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Diagnosis and treatment of human hydatidosis

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Introduction

Hydatid disease, hydatidosis and echinococcosis are all terms describing infection with the metacestode of the tapeworm, *Echinococcus* (Figure 1). The organism requires two mammalian hosts for completion of its life-cycle, a definitive (final) host in which the adult, strobilar stage develops in the small intestine, and an intermediate host in which the cystic metacestode usually develops in the viscera. The definitive host is always a carnivore. It becomes infected by ingesting protoscoleces which are produced by asexual multiplication of the metacestode. There may be several thousand protoscoleces within a single cyst, and each one is capable of developing into a sexually mature adult worm (4–7 mm length). Adult worms produce eggs (30–40 μm diameter), each containing a single embryo (oncosphere), which are voided in the faeces of the definitive host. The eggs (40 μm), which are capable of surviving in the environment for varying periods,

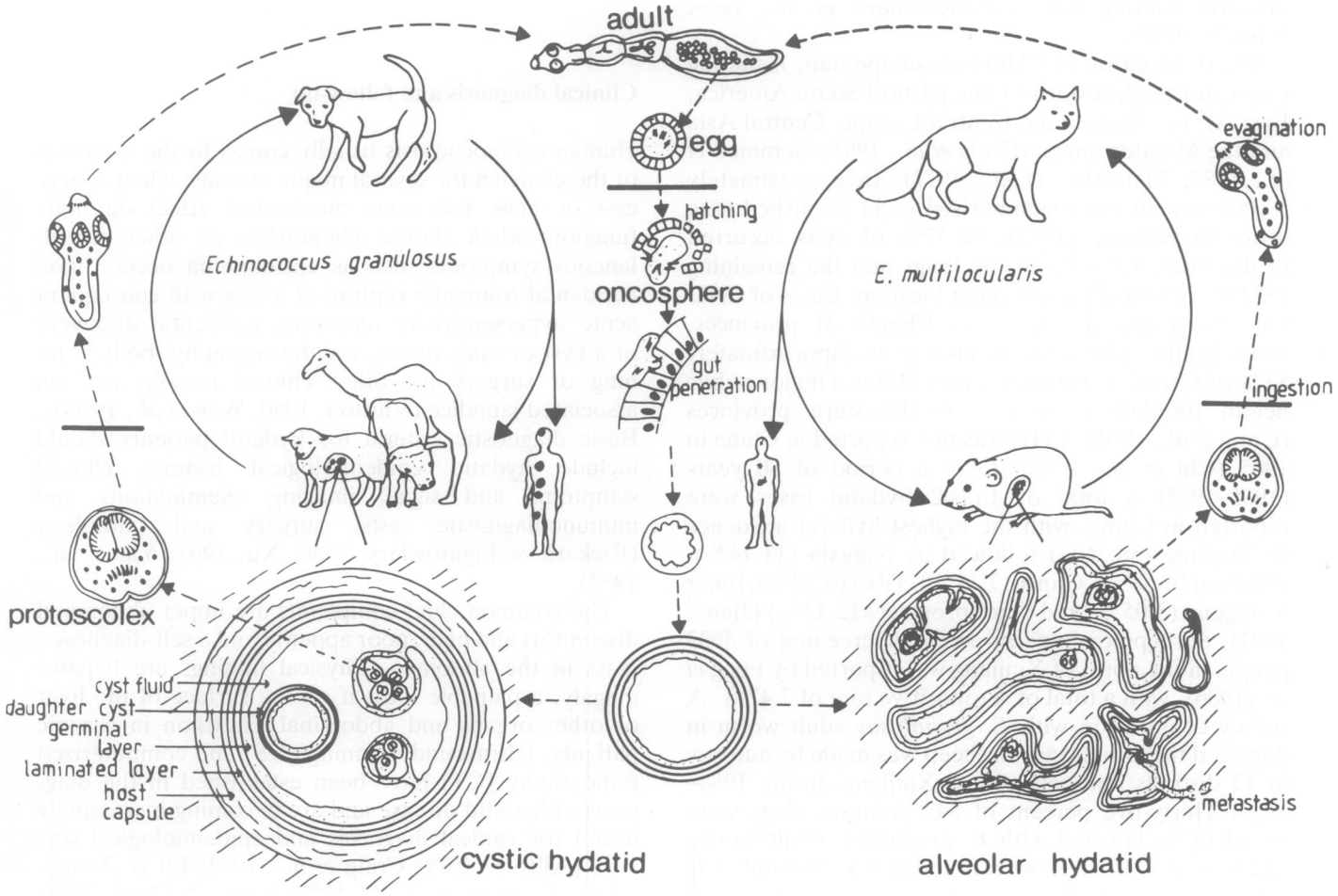

Figure 1 Life cycle of *Echinococcus (E.) granulosus* and *E. multilocularis*.

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are infective upon ingestion for numerous species of herbivorous or omnivorous intermediate hosts, such as livestock and humans (Thompson, 1986).

