COMBINED CHEMOTHERAPY AND SURGERY
FOR HYDATID BONE DISEASE

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Surgical treatment of hydatid bone disease is rarely completely successful because radical excision is only possible at certain sites and secondary infection frequently occurs. Antihelmintic drugs have in the past been only palliative due to poor absorption and consequent low concentration in serum or cysts.

We report five patients with Echinococcus granulosus infestation treated with a new chemotherapeutic agent albendazole; in two it was given postoperatively, in two pre-operatively and one child is being followed expectantly. We believe that a combination of chemotherapy and surgery may be efficacious in the treatment of hydatid bone disease.

Hydatid disease is caused by a parasitic tapeworm Echinococcus. The disease was known to Hippocrates, but the complete life-cycle was not documented until the nineteenth century (Lewis, Koss and Kerstein 1975). Although 12 different species have been identified, only two of these, Echinococcus granulosus and Echinococcus multilocularis are known to affect man; the latter is extremely rare in the United Kingdom and it does not affect bone.

The precise incidence of human hydatid disease is not known, but up to 30% of asymptomatic young farmers in mid-Wales have positive hydatid serology (Clarkson 1978), indicating that the disease is perhaps not so rare in these rural areas where sheep and dog infestation ranges from 15% to 26% (Walters 1978).

Bone hydatidosis is rare, and the incidence in relation to infestation of other organs is 4% in Kuwait (El Gazzar and McCreddie 1962), 2% in South America and less than 1% in Australia (Alldred and Nisbet 1964). The disease is most debilitating, and although compatible with long-term survival, it is difficult to eradicate as it continues its slow relentless expansion. Treatment until very recently has been entirely surgical, which at best is often palliative and may even increase the risk of dissemination. Effective chemotherapy would therefore be of great therapeutic benefit.

We describe five cases of long-standing bone infestation treated with albendazole in an attempt to kill the parasites with chemotherapy before surgical excision, should this be necessary.

PARASITOLOGY

Echinococcus, a cestode worm, requires a carnivore and herbivore to complete its life-cycle (Fig. 1). The definitive hosts are dogs, foxes and other sylvatic carnivores. The tapeworm lives in the small bowel and infected ova are shed in the faeces. When ingested by intermediate...
hosts such as man, sheep or cattle, the larvae enter the portal circulation, eventually reaching the liver where most (60%) are trapped, but some pass through the microcirculation to the lungs and occasionally to other parts of the body where they form cysts. The life-cycle is completed when the definitive host consumes infested viscera of the intermediate host.

PATHOLOGY
Primary hydatid disease of bone, due to Echinococcus granulosus, occurs when a blood-borne scolex settles in bone. One of the main features is that growth is a very slow process, and therefore bone cysts are virtually unknown in children even though infestation probably occurs at that time (Kumar, Cornah and Morris 1984).

The growth in bone differs from that elsewhere in that uniform enlargement does not occur. The resistant nature of osseous tissue restricts the parasite’s growth and it accommodates by spreading along the medullary and trabecular canals. The result is fragmentation and conglomeration of daughter cysts rather than a single one. Slow resorption of the trabeculae, without cortical expansion, occurs as a result of pressure. If the cortex is breached, then normal uniform expansion occurs in the surrounding soft tissues. Articular cartilage and intervertebral discs offer little resistance to growth.

CLINICAL FEATURES
The disease affects the long bones, spine, pelvis and ribs in descending order of frequency (Porat and Joseph 1978; Alldred and Nisbet 1964; Saidi 1976). Patients usually present because of pain, swelling or pathological fracture. In addition, spinal disease may present as neurological compromise. The radiographic features are multilocular cysts without cortical expansion, producing a honey-comb appearance (see Figs 2 and 4). As the parasite does not elicit any inflammatory reaction, there is little osteitis or sclerosis. Vertebral hydatid disease may show as destruction with spread across the intervertebral disc. Paraspinal extension and involvement of a contiguous rib are highly suggestive of the disease (Saidi 1976; Braithwaite and Lees 1981).

More recently computerised tomography and magnetic resonance imaging have been added to the arsenal of investigations and are particularly helpful in assessing accurately the extent of the disease and the degree of soft-tissue involvement (Fig. 3). The differential diagnosis includes aneurysmal bone cysts, giant-cell tumours, solitary cysts, neurofibromatosis, fibrocytic disease, chondrosarcoma and tuberculosis (Booz 1972).

