every 5 cigarettes smoked daily, 95% confidence interval 1·11 to 2·14) but was not a risk factor for sudden infant death syndrome in infants over 24 weeks. On the other hand, when paternal smoking in the absence of maternal smoking was studied there was no significantly increased risk for the young infants with sudden infant death syndrome. The older infants who died were, however, at a significantly increased risk of sudden infant death syndrome if their fathers smoked (estimated relative risk=2·81 for every 5 cigarettes smoked daily, 95% confidence interval 1·11 to 7·15).

There are two types of explanation for how smoking could be causally related to postnatal deaths: smoking during pregnancy may leave the newborn infant more vulnerable, or postnatal passive smoking by the infant may increase the risk of death. These data provide some evidence for the passive smoking mechanism in older infants but not in younger infants, in whom maternal smoking during pregnancy appears to be an important factor lasting well beyond the neonatal period.

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1 Knowelden J, Keeling J, Nicholl JP. *A multicentre study of post-neonatal mortlity*. London: HMSO, 1985.

Computer viruses

Dr John Asbury points out that "a computer virus is a small piece of computer code which has been maliciously inserted on computer storage media" (23 July, p 246). Although this is true in most cases, there remains the possibility that some of these viruses have "evolved" out of random mutations of computer programs.

Some computer viruses are extremely small, consisting of short lengths of machine code. There are many small machine code lengths built in as part of the operating systems of computers to fulfil various tasks, such as reading, writing, and erasing data. Anyone who has ever used a computer will be extremely familiar with computer failures, or "crashes," when all the data in a computer's memory are scrambled and data are lost. This scrambling consists of random substitution of the computer memory locations with tiny fragments of machine code one or two bytes long. It is entirely possible, considering the number of times such events occur and the few substitutions required to mutate an existing length of machine code into a virus (analogous to base pair substitution in DNA), that such viruses will be thrown up quite regularly. Most will be fatal mutations and will wipe themselves out. Others will be stillborn, stable but non-functioning. Even fewer will emerge as infectious viruses. According to Darwinian natural selection, the viruses that are adapted to survive hidden inside computer systems will be the most successful and may proliferate, either as a result of the initial mutation or as a result of subsequent non-fatal mutations.

Thus it is that life of a sort may have evolved in the computer systems designed by humans. The worrying thing is, as Dr Asbury suggests, that these new viruses may be very dangerous indeed, much more so than their biological counterparts. The AIDS virus may eventually kill many thousands of people. *Yersinia pestis* killed many millions in the Black Death. But a lively virus in the control system of an intercontinental ballistic missile may prove a greater human pathogen than any mere biological microbe.

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Drug Points

Hypomagnesaemia and hypocalcaemia after treatment with mitozantrone

Drs K D GRIFFITHS and D H PARRY (Ysbyty Gwynedd, Bangor, Gwynedd LL57 2PW) write: Hypomagnesaemia hypocalcaemia, and hypoparathyroidism have been reported in patients with acute leukaemia and breast carcinoma after chemotherapy.[1,2] We describe a patient with metastatic breast carcinoma who was given chemotherapy which included mitozantrone and developed hypomagnesaemia and hypocalcaemia apparently unrelated to hypoparathyroidism. As far as we are aware these biochemical abnormalities have not been reported with mitozantrone.

A 52 year old woman was referred with recurrent breast carcinoma eight years after a left mastectomy and bilateral salpingo-oophorectomy. After surgery she was treated with tamoxifen and aminoglutethimide and had been receiving thyroxine for several years. Nine months before this referral she had received radiotherapy to the sternum and ribs for painful metastases. Examination showed a mass in the contralateral breast, lymphadenopathy in the neck, and a mass in the left lower abdomen. Routine biochemical investigations gave normal results.

One month later, just before cytotoxic treatment was started, the results of biochemical investigations were: normal urea, creatinine, and albumin concentrations; potassium concentration normal at 3·6 mmol/l; calcium concentration 2·09 mmol/l; alkaline phosphatase activity 484 U/l; aspartate transaminase activity 149 U/l; alanine transaminase activity 83 U/l; and γ-glutamyltranspeptidase activity 33 U/l. An isotope bone scan confirmed multiple areas of increased uptake consistent with widespread metastases.

Chemotherapy with mitozantrone 20 mg (10 mg/m^2), cyclophosphamide 1·2 g (0·6 g/m^2), and vincristine 2 mg was given intravenously. Four days later she was admitted to hospital as an emergency with a grand mal fit having had persistent nausea, vomiting, and diarrhoea. The abnormal biochemical findings were: potassium concentration 2·1 mmol/l, chloride concentration 93 mmol/l, aspartate transaminase activity 73 U/l, alanine transaminase activity 30 U/l, γ-glutamyltranspeptidase activity 25 U/l, calcium concentration 1·54 mmol/l (with a normal albumin concentration), and phosphate concentration 0·91 mmol/l. Magnesium concentration measured a day later was 0·19 mmol/l. Parathyroid concentration was 0·7 ng/ml (reference range less than 0·2 ng/ml), and vitamin D concentration was normal. A random measurement of urinary calcium did not show a significantly increased excretion. No brain metastases were evident on computed tomography.

