Our patient had no features of phenytoin toxicity despite a concentration of 31.3 mg/ml. After starting tobitamide the phenytoin concentration decreased to 27.4 mg/ml. The total concentration was measured, not the free level. Neither the Committee on Safety of Medicines nor the manufacturer knows of any other cases of phenytoin toxicity produced by tobitamide.

2 Pannenkov JK, cited by Wesseling et al.

Convulsion and coma after intranasal desmopressin in cystic fibrosis

Dr E J Simmonds, M JMahon, and J Mlittlewoood (Regional Cystic Fibrosis Unit, St James’s Hospital, Leeds LS9 7TF) write: Desmopressin has been advocated as a treatment for nocturnal enuresis.2 We report on a child with cystic fibrosis who developed water intoxication while being treated with desmopressin. She passed urine again and continued to make good progress apart from recurrent nasal polyps requiring operative removal. By the age of 12, however, she had developed chronic Pseudomonas aeroginosa respiratory infection and began three monthly admissions for intravenous antibiotics.3 During one of these she started taking intranasal desmopressin (DDAVP) in a concentration of 0.64 µg/ml (130 mg three times a day). Pancreatic and vitamin supplements were continued. She also had primary nocturnal enuresis which was treated with desmopressin nasal spray. She was given four doses on consecutive nights: 0 µg, 20 µg, 20 µg, 10 µg.

On the morning after her fourth dose of desmopressin the patient developed headache, nausea, and vomiting. She had remained dry for the first time the previous night. On examination she had a sharp weight gain since treatment started: 41.35 kg to 43.15 kg. On the third day of treatment serum sodium concentration rose to 146 mmol/l and on the fourth day this had fallen to 110 mmol/l. Later that day she had a convulsion lasting about five minutes and subsequently remained comatose. Her desmopressin was discontinued and she was managed with fluid restriction alone to prevent possible pontine myelo-lysis.4 Twenty eight hours after her last dose of desmopressin she passed urine again and continued to pass good quantities of dilute urine. Forty hours after fluid restriction was started intravenous fluids with her normal daily sodium requirements were started. Her serum sodium concentration rose and five days later was normal (135 mmol/l).

Forty eight hours after her convulsion she was still comatose. Physical examination showed response only to deep pain, poor corneal reflexes, absent cough reflex, and absent peripheral reflexes. Her body temperature was normal and her umbilical puncture showed nothing abnormal. She gradually regained consciousness and over two weeks returned to her normal state of health.

This patient with cystic fibrosis had a severe adverse response to intranasal desmopressin used in doses recommended by the manufacturer; several authors have reported that desmopressin by this route is safe for both short5 and longterm6 treatment of nocturnal enuresis. There are no reports of water intoxication, although toxicity is the basic defect in a few patients treated with intranasal desmopressin for diabetes insipidus.7 It is not clear why our patient responded as she did. Desmopressin is thought to act at the AP1 receptor and our patient had no neurological defects as assessed by a standard neurological examination in the hospital and at home. She had had no intake of drugs or alcohol.

Severe hypersensitivity reaction to fenbufen

Dr M M Muthiah (Bassettlaw District General Hospital, Worksop S81 0BD) writes: The common side effects of the non-steroidal anti-inflammatory drug fenbufen and its gastroprotectant, showed a postural, renal and neurological symptoms.1 The potentially serious side effects are peptic ulceration and gastrointestinal haemorrhage. I report a serious systemic reaction. A 5 year old girl was taking fenbufen 900 mg/day for a painful left knee. She took it for 10 days, and four days after stopping the drug she was well. Two days later she fell to the floor and became unwell with throat pain, fever, and rigors. There was no history of arthritis, drug allergy, or a family history of rhematoid arthritis. She was ill (temperature 40°C) with generalised lymphadenopathy and an extensive erythematous exfoliative rash affecting the whole body and face. The left knee was swollen and tender. Investigations showed: haemoglobin 133 g/l, white cell count 42 x 10⁹/l, eosinophils 10 x 10⁹/l, neutrophils 14 x 10⁹/l, platelets 135 x 10⁹/l, prothrombin time 2.4 s, activated partial thromboplastin time 41 s (control 21-32), fibrinogen normal. Aspartate aminotransferase activity was 15 IU/l (normal 0-9) and alanine aminotransferase 2190 IU/l (230-460), alkaline phosphate 1233 IU/l (100-280), and albumin 30 g/l. A Paul-Bunnell test, autoantibody screen, and toxo-Iasoma antibody titres were all negative. Erythrocyte sedi-