Human hydatidosis occurs commonly as two forms which differ in pathology, morphology, clinical manifestations and epidemiology. One is cystic hydatid disease (CHD), caused by infection with the larval stage of *Echinococcus granulosus*. *E. granulosus* is transmitted primarily in domestic cycles between dogs and livestock, especially sheep. The other form is alveolar hydatid disease (AHD), caused by *Echinococcus multilocularis*. The most common life cycle of *E. multilocularis* involves transmission between foxes (host to adult worm) and microtine rodents as intermediate hosts (larval worm). A rare case of mixed cystic and alveolar hydatidosis was reported from China (Wen *et al.*, 1992). A rare third form called polycystic hydatid disease (PHD), with characteristics intermediate between CHD and AHD, reported from Panama, Ecuador, Colombia, and Venezuela is caused by *Echinococcus vogeli*. According to 18 recorded PHD cases, larval *E. vogeli* in humans produces a relatively large tumour-like mass, with fluid-filled cysts, brood capsules, and numerous protoscoleces. The primary localization is in the liver, but cysts may spread to contiguous sites. The disease appears less progressive than AHD. The main neutral intermediate host is the paca (*Cuniculus paca*); man probably obtains the infection by contamination from faeces of infected hunting dogs (D'Alessandro *et al.*, 1979; Rausch, 1986).

The distribution of CHD is cosmopolitan, including north and northwestern China, parts of South America, East Africa, Australasia, Central Europe, Central Asia and the Mediterranean (Craig *et al.*, 1991; Gemmell *et al.*, 1987; Matossian *et al.*, 1977). In approximately 30,000 human cases summarised in 11 published case series by Schantz (1972), 52–77% of cysts occurred in the liver, 8.5–44% in the lungs and the remaining 13–19% in virtually every other location. Cases of CHD have been recorded in 21 of China's 31 provinces, municipalities and autonomous regions (approximately 87% of China's territories) and CHD is a major public health problem in several northwestern provinces (Craig *et al.*, 1991). CHD was first reported in China in 1905 (Chi *et al.*, 1990). Over a period of 80 years (1905–1985) a total of 16,642 hydatid cases were reported in China, with the highest hydatid incidence in Xinjiang (58.36%) followed by Ningxia (11.14%), Qinghai (10.58%), Gansu (7.11%), Tibet (6.72%), Inner Mongolia (3.95%) and other provinces (2.13%) (Jiang, 1991). Seroepidemiological hydatid screening of 4633 people in the north of Xinjiang was reported by Feng *et al.* (1986), with a total of seropositive rate of 7.47%. A survey of infection with *E. granulosus* adult worm in dogs and the larval stage in sheep was made by autopsy in 12 districts and counties of Xinjiang during 1984–1989. Thirty-five percent of 542 domestic dogs were found to be infected with *E. granulosus* adult worms and 60% of 7745 sheep were found to have hydatid cysts in liver, lungs and other organs (Chai, 1989). All of these data indicate that hydatid disease constitutes a serious public health and livestock production problem, particularly in north and northwestern China. Under the World Health Organization's classification of hyperendemicity for *E. granulosus* (Eckert *et al.*, 1981), i.e. an annual surgical incidence of > 10 per 100 000 population, and > 50% prevalence rates in sheep, virtually the whole of west and northwest China can be included.

The transmission of AHD is restricted to the northern hemisphere with a higher prevalence in Alaska, Central Western Europe, Siberia, Japan and China. *E. multilocularis* is considered to be one of the most lethal helminth infections of humans. AHD was not formerly ascribed to *E. multilocularis* until Rausch and Schiller's study of Alaskan patients (Rausch & Schiller, 1951). The first AHD patient in China was described much later in 1965 (Yao, 1965). Approximately 207 AHD cases have been reported from the Xinjiang, Ningxia, Qinghai, Gansu, Sichuan, Tibet and Heilongjiang regions and provinces in China (Jiang, 1991; Li *et al.*, 1991, Wen *et al.*, unpublished). In 1991, 797 people were examined from Hanchuan commune in Zhang County (Gansu, China). This region includes the village of Ban Ban Wen, from which 26 (40%) of a total of 65 cases originated and of which 26/161 (16.2%) liver-scanned by ultrasound with serological confirmation were diagnosed as having AHD. The estimated total population of the three communes was approximately 16,000. Therefore, using a 5% prevalence rate for human AHD in this region and assuming equal infection pressure, up to 800 cases of AHD could be expected to occur in the region (Craig *et al.*, 1992).