CASE REPORTS
Case 1. A 51-year-old farmer from mid-Wales presented in September 1981 with a two-year history of pain and weakness of the right thigh. Exploratory surgery revealed a hydatid cyst of the upper right femur with soft-tissue extension, and this was locally excised. Eleven months later he sustained a pathological fracture of the femoral neck which was treated conservatively, but failed to unite.

In March 1983, because of continuing pain and swelling, he was treated with mebendazole (50 mg/kg daily) for two months followed by a month's course of albendazole (10 mg/kg daily). In July 1983 a cyst 11 cm long was excised, and despite a further one month's course of albendazole his leg continued to discharge white fluid and "membranes".

Three months later he was referred to the University Hospital, Nottingham for chemotherapy. CT staging revealed five hepatic cysts – one cyst 4 cm in diameter in the left lobe, the remainder in the right lobe being up to 15 cm in diameter. CT scans and conventional radiology showed destruction of the upper right femur and an un-united femoral neck fracture (Fig. 2). Serological investigations showed a positive complement-fixation test (CFT) of 1 in 128 and positive latex agglutination test (LAT) and enzyme-linked immunosorbent assay (ELISA) test. He was treated with albendazole (10 mg/kg) for two months before all five hepatic cysts were removed (by DLM).

Six weeks later exploration of the right thigh (by RCM) revealed a large cavity in the proximal femur extending 7 cm down the medullary canal. In addition, there was considerable soft-tissue extension posteriorly. The disease was excised and a Charnley low-friction arthroplasty performed with a cemented long-stem prosthesis, the wound being irrigated with 0.5% silver nitrate solution. Postoperative recovery was complicated by a chest infection and a small pulmonary embolus.

At follow-up 16 months later he was asymptomatic and able to engage fully in farm work. Radiographs and CT scans did not show any evidence of recurrence. Fresh specimens of both the hepatic and the bone cysts were injected intraperitoneally into gerbils and, despite six months' incubation, no cysts developed. Microscopy showed no live protoscolices. More recent serological investigations showed normal complement-fixation (1 in 16).

Case 2. A 56-year-old Cypriot lady presented to the University Hospital in 1984 with spinal disease and nerve root compression. She was known to suffer from hydatid disease, having had a hepatic cyst removed 17 years previously and another cyst removed from the left iliac fossa five years later. She had increasing back pain, weakness of both legs and had developed parasthesia and loss of proprioception several months previously. Bladder and anal sphincter control were deficient.

Fig. 2
Case 1. Radiograph of the upper right femur with an un-united fracture of the femoral neck in a 51-year-old man with hydatid disease.
Examination revealed a large mass in the left iliac fossa and another smaller one posteriorly over the lower lumbar spine. Serology was indeterminate – a positive ELISA but negative CFT (1 in 16). Radiographs and CT scans demonstrated destruction of the bodies of the fourth and fifth lumbar vertebrae with extension into the spinal canal and neural arches posteriorly as well as the formation of a retroperitoneal mass anteriorly (Fig. 3).

She was treated for one month with albendazole (10 mg/kg) prior to surgical decompression from L3 to L5 and posterior stabilisation using Luque rods and segmental wiring extending from the sacrum to T12. Four weeks later, via an anterior retroperitoneal approach, the diseased bodies of L4 and L5 were removed and replaced with a large cortocancellous strut graft and cancellous chips. Postoperative recovery was remarkably uneventful and she was able to walk with crutches using a splint to correct her pre-existing left foot-drop. Twelve months later her only problem was intermittent S1 root pain. Follow-up CT scans did not reveal any recurrence. Fresh samples of daughter cysts were examined microscopically and injected intraperitoneally into gerbils. No live protoscolices were seen and no cysts developed.

Case 3. A 14-year-old schoolboy developed a pathological fracture through a cyst of the left humerus in 1979 (Fig. 4) which refractured at two and again at six months. Subsequent exploration and curettage was undertaken because of discomfort, and the histological examination of biopsy specimens confirmed the diagnosis of hydatid disease. He was treated for one month with albendazole (10 mg/kg daily). At his three-year follow-up he had no evidence of recurrence.