mentation rate, chest radiograph, radiograph of the left knee, and calcium and phosphate concentrations were all normal. She improved rapidly and was discharged after four days. At this stage a liver biopsy showed swollen liver cells with focal cholestasis. Portal areas contained polymorphs with proliferation of bile ductules. The appearances were those of a resolving hepatitis. Lymph node biopsy showed fatty infiltration with atrophy and no evidence of lymphoma. Liver biopsy of the original liver was unremarkable,1 and there were no signs of the underlying non-steroidal anti-inflammatory drugs. Follow up over a year confirmed that she was well with normal full blood count and liver function values.

Fenbufen was first marketed in the United King-

dom in 1980 and was the most commonly reported suspect drug on yellow cards in 1986 and 1987. Eighty per cent of the reactions concern mucocutaneous reactions, including erythema multiforme and Stevens-Johnson syndrome. There have been no reports of Stevens-Johnson syndrome in patients taking fenbufen. The rapid resolution of clinical and laboratory abnormalities with prednisolone was consistent with this. The differential diagnosis is angioimmunoblastic lymphadenopathy, which is known to occur as a hypersensitive reaction to therapeutic agents.

Azaaprazone induced hepatitis

Dr T C N Lo and I W Dymock (Department of Medicine, Stepping Hill Hospital, Stockport) write: Hepatitis is a rare adverse effect with the non-steroidal anti-inflammatory drug fenbufen—a well-known hypersensitivity side effect of most non-steroidal anti-inflammatory drugs—and several cases of fatal hepatitis have been reported.1 Nevertheless, complete recovery after early withdrawal of the offending drug usually occurs if the possible link is recognised.2 We report a case of azaaprazone induced hepatitis in which complete recovery followed withdrawal of the drug.

A 57 year old woman was given azaaprazone (Rheumox) 600 mg twice daily for osteoarthrits of both knees. Two weeks later she developed a macular erythema multiforme with slight involvement of the mucous membranes of the lips and mouth. She was admitted to hospital a week later. Despite this there was no lymphadenopathy, hepatosplenomegaly, or ascites. She had no history of recent travel, contact with jaundiced patients, blood transfusion, infections, or drugs. She made a rapid recovery and did not abuse alcohol. Laboratory investigations showed: haemoglobin 133 g/l, white cell count 11 x 10⁹/l with 4% eosinophils, plasma total bilirubin concentration 42 µmol/l, aspartate transaminase 500 IU/l, γ glutamyltransferase 22 IU/l, alkaline phosphate 2190 IU/l, prothrombin time 17 s (control 12). She was negative for antinuclear factor, antichondrocal antibodies, and antismooth muscle antibodies and had had no recent infections. She was negative for Epstein-Barr virus, cytomegalovirus, varicella zoster, or rubella. Tests for hepatitis A and B were also negative.

Azaaprazone was stopped and her jaundice and rash resolved within one week of admission. A per-

cutaneous liver biopsy performed 10 days after admission showed mild centrilobular cholestasis, slight fatty change, and scanty inflammatory cells distributed widely throughout the liver parenchyma. The Kupffer cell hyperplasia and schistosome scores were Scarff Schiff positive, diastase resistant material. Several portal tracts showed moderate to severe chronic inflammatory changes. There were occasional persistent hepatits with occasional multinucleated giant cells and ill defined granuloma. The overall histological pattern was thought to be compatible with granuloma formation consistent with drug in-

duced hepatitis. She remained well with normal liver function values one month and three months after discharge.

The manufacturers have received only two reports of “suspected” adverse reactions affecting the liver since azaaprazone was marketed in 1976. In each case the link could not be substantiated because of lack of definite temporal relations between drug ingestion and the onset of symptoms and both patients were taking several drugs. The two week interval between the start of treatment and the onset of symptoms in our patient together with negative virological and immunological results ruled out a drug induced hypersensitivity reaction, though the underlying mechanism is still unknown.3 We have reported this case to the Committee on Safety of Medicines.

We thank Dr N L Reeve for his help in reporting the histological findings in this paper.