Clinical diagnosis and follow-up

Human echinococcosis usually comes to the attention of the clinician for several major reasons: when a large cyst or mass has some mechanical effect on body function; when allergic phenomena or other miscellaneous symptoms such as eosinophilia occur; upon accidental traumatic rupture of a cyst with consequent acute hypersensitivity reactions; accidental discovery of a cyst or mass during roentgenography, body scanning or surgery for other clinical reasons and an associated jaundice (Vuitton, 1990; Wen *et al.*, 1990b). Basic diagnostic criteria for hydatid patients should include hydatid epidemiological history, clinical symptoms and signs, imaging examinations and immunodiagnostic tests, surgery and pathology (Rickard & Lightowlers, 1986; Xu, 1991; Yao *et al.*, 1983).

The common chief complaints are upper abdominal discomfort and pain, poor appetite and a self-diagnosed mass in the abdomen. Physical findings are hepatomegaly, a palpable mass if on the surface of the liver or other organs and abdominal extension in chronic patients. Ultrasound scanning (US) and computerized tomography (CT) have been established in the diagnosis of hydatid disease and are becoming increasingly useful for clinical diagnosis and epidemiological surveys (Alltree, 1979; Craig *et al.*, 1992; Lu & Zhang, 1988; Macpherson *et al.*, 1987; Niron & Oxer, 1981; Weiler *et al.*, 1985). Under CT or US scanning a typical CHD cyst appears as a round or ovoid space-occupying lesion or hypoechogenic area, and 'double layers and

arc calcification' can be considered as specific for a hydatid cyst rather than other cystic diseases. An AHD lesion is characterized by an irregular parenchymal focus or hyperechogenic area with calcifications either in nodular spots and/or ring forms. Although the liquid-filled cavity caused by central necrosis in the AHD focus at a late stage is often confused with a CHD cyst on CT or US scan it may usually be distinguished by the fact that the AHD liquid-filled cavity is irregular and often surrounded by a mass of scattered calcification (Liu *et al.*, 1992; Lu & Zhang, 1988; Macpherson *et al.*, 1987; Weiler *et al.*, 1985).

A hydatid patient should have a positive serological response in more than one test. Almost all available serological assay methods have been used for diagnosis of human hydatidosis including the following: intradermal test (ID), complement fixation test (CFT), indirect haemagglutination (IHA), latex agglutination (LA), indirect fluorescent antibody (IFA), enzyme-linked immunosorbent assay (ELISA), immunoelectrophoresis (IEP), counter-immunoelectrophoresis or immunoelectrodiffusion (CIEP, IED) and arc double diffusion (DD5). Hydatid serology has been reviewed by Rickard & Lightowlers (1986) and Schantz & Gottsttein (1986). Differentiation between human AHD and CHD is possible using the Em2-ELISA (Gottstein *et al.*, 1983). The above serological methods serve to confirm the diagnosis and are often used for post-therapy surveillance of the patient. IHA or ELISA in combination with either DD5 or IEP are satisfactory for such applications (Rickard & Lightowlers, 1986).

Use of US and/or CT scan for follow-up of hydatid patients during and after treatment has become an essential method. Significant indicators of response to treatment are collapse or disappearance of the cysts or lesion, shrinkage, change of shape, increase in density and calcification in the cyst or the lesion in comparison with that seen before treatment (Morris *et al.*, 1984; Saimot *et al.*, 1983; Singcharoen *et al.*, 1985; Wen *et al.*, 1990b). However, follow-up is not always straightforward when using imaging methods, particularly for evaluation of AHD treatment (Wilson *et al.*, 1987; Wen *et al.*, unpublished). Serology has been shown to be potentially useful for follow-up in CHD and in some AHD cases by use of specific circulating antigen and cystic fluid antibodies immune complexes, Em2 antibodies and Western blotting (Smyth & Barrett, 1980; Craig, 1986; Gottstein *et al.*, 1991; Matossian *et al.*, 1992; Ito *et al.*, 1992).

Surgical treatment

Surgery is the principal form of treatment for human hydatidosis (French, 1984; Schantz, 1972; Xu, 1991; Yao *et al.*, 1983; Zou *et al.*, 1991). Surgical treatment for CHD patients commonly involves endocystectomy for cysts located in the lungs and abdominal cavity and endocystectomy with puncture, aspiration, protoscolicide and reaspiration (PAPR) for cysts located in liver, spleen, kidneys and other organs, because of the hard and thick wall formed by the host response. French (1984) has reported that, of 516 hydatid cases in Kenya receiving treatment, 302 patients underwent surgery with a cure rate of 50%, some 20% being unsuitable for surgery and recurrence occurring in the remaining 30%. In recent years some new and encouraging methods of surgical management have been reported. One hundred and twenty cysts were punctured in 37 patients with inoperable echinococcosis of the liver, peritoneum, spleen, kidneys, muscles and bone by the procedures of puncture, aspiration, injection and reaspiration (PAIR) under ultrasonographic guidance (Gargouri *et al.*, 1990). In 70% of patients good results were obtained. Percutaneous drainage under ultrasonographic guidance has been carried out on 12 patients with liver and abdominal cysts and the procedure seems to be therapeutically successful, safe and practicable (Filice *et al.*, 1990). Surgery in 20 hepatic CHD patients was performed by endocystectomy incorporating the smearing of medical glue onto the wall of the cyst fibrous layer for the prevention of biliary leakage after surgery (Luan *et al.*, 1991).

