cell count $16.5 \times 10^9/l$ ($16\,500/mm^3$), 90% neutrophils; ESR 131 mm in the first hour; serum uric acid 0.15 mmol/l (2.5 mg/100 ml). Aspiration of fluid from the knee confirmed the presence of crystals. X-ray pictures showed chondrocalcinosis of knees, shoulders, and hips. There were streaks of calcification in the annulus fibrosus ligament of the lumbar spine. He was given phenylbutazone and immediately improved. Subsequent investigations showed a raised serum iron concentration and liver biopsy confirmed the diagnosis of haemochromatosis.

Case 3—A 78-year-old man was admitted to hospital with a two-month history of pain in the neck and lower back accompanied by such severe stiffness that he could hardly move. Four years previously he had an episode of swelling of the left knee. All movements of the cervical and lumbar vertebrae were greatly limited and accompanied by severe pain. There was effusion in the left knee with warmth and tenderness. The white cell count was $8.0 \times 10^9/l$ ($8000/mm^3$), and the ESR 42 mm in the first hour. Aspiration from the left knee showed calcium pyrophosphate crystals. X-ray examination of left knee showed chondrocalcinosis. He was treated with indomethacin, improved remarkably, and was discharged after only one week in hospital.

Comment

These three cases illustrate some unusual clinical manifestations of pyrophosphate arthropathy. All patients presented with an acute illness of sudden onset, and all required admission to hospital. In the first case septic arthritis was simulated in a joint resembling a neuropathic joint. Destructive arthritis associated with pyrophosphate crystals had been described by Richards and Hamilton². In the second case the acute onset of localised spinal pain suggested the possibility of acute disc prolapse. The cause of the spinal symptoms is uncertain, though there was calcification of the annulus fibrosus ligament similar to that described by Richards and Hamilton³. In the third case the association of stiffness and restriction of movement suggested the diagnosis of polymyalgia rheumatica.

We suggest that deposition of crystals in various sites caused these patients' symptoms, but it is difficult to prove. Radiological proof of chondrocalcinosis is not sufficient evidence for pyrophosphate arthropathy, since calcification may well be symptomless in older people. The association of symptoms with pyrophosphate deposition was suggested by their acute onset, inflammatory features such as raised ESR, the finding of effusions containing pyrophosphate crystals, and rapid response to non-steroidal anti-inflammatory drugs.

¹ McCarty, D J, *Bulletin on the Rheumatic Diseases*, 1974, **25**, 804.

² Richards, A J, and Hamilton, E B D, *Annals of Rheumatic Diseases*, 1974, **33**, 196.

³ Richards, A J, and Hamilton, E B D, *Rheumatology and Rehabilitation*, 1976, **15**, 138.

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Profound hypothermia on combined lithium carbonate and diazepam treatment

We report a case of profound hypothermia occurring on at least three occasions on combined lithium carbonate and diazepam treatment, but not occurring on either drug alone.

Case report

A 38-year-old woman with profound mental retardation since birth, but no evidence of genetic or metabolic defect, was treated with lithium carbonate to alleviate aggressive behaviour. The latter was added in August 1974 to a regimen of diazepam and perphenazine. Her first episode of

hypothermia was reported in September 1974, when further phenothiazine treatment was discontinued. Occasional episodes of hypothermia continued to be reported, with lethargy and temperatures "below 35°C." For six months from February 1975 she was maintained on diazepam alone with no reported hypothermia. Lithium was then begun again because of increasing aggression, and again hypothermia was reported. Because we felt that she needed these drugs, if possible, and because their role in causing hypothermia was doubtful we arranged two eight-week double-blind trials. Clothing was standardised and room temperature ranged 19–24°C. In April 1976, the first trial began of lithium carbonate (1 g daily) alternating with placebo weekly. Diazepam (30 mg daily) was given throughout. Rectal temperatures, room temperatures, and blood pressure were measured at 1000 and 2000. No hypothermia was reported. The morning temperature on lithium was slightly lower than that on placebo ($P < 0.05$).

Rectal temperature with two drug regimens

Time	Lithium + diazepam	Placebo + diazepam
1000	35.989 ± 0.607	36.333 ± 0.416
2000	36.111 ± 0.432	36.350 ± 0.357

After this trial, the patient continued on combined lithium and diazepam treatment and after 17 days of this she became profoundly hypothermic, her temperature falling from 35.4°C to 32°C over two hours. The patient was comatose, with reduced reflexes, dilated pupils, a systolic blood pressure between 40 and 60, pulse rate of 40, no piloerector response, and warm peripheries. All drug treatment was stopped and with warming, her temperature rose to 35.6°C over the next eight hours. A second trial of lithium carbonate (1 g daily) alone alternating with placebo was instituted. No significant temperature differences between lithium and placebo periods occurred. No hypothermic episodes occurred. Lithium carbonate (1 g daily) plus diazepam (20 mg daily) were started again. Five days later, the patient became profoundly hypothermic: her temperature dropped from 35.5°C to 30°C in eight hours, and her physical state was similar to that noted on the first occasion. Again, her temperature rose to 32.4°C over ten hours reaching 35°C within 24 hours.

Observations continued for a further six weeks on no drug treatment and no hypothermia was reported. Subsequently when she started on lithium carbonate (1 g daily) and diazepam (30 mg daily) 36 hours later she became hypothermic, her rectal temperature falling from 35.2°C to 32.8°C in four hours.

Discussion

Irvine¹ reported the occurrence of hypothermia in an 84-year-old man given diazepam (10 mg four times daily) for a week, who died. Mild hypothermia was seen at the other extreme of life—a temperature of 34.9°C and hypotonia being seen together with cyanosis in a newborn infant born to a mother taking lithium.² Chlorpromazine is also associated with loss of temperature regulation due to lethargy and impairment of piloerection and vasoconstriction.³

Our patient did not develop hypothermia on lithium or diazepam alone, but exclusively on combined treatment. Throughout, she was active and aggressive, so that inactivity may be excluded as the cause. Normal serum thyroxine concentrations precluded thyroid malfunction, a known cause of hypothermia.⁴

The duration of treatment required to produce hypothermia appears to have progressively shortened in the patient. Since hypothermia is potentially fatal, we did not feel it was ethical to pursue this investigation further.

If this response is not idiosyncratic, then there may be potential danger to patients prescribed these drugs in combination.

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¹ Irvine, R E, *British Medical Journal*, 1966, **2**, 1007.

² Tunnesan, W W, *et al*, *Journal of Pediatrics*, 1972, **81**, 804.

³ Hollister, L E, *et al*, *Clinical Pharmacology and Therapeutics*, 1960, **1**, 284.

⁴ Jones, I H, and Moode, T W, *Gerontologia Clinica*, 1964, **6**, 252.

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