Case 4. A 66-year-old woman from South Wales was first diagnosed as having hydatid disease at the age of 17 years, when a hepatic cyst was removed. Some 15 years later she developed pain in the left hip and was found to have hydatid disease of the ilium; this was subsequently excised locally on three separate occasions. She presented to the University Hospital after another local recurrence complicated by secondary osteomyelitis due to Staphylococcus aureus and Pseudomonas aeruginosa infection (Fig. 5). She was treated with albendazole (10 mg/kg daily) and gentamicin and azlocillin for one month. There was a marked reduction in pain and discharge, but it is too early to draw firm conclusions as to the outcome.

Case 5. A 72-year-old Cypriot lady had a long history of Echinococcus granulosus infestation, with cysts in the quadriceps, pancreas, kidney, right femur and pelvis necessitating nephrectomy, above-knee amputation of the right leg and partial excision of the ilium. In July 1983 she developed a cyst in the right iliac fossa and phantom pains of the right leg. A CT scan demonstrated recurrent cysts in the ilium and surrounding soft tissues. She was treated with albendazole (10 mg/kg daily) for two months. This produced a definite symptomatic response and a reduction in diameter of the cysts, thereby avoiding the need for operation; but her symptoms recurred two years later.

**DISCUSSION**

Until recently treatment of osseous hydatid disease has been entirely surgical, the aims being removal of the cyst and surrounding bone, replacement of bone defects with bone grafts or a prosthesis, avoidance of secondary infection, and prevention of recurrence. Unfortunately these goals are rarely achieved completely in this relentless disease.
Pintilie et al. (1966) and Alldred and Nisbet (1964) advocated wide surgical excision when treating disease in long bones, but followed a more conservative approach when treating disease in the axial skeleton. More recently Booz (1972), Hooper and McLean (1977) and Duran et al. (1978) have advocated thorough mechanical curettage to remove macroscopic cysts and "chemical" sterilisation of the scolices using formalin, 0.5% silver nitrate or hypertonic saline, any major defect being filled with autogenous bone graft. Most "scoeleidal" agents do not kill all microscopic daughter cysts, and therefore recurrence is likely, and surgery is often only palliative. Effective chemotherapy would therefore be of great benefit.

The benzimidazole derivative mebendazole has been shown by Heath and Chevis (1974) to kill the germinal membrane of echinococci in mice by limiting glucose uptake. The first report of the use of high-dose mebendazole was encouraging (Bekhti et al. 1977); however, this was not universal (Braithwaite 1981). The variable success was thought to be due to the insolubility of mebendazole with its consequent poor absorption leading to low concentrations in serum and cysts (Morris and Gould 1982).

Mebendazole, another antihelmintic, is a relatively new compound offering the distinct advantages of better absorption and higher levels of the active metabolite mebendazole sulphoxide in the cysts and in blood (Morris et al. 1983). Considerable success has been achieved in treating lesions elsewhere (Morris et al. 1985). Saimot et al. (1983) have reported treatment in four patients with disease of the vertebral column, three of whom showed a favourable response, and one case of pathological fracture of the femur which initially responded to therapy but later worsened despite adequate levels of the active metabolite in bone.

The five patients with Echinococcus granulosus infestation whom we have treated with albendazole provide some encouraging results. In three, with disease of the humerus, femur and spine respectively, there is evidence of at least a parasitostatic effect in that no recurrence occurred within 12 months; in two of these patients parasitic material obtained at operation was injected into the peritoneum of gerbils and no cysts developed despite six months' incubation, and no live protoscolices were seen on microscopy. Of the other two patients, one had evidence of regression, and with the other it is too early to assess the results.

We feel that albendazole has a role in the treatment of bone hydatid disease, but can only be expected, at best, to kill the parasites. It will not improve the strength of the weakened bones and must therefore be combined with surgical excision and bone grafting or prosthetic replacement, where this is indicated and safe.

Conclusions. Undoubtedly the best chance of complete cure by surgical treatment involves radical excision together with irrigation using scoleidal agents; this is only feasible at certain sites such as ribs, fibulae or scapulae. Usually the disease is so extensive that only palliative excision is possible. In addition, with surgical treatment there is a risk of producing an acute anaphylactic reaction or encouraging further dissemination if the antigenic hydatid fluid escapes into the surrounding tissues.

The discovery of an effective oral or parenteral medication able to destroy the parasite and stabilise the cyst has long been a cherished hope. Our preliminary results using albendazole suggest it will be efficacious, so reducing the risk of dissemination and avoiding excessive removal of healthy tissue.

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REFERENCES