The surgical treatment of AHD cases is usually more difficult and a different approach is used: (1) when the lesions are sufficiently localized within half of the liver, then regular hepatectomy or hepatolobectomy is the method of choice; (2) when the lesions occupy more than half the liver, then tentative irregular hepatectomy or hepatobectomy can be effective, but this requires excision of large, necrotic, purulent cavities; (3) when the lesions are unresectable surgical drainage procedures are performed, which include drainage of liver abscesses or biliary ducts (Vuitton, 1990; Wen *et al.*, unpublished). Since Yao (1965) reported the first AHD case in China, Xinjiang Medical College has treated 90 AHD patients. 10–15% were treated by regular hepatectomy, 20–25% by tentative irregular hepatectomy, 35–40% by clearance of necrotic cavities and surgical drainage because of unresectable lesions, and 20–30% were too advanced to be treated by surgery. The mortality at 5 years is 10–15% and the longest survival in the series was over 28 years after operation (Li *et al.*, 1991; Wen *et al.*, unpublished; Yao, 1985; Yao *et al.*, 1983). Seventeen patients with incurable AHD were treated by liver transplant between 1966–1989, and the survival rate at 15 months was 75% (Bresson-Hadni *et al.*, 1991). Orthotopic liver transplantation is feasible, particularly for those patients with parasitic Budd-chiari syndrome or complicated secondary biliary cirrhosis (Vuitton, 1990).

One of the major surgical complications of hydatidosis is recurring (secondary) cystic echinococcosis after operation for primary hydatid disease. Two–11% was reported by Schantz (1972) and it may be as high as 30% (French, 1984) in some areas. A 10–21% recurrence rate was recorded by Wen *et al.* (1989a). Obviously, use of an effective protoscolicidal adjunct to hydatid surgery is an important procedure which may reduce the recurrence rate. Several common protoscolicidal agents have been used in hydatid surgery including 4–10% v/v formalin, 3–5% v/v hydrogen peroxide, 95% v/v ethanol solution, 1% w/v cetrimide, and hypertonic sodium chloride solution (Filice *et al.*, 1990; French, 1984; Gargouri *et al.*, 1990; Macpherson *et al.*, 1982; Wen *et al.*, 1989a; Xu, 1991). To evaluate protoscolicidal efficacy, 11 orthodox chemotherapeutic

agents and 3 traditional Chinese medicines were tested by protoscolex responses at 5, 10, 15 and 20 min *in vitro*, and by inoculation of mice (Wen *et al.*, 1989a). On the basis of morphologic changes, eosin uptake rate for viability and reinfection rate by mouse passage, protoscolidal agents were divided into three groups: (1) completely effective agents in the order—15–20% w/v sodium chloride solution, 70–95% v/v ethanol, a mixed solution of 10% w/v sodium chloride and 0.05% w/v peracetic acid, a mixed solution of 0.125% v/v acetic acid and 10% w/v sodium chloride, 1.5–3% w/v hydrogen peroxide, and 0.5% w/v iodine; (2) partially effective agents—4–10% w/v formalin, 0.25% w/v acetic acid, 0.01% w/v potassium permanganate and 0.1% w/v peracetic acid; (3) ineffective agents—5–20% w/v arecoline solution, 5–20% w/v liquor omphaliae solution and 5–20% w/v pelletierine solution.

Thus, for surgery of CHD patients the following was recommended: aspiration of cystic fluid, injection of 15–20% w/v sodium chloride solution into each cyst for 10 min and reaspiration, removal of endocyst, scrubbing of the exocystic wall with a small gauze soaked in 70% v/v ethanol three times and then suture of the wall. Oral administration of albendazole or other antihydatid drugs should be also considered before and after surgery for the prevention of hydatid recurrence after surgical treatment (Wen *et al.*, 1989a).

Chemotherapy

Mebendazole

Surgery for recurrent or disseminated hydatid disease is only a tentative treatment and often results in further recurrence and even mortality. Literature on the chemotherapy of CHD and AHD in man supports the successful use of benzimidazoles (Akovbiantz *et al.*, 1977; Ammann *et al.*, 1988, 1990; Schantz *et al.*, 1982; Bryceson *et al.*, 1982; Davis *et al.*, 1986; Eckert, 1986). Studies on the chemotherapy of human hydatidosis with the benzimidazoles, coordinated by the WHO, were conducted in seven clinical centres. Treatment with mebendazole was fully successful in 8 of 85 CHD (9%) patients and partially successful in 4 (5%) others (Davis *et al.*, 1986). Additionally, French (1984) reported a substantial reduction in postoperative recurrence in 131 CHD patients who received mebendazole.