She was treated with intravenous and oral calcium supplements, vitamin D (as alfacalcidol), and intermittent intravenous magnesium sulphate infusions. The calcium concentration fell to 1·20 mmol/l after admission in spite of replacement treatment, and magnesium concentrations fell rapidly when infusions were stopped, rarely rising above 0·5 mmol/l. The serum albumin concentration was always within normal limits. Initially there was considerable clinical improvement, but continuous replacement treatment with calcium and vitamin D was required to maintain normal serum calcium concentrations.

The initial response to the cytotoxic drugs was complete disappearance of soft tissue disease. Because of the metabolic complications, however, no further chemotherapy was given, and she died of progressive metastatic disease five months later.

The grand mal fit was probably caused by rapid onset of hypocalcaemia and hypomagnesaemia. This rapid onset, occurring within four days, was much faster than has been reported with other drugs having this effect. The probable explanation is that the chemotherapy induced proximal renal tubular damage causing severe loss of magnesium with a concurrent reduction in serum calcium concentration. This would be supported by the low concentrations of potassium and phosphate. The vomiting and diarrhoea may also have been contributory. Similar observations have been made with different cytotoxic drugs,[3] but, unlike Freedman *et al*,[1] we found no evidence of hypoparathyroidism. The side effects of the cytotoxic drugs may have been enhanced by pre-existing impaired liver function related to hepatic metastases. The doses were related to body surface area, and, because the patient was grossly overweight, the dose of drug given may also have been important.

We consider that these profound metabolic abnormalities were probably caused by the cytotoxic chemotherapy, perhaps by inducing renal tubular damage. The case was unusual in that although the patient received continuous calcium, vitamin D, and magnesium replacement until the time of her death satisfactory control was never achieved. As far as we know this has not been reported previously in association with mitozantrone.

1 Freedman DB, Shannon M, Dandona P, Prentice HG, Hoffbrand AV. Hypoparathyroidism and hypocalcaemia during treatment for acute leukaemia. *Br Med J* 1982;**284**:700-2.
2 Gomez-Camphera FJ, Gonzalez P, Camillo A, Estelles MC, Rengel M. Cisplatin nephrotoxicity: symptomatic hypomagnesaemia and renal failure. *International Journal of Nephrology* 1986;7:151-2.
3 Womer RB, Pritchard J, Barratt TM. Renal toxicity of cisplatin in children. *J Pediatr* 1985;**106**:659-63.

Small bowel perforation associated with an excessive dose of slow release diclofenac sodium

Mr M DEAKIN and others (Queen Elizabeth Hospital, Birmingham B15 2TH) write: Intestinal perforation associated with the ingestion of indomethacin is a well documented but uncommon side effect with a high risk of death. There have been seven deaths among the 18 cases reported to the Committee on Safety of Medicines (personal communication). Osmosin, a long acting preparation of indomethacin, was withdrawn because of a number of reported perforations, possibly due to increased local toxicity associated with the formulation and drug delivery system.[1] The risk of perforation is also present with other non-steroidal anti-inflammatory drugs thought to have a lower incidence of side effects.[2]

A 70 year old man was referred with a 24 hour history of pain in the left iliac fossa. He had a fever and signs of localised peritonism in his left iliac fossa. Twenty seven years previously he had had a laminectomy for a prolapsed intervertebral disc. He had suffered with continuous low back pain for many years and had been taking a combination of dipipanone hydrochloride and cyclizine hydrochloride (Diconal) twice daily for two years. Two weeks before admission he had been prescribed the recommended dose of diclofenac sodium, 100 mg daily, in a sustained release preparation (Voltarol Retard). During the week before admission he had increased the dose to 100 mg four times daily.

An initial diagnosis of acute diverticulitis was made, and he was treated with parenteral antibiotics. His fever and abdominal tenderness resolved over 48 hours. Six days after admission he developed increasing abdominal distension and then had a sudden onset of generalised pain and tenderness. A laparotomy was performed, and he was found to have two perforations in the terminal ileum, each about 3 mm in diameter. The terminal ileum otherwise seemed to be normal. A biopsy specimen from the edge of a perforation showed no specific features. The perforations had sealed initially and had remained confined within a small abscess cavity beside the sigmoid colon in the left iliac fossa, thus accounting for his localised signs at presentation. The abscess had ruptured subsequently into the peritoneal cavity. The two holes were oversewn with cat gut, and he made an uneventful recovery. Blood cultures and faecal samples were negative for salmonella.

To our knowledge this is the first reported case of small bowel perforation associated with the ingestion of slow release diclofenac sodium (a phenylalkanoic derivative). Non-steroidal anti-inflammatory drugs, including indomethacin and fenamic acid derivatives, given orally or parenterally to rats cause small bowel perforation within three or four days.[3,4] This effect is dose dependent, is believed to be caused by reduced prostaglandin synthesis by the small bowel mucosa, and can be prevented by giving prostaglandin E_2.[5]

Our patient was suffering from pain that had been difficult to control over a long time, and he had increased his dose of diclofenac sodium to four times the recommended dose. The perforation could have been caused by high local drug concentrations, a factor that might have been exacerbated by taking the combination of dipipanone hydrochloride and