10 children receiving high dose ifosfamide showed hypophosphataemia in two and considerable phosphaturia in three.

Comment

The three children described developed symptoms and radiological features of rickets with hypophosphataemia despite a normal plasma calcium concentration. The low plasma phosphate concentrations were due to renal tubular damage that resulted in phosphaturia. All were treated with oral phosphate supplements. The two adults previously reported with Fanconi's syndrome after chemotherapy with ifosfamide both had pronounced hypophosphataemia.[2,3] In contrast, the renal tubular damage caused by cisplatin leads to hypomagnesaemia, which was not present in our patients.

The renal tubular problems in our three children were probably caused by ifosfamide. The children all received 9 g/m² per course, given by continuous infusion over three days with mesna and hydration of 3 l/m²/day. This dose schedule has not been widely used elsewhere but is included in the current study of Ewing's tumour by the United Kingdom Children's Cancer Study Group. The short term toxicity of this regimen is tolerable,[5] but this is the first report of long term toxicity.

Hypophosphataemia causes muscle weakness, and rickets develops over several months. These cases and the pronounced phosphaturia found in a further three of 10 children receiving high dose ifosfamide treatment suggest that up to 45% of children receiving this treatment are at risk of developing rickets. Plasma phosphate concentrations should be measured regularly in all such children and phosphate supplements given if hypophosphataemia develops. Further follow up will determine whether the renal damage is reversible.

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Fetal haemodynamic response to acute maternal hyperoxygenation as predictor of fetal distress in intrauterine growth retardation

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Doppler ultrasound has confirmed the redistribution of blood flow that occurs secondary to chronic hypoxia (the so called brain sparing effect) in fetuses with intrauterine growth retardation.[1] We recently found that acute transmaternal treatment with oxygen induced pronounced haemodynamic modifications in these fetuses with temporary return of blood flow velocity waveforms towards normal.[2] This paper reports an investigation assessing the diagnostic value, if any, of the fetal vascular response to transmaternal oxygen as a method of grading fetoplacental compromise in fetuses with retarded growth.

Patients, methods, and results

After getting informed consent we studied 22 fetuses fulfilling the following criteria: (*a*) ultrasonic evidence of abdominal circumference below the fifth centile[3]; (*b*) no evidence of congenital abnormality; (*c*) Doppler velocity waveforms in umbilical artery, descending thoracic aorta, and internal carotid artery abnormal (below the 10th and above the 90th centiles) compared with our reference ranges (see figure); (*d*) reactive cardiotocograms at the time of Doppler measurements.

Fetal blood flow velocity waveforms were recorded from the umbilical artery, descending aorta, and internal carotid artery by means of a commercially available pulsed Doppler system (Ansaldo Esacord 80). Waveforms were obtained as described[2] and