Using a mouse model of secondary echinococcosis oral (50–150 mg kg^{-1} day^{-1} for 60–100 days) and intraperitoneal (2 ml; 0.5% w/v for 12 doses) treatment with mebendazole resulted in complete rupture of all hydatid cysts and extensive damage of their germinal layers (Ding *et al.*, 1986). Long term follow-up (3–7 years) of 15 CHD patients treated with a high-dose mebendazole regime was reported by William & Schantz (1984). Most of the patients showed both objective and clinical improvement, although two had relapsed 1–6 years after completing therapy. Generally, simple single cysts in the lung and liver showed the best response while multiple complex cysts and bone cysts showed little or no objective improvement (William & Schantz, 1984). In northwestern China 13 inoperable AHD patients were treated with mebendazole, 1.2–1.5 g daily, for a course of 30 days with an interval of 1–4 weeks between courses. After 1–16 courses of therapy most patients remained stable and, in one patient, the mass diminished from 12 × 8 cm to 8 × 5 cm. Prolonged treatment with a higher dose of mebendazole is required, particularly for AHD patients (Yao *et al.*, 1985a). The results of a prospective controlled long-term chemotherapy study by the Swiss Echinococcosis Study Group, comprising 60 patients with non-resectable alveolar echinococcosis, demonstrated the efficacy of mebendazole therapy primarily by a marked increase in the survival of treated patients (96% at 5 years and 84% at 10 years) which was significant compared to historical controls (Ammann *et al.*, 1988). The recurrence rate was investigated in 19 patients with non-resectable alveolar echinococcosis after discontinuation of long-term therapy with mebendazole (average treatment 4.3 years). Recurrence occurred in 7/19 AHD patients (37%) at an average of 1.6 years after discontinuation of mebendazole. However, all of the recurrence cases responded favourably to reintroduction of chemotherapy. All of these data indicate that mebendazole therapy is parasitostatic rather than parasiticidal (Ammann *et al.*, 1990).

Albendazole

Shortcomings of mebendazole chemotherapy include low (possibly nontherapeutic) serum concentrations of the drug in some patients and continued survival of the larval cestode, as judged by animal inoculation studies, for as long as 48 months after start of treatment (Wilson *et al.*, 1987). Chemotherapy with albendazole as a clinical treatment for human hydatidosis is now more frequently used than mebendazole (Davis *et al.*, 1986; Horton, 1989; Morris *et al.*, 1985; Saimot *et al.*, 1983; Todorov *et al.*, 1988; Wen *et al.*, 1990b; Zou *et al.*, 1988). Albendazole and mebendazole are benzimidazole carbamates with poor solubility. However, albendazole tends to produce high concentrations of its main metabolite, albendazole sulphoxide (ABZSX), (Wilson *et al.*, 1987; Woodtli *et al.*, 1985) and significant effects of ABZSX on the viabilty of hydatid protoscoleces *in vitro* and *in vivo* have been described (Bogan & Marriner, 1980; Chinnery & Morris, 1986; Meulemans *et al.*, 1984; Morris & Gould, 1982; Wen *et al.*, 1988; Zhang & Wen, 1989).

The mode of action of benzimidazoles (BZs) seems to involve interaction with tubulin. Thus: (1) selected, commercially-available BZs have been shown to inhibit polymerisation of mammalian tubulin (Lacey *et al.*, 1987). (2) several known mammalian microtubule inhibitors also inhibit the binding of [^{3}H]-mebendazole to helminth tubulin and have high ovicidal and larvicidal activity. Preliminary investigations of other unrelated anthelmintics (e.g. the avermectins, levamisole, salicylanilides) have shown that none inhibits [^{3}H]-mebendazole binding to tubulin at concentrations that account sufficiently for their anthelmintic activity (Lacey, 1990). (3) the extent of charcoal-stable binding of BZs, an indication of the binding strength of BZs to tubulin, correlates with the efficacy of BZs in the range

of drug-sensitive and non-sensitive helminth species. (4) The levels of resistance of BZs of different isolates of the same species, detected by both *in vitro* and *in vivo* techniques, correlate with the extent of [^{3}H]-mebendazole binding (Russell & Lacey, 1991). However, it should be born in mind that for other possible mechanisms, such as inhibition of fumarate reductase and glucose uptake, a correlation between reduced enzyme activity and drug resistance also exists (Lacey, 1990).

Chemotherapy with albendazole has been shown to be successful in several experimental animal models. Thus 20–100 mg kg^{-1} doses reduced parasite weight, increased the length of survival of infected animals and decreased secondary infection rate after intraperitoneal inoculation (Taylor & Morris, 1989; Taylor *et al.*, 1988; Vanparijs, 1990; Wen *et al.*, 1990a). Since 1983, data have been collected on the outcome of treatment of apparently active *E. granulosus* hydatid cysts with albendazole (Horton, 1989). Most patients received 800 mg albendazole daily in cycles of 28 days with 14 days between cycles, and a mean duration of 2.5 cycles (range 1–12). From an initial set of over 500 cases 253 patients were evaluated for efficacy, with 269 hepatic, 86 pulmonary, 50 peritoneal and 51 cysts at other sites being individually assessed. Seventy-two patients (28.5%) were regarded as cured, 129 (51%) as improved, 46 (18.1%) as unchanged and 6 (2.4%) were worse. Forty-seven patients underwent surgery after treatment and viability was demonstrated in only 5 cysts (10.6%). Recurrence was observed in 4 of 29 non-surgical cases (13.8%) for whom a follow-up of at least 24 months was available. Thirty-five cases of *E. multilocularis* infection were assessed with a cure observed in 2, improvement in 4, stabilization in 25 and progression in 4 cases. Side effects of treatment were uncommon. Abnormalities of liver function occurred in about 20% (4% withdrawn) and there was a tendency for leucopenia to occur in *E. multilocularis* patients (Horton, 1989). Albendazole appeared to be effective both for chemotherapy of inoperable hydatid cases and for prophylaxis before surgery.

A group of CHD patients treated by combined albendazole (3 courses) and surgery was compared with a group of CHD patients who underwent surgery without chemotherapy (Wen *et al.*, 1990b). The basic criteria for assessing anti-hydatid effects were (a) endocyst rupture rate, (b) histopathologic changes of the cysts, (c) protoscolex viability and (d) pathological changes, which were divided into three degrees: (i) normal structure of germinal and laminated layers, (ii) degeneration of germinal and laminated layers, and (iii) necrosis of germinal and laminated layers. In the 21 patients who formed the ABZ treated group the prevalence of endocyst rupture (77.3%) was much higher than that of the 80 patients in the surgery-only control group (15.2%), and the rodent re-inoculation infection rate in the ABZ treated group (7.69%) was much lower than that in the control group (100%). There was also a significant difference ($P < 0.01$) between these groups in the protoscolex eosin uptake test, as well as in both the gross and histopathologic characteristics of germinal and laminated layers of the hydatid cysts. These observations indicated a significant overall therapeutic effect of albendazole in CHD patients. Of the 38 inoperable CHD cases, the hydatid cysts were affected to varying degrees in different individuals. Chemotherapeutic effects were evaluated as (1) successful, if clinical symptoms and signs disappeared or were markedly alleviated, if hydatid cysts became fibrotic, solid and calcified, or were shown to disappear by ultrasound or CT scan. (2) Improved, if clinical symptoms and signs were alleviated gradually, if cysts size diminished by at least 2 cm on ultrasound or CT scan, and/or the cysts were partially calcified. (3) No effect, if clinical manifestations were aggravated, if the size and shape of the cysts did not change, or even increased. In successful treatment, some smaller cysts in the abdominal cavity or liver disappeared rapidly and completely while the larger ones either diminished in size or increased in density. Treatment of these patients was successful in 8 (21%), improved in 21 (55.3%) and had no effect in 9 (23.7%). Analysis of these results has indicated several parameters which could be used to assess hydatid chemotherapy including cyst size, thickness and location. In general, better results were obtained with smaller, thin-walled cysts located near the centre of the liver rather than bigger, thick-walled cysts located at the liver edge. The success of treatment by surgery and/or chemotherapy will depend also upon the patient's condition and cyst number as well as size and cyst location.

In a study of 19 AHD patients, preoperative treatment with ABZ (20 kg^{-1} day^{-1}) was given for 2 to 6 weeks followed by surgery to evaluate efficacy (Wen *et al.*, unpublished). This was based on gross morphology and pathological characteristics of surgically-excised lesions and on inoculation of excised material into mice. Seven patients who started on ABZ later were shown to have evidence that the metacestodes were dead and the cystic structure damaged so that the foci were probably inactive at the time of initial diagnosis, as has been described in same Alaskan AHD patients (Condon *et al.*, 1988). The remaining seven AHD cases, whose excised tissue was still active, continued to receive albendazole after surgery for 6–18 months and were followed up twice a year. Five AHD patients with ABZ alone have had varied responses to chemotherapeutic treatment. Two of them felt better and ultrasound and/or CT scan follow-up showed calcification and reduction in the size of the AHD lesion; two patients showed no changes and one died. Of a total of 19 AHD patients three (15.8%) died from hepatic failure or secondary infection and malnutrition during or after treatment, indicating significant problems in treatment with surgery and chemotherapy for some chronic AHD cases.

Recently, six PHD patients with infection caused by *E. vogeli* were treated with continuous oral albendazole (10–12 mg kg^{-1} day^{-1}) for 3–8 month and discontinuous administration, consisting of a series of at least three 30-day cycles separated by 15 day drug-free intervals (Meneghelli *et al.*, 1992). Follow-up ranged from 10–30 months. Considerable clinical improvement and cyst reduction or disappearance occurred in four patients. Clinical improvement, but no changes in the hepatic alterations detected by CT scan, occurred in the other two patients. The results indicated that albendazole is also effective for the treatment of PHD.

Use of benzimidazoles in combination with cimetidine

Cimetidine is widely used in the treatment of peptic ulcer. The use of cimetidine leads to a decrease in the *N*-demethylation rate of [^{14}C]-aminopyrine and an increase in the plasma concentrations of benzimidazoles. Luder *et al.* (1986) found higher fasting serum mebendazole concentrations in seven AHD patients receiving cimetidine (1 g day^{-1}) concomitantly. It has been reported that combined administration of cimetidine and mebendazole at sufficient doses may have resulted in therapeutic effects in eight CHD patients unresponsive to mebendazole given alone (Bekhti & Pirotte, 1987). As far as we know, the combined use of albendazole and cimetidine has not yet been assessed. A comparison of plasma concentrations of albendazole sulphoxide in 19 CHD patients treated with and without cimetidine was made by Wen *et al.* (unpublished). All patients volunteered to receive oral albendazole (20 mg kg^{-1} day^{-1}) and seven of them received cimetidine (20 mg kg^{-1} day^{-1}) concomitantly for 7 days prior to surgery. Samples of cystic fluid were collected at 4 h after the morning dose of albendazole and concentrations of albendazole sulphoxide (ABZSX) were measured by h.p.l.c. Concentrations of ABZSX in the combined group (719 ± 341 μg l^{-1}) were significantly higher than in the albendazole alone group (411 ± 130 μg l^{-1}, $P < 0.05$). Better clinical responses were obtained with higher ABZSX concentrations in cystic fluid in the combined administration group, which should encourage further clinical trials of the chemotherapy of hydatidosis using a combination of a benzimidazole and cimetidine.

Praziquantel

Praziquantel is an isoquinoline that is active *in vitro* against protoscoleces of *E. granulosus* at concentrations as low as 20 μg l^{-1} (Morris *et al.*, 1987b), and in only 3 days (Morris *et al.*, 1988). It also has anti-hydatid activity in animal models (Richard *et al.*, 1988). Thomas & Gonnert (1978) reported that praziquantel showed activity in rodents against the infectious protoscoleces of *E. multilocularis* but that it failed to inhibit the growth of the hydatid cysts. Yao *et al.* (1985b) reported both animal experiments and clinical trials with praziquantel for the treatment of abdominal hydatidosis due to *E. granulosus*. These involved intraperitoneal inoculation of protoscoleces into mice and administration of a diet with praziquantel at a dosage of 1000 ppm for 6, 12 and 24 days. On autopsy, it was seen that most of the protoscoleces were dead and the germinal layer broken into fragments. One hundred and one CHD patients were treated with praziquantel at a dose of 25 mg kg^{-1} day^{-1} for 10 days resulting in significant efficacy as assessed by histopathological examination and clinical follow-up (Yao *et al.*, 1985b). Twenty-five CHD patients (12 cysts in liver, 13 in lungs) were treated with oral praziquantel every 8 h at a dose of 40 mg kg^{-1} day^{-1} for 7 days, then underwent surgery (Chen *et al.*, 1989). The eosin uptake rates of protoscoleces were higher in the patients with in-liver hydatid disease (63%) than in those with lung hydatid cysts (37%). Mean concentrations of praziquantel were 0.533 μg ml^{-1} in blood, 0.087 μg ml^{-1} in cystic fluid and 0.149 μg ml^{-1} in the cystic wall in those with liver cysts compared with values of 0.494 μg ml^{-1} in blood, 0.026 μg ml^{-1} in cystic fluid and 0.067 μg ml^{-1} in cystic wall in those with lung cysts 4 h after taking the morning dose. The clinical outcome in both groups, compared with 60 CHD cases in a surgery-alone control group, indicated that praziquantel was an effective anti-hydatid agent. Taylor *et al.* (1988) reported an additive effect of a combination of praziquantel and albendazole against *E. granulosus in vitro* and *E. multilocularis in vivo* in cotton rats. Praziquantel (100 mg kg^{-1}) was ineffective but 500 mg kg^{-1} significantly inhibited growth. A combination of albendazole and praziquantel was no more effective than either agent alone. For human AHD 14 cases were treated by surgery and praziquantel (25–50 mg kg^{-1} day^{-1} for 20–30 days) for 2–3 courses (Li *et al.*, 1991). All of the patients were followed up for between 0.5–6 years. Ten of them improved and four of them died (two of portal hypertension, one of general debilitation and one of gynaecological carcinoma).

Side-effects of benzimidazoles

Although the doses of mebendazole and albendazole given to patients are generally well tolerated the following clinical symptoms and signs have been interpreted as possible or probable adverse drug reactions: severe abdominal pain, nausea and/or vomiting, dizziness, vertigo and/or headache, fever, skin eruptions and/or pruritus, hair loss, clinical jaundice, serum transaminase level above 100 u l^{-1}, leucocyte counts down to 4000 mm^3, and a haemoglobin level below 9 g l^{-1}. Such side effects were recorded in 8 out of 139 (5.8%) patients (French, 1984), 24 out of 195 (12.3%) patients (Davis *et al.*, 1986), 29 out of 253 (11.5%) patients (Horton, 1989), and 13 out of 79 (10.3%) patients (Wen *et al.*, 1990b). In 3–4% hydatid patients treament was stopped temporarily or permanently because of suspected adverse reactions. The reasons for stopping therapy were high levels of serum transminase, allergic conditions, and gastrointestinal disorders. Albendazole was found to be hepatotoxic but transaminase abnormalities have been shown to be reversible (Morris & Smith, 1987a; Wilson *et al.*, 1987). Evidence in a sheep model suggests that albendazole at this dose may be teratogenic and embryotoxic, but mouse model studies have shown no evidence of this (Morris *et al.*, 1985; Wen *et al.*, 1989b). Nevertheless, all females of reproductive age should be warned about albendazole, particular for long-term chemotherapy.

Liposome-entrapped anti-hydatid drugs

It has been suggested that entrapment of anti-hydatid drugs in liposomes may improve their bioavailability as a result of enhanced gut and liver uptake and, also, may reduce their toxicity (New, 1990).

Wen *et al.* (unpublished) measured albendazole and its main metabolites by h.p.l.c. in normal uninfected rats divided into four groups, each receiving albendazole orally either in free form or entrapped in liposomes. In two of the groups cimetidine was given 1 h prior to albendazole administration. Albendazole meta-

bolism is so rapid in the rat that at 1 h after administration concentrations of parent drug are barely measurable and albendazole sulphoxide is the predominant metabolite observed at all times up to 24 h. Compared with controls, liposomal administration of albendazole resulted in significantly higher blood concentrations of ABZSX than of ABZ at 4, 7, and 9 h after a single morning dose (50 mg kg^{-1}). Administration of cimetidine had no effect on circulating concentrations of ABZ or ABSX. Separate experiments in which liver concentrations of ABZ, ABZSX and ABZSN were measured at 6 h or at 24 h confirmed that liver concentrations of albendazole were also higher in the liposomal group. Furthermore, in both free and liposomal albendazole groups cimetidine appeared to delay the appearance of drug metabolites in the bloodstream. Liver albendazole concentrations mirrored exactly those of sulphoxide in all groups and both of these compounds were present in higher concentrations in the liver at 24 h than in the blood at the same time. At 24 h there was no evidence to suggest that albendazole concentrations increased at the expense of those of the sulphoxide in the cimetidine groups.

Therapeutic problems and future prospects

Although scientists and clinicians have accumulated much experience in the diagnosis and treatment of human echinococcosis, there are still many questions and problems. Among the most pressing of these are early and accurate diagnosis by imaging, immunological techniques or needle biopsy, development of reliable follow-up methods and a need for rapidly acting, effective and safe protoscolicides, development of PAIR techniques under ultrasound guidance, improvement in surgical procedures and chemotherapeutic approaches for the increase of clinical cure, prevention of secondary infection and reduction of other complications.

With regard to benzimidazole chemotherapy for human hydatid disease, all studies show similar rates of success (10–30%), improvement (40–60%) and no change (10–30%) (Davis *et al.*, 1986; French *et al.*, 1989; Horton, 1989; Todorov *et al.*, 1992; Wen *et al.*, 1990b; Yao *et al.*, 1985a). Experience with benzimidazole has indicated that the poor water solubility of ABZ and MBZ causes great variability in their absorption in hydatid patients. Thus, a key point is how to increase the oral bioavailablity of benzimidazoles. One approach, exemplified by combined therapy with cimetidine, is by alteration of metabolism. Another is enhancement of absorption and tissue uptake by newer methods of drug delivery (e.g. in liposomes). Our preliminary animal studies have shown that both cimetidine co-administration and administration in liposomes alters the kinetics and bioavailability of albendazole, giving rise to the hope that further improvements may be obtained in therapy by optimisation of combined therapy and delivery systems. Combined treatment with cimetidine should be advantageous, as might be expected on the basis of the mechanism of action of cimetidine as an inhibitor of mebendazole metabolism (Bekhti & Pirotte, 1987). However, the observed effect appears to last no more than 24 h and requires further study. Liposomal albendazole therapy is currently being assessed with and without cimetidine treatment in experimental rodent secondary echinococcosis (Wen *et al.*, unpublished).

Since the mid 1970s significant advances have been made in the chemotherapy of the metacestode stage of *Echinococcus*. *In vitro* and *in vivo* techniques for drug testing are now available and considerable clinical, pharmacological and parasitological knowledge has accumulated. Experience from animal experiments and human trials provide an encouraging basis for future studies, which should include research into new formulations of benzimidazoles, combinations of existing anti-hydatid drugs and a continued search for new and effective agents.

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