Biological, Epidemiological, and Clinical Aspects of Echinococcosis, a Zoonosis of Increasing Concern

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INTRODUCTION

Echinococcosis is a zoonotic infection caused by cestode species of the genus *Echinococcus.* The life cycles of these parasites involve two mammalian hosts (see Fig. 1). The adult cestode inhabits the small intestine of a carnivore (definitive host) and produces eggs containing infective oncospheres. Either cestode segments (proglottids) containing eggs or free eggs are released from the intestinal tract of the carnivore into the environment. After oral uptake of eggs by an intermediate host animal, a larval stage, the metacestode, develops in internal organs. Typically, the mature metacestode produces numerous protoscoleces, each having the potential to develop into an adult cestode after being ingested by a suitable definitive host. Accidentally, eggs are also ingested by humans and other "aberrant" hosts that do not play a role in the natural cycle. On rare occasions, the spectrum of aberrant hosts may even include definitive hosts (i.e., dogs). Whereas the infection of carnivores with immature or mature intestinal stages of *E. granulosus* does not cause morbidity, the invasion of various organs (mainly liver and lungs) of intermediate or aberrant hosts by metacestodes can cause severe and even fatal disease (echinococcosis).

Of three forms of echinococcosis occurring in humans (Table 1) cystic echinococcosis (CE) and alveolar echinococcosis (AE) are of special importance due to their wide geographic distribution and their medical and economic impact. Polycystic echinococcosis is less frequent and is restricted to Central and South America.

This review is focused on selected biological, clinical, and edpidemiological aspects, including the emergence or reemergence of infections in regions where they were previously absent or found at lower levels.

E. GRANULOSUS AND CYSTIC ECHINOCOCCOSIS

The Parasite and Its Life Cycle

E. granulosus is a small tapeworm (approximately 2 to 7 mm in length) with typically three segments and other morphological characteristics which allow a species diagnosis (193) (Table 1). In the natural cycle, dogs and other canids are typical definitive hosts and ungulates (sheep, goats, pigs, horses, etc.) intermediate hosts (Fig. 1). The latter harbor the metacestode

stage. This stage can also develop in a broad range of other mammals, such as marsupials, hares, rabbits, rodents, carnivores, nonhuman primates, and humans. These and other hosts play a role in the transmission cycle (intermediate hosts) or are dead ends of the development (aberrant hosts).

During the past four decades, considerable phenotypic and genetic variability has been observed within the species *E. granulosus* and several strains have been identified (Table 2) (150, 194, 195, 210). A common feature of all strains (except the lion strain) is the utilization of dogs and other canids as definitive hosts, but the strains exhibit several differences in
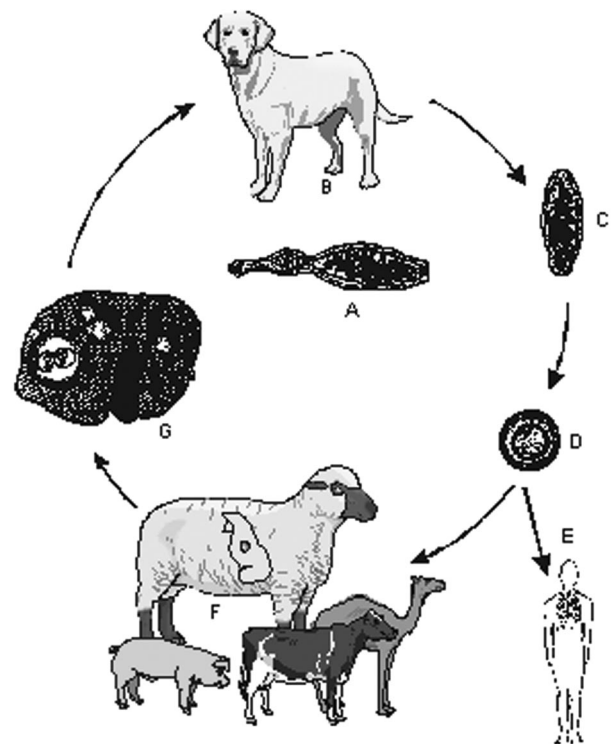

FIG. 1. Life cycle of *E. granulosus* (common sheep strain). (A) Adult parasite. (B) Domestic dog as principal definitive host; wild canids (dingo, hyena etc.) can be involved in the cycle. (C) Proglottid with eggs. (D) Egg with oncosphere. (E) Infection of humans. (F) Sheep as principal intermediate hosts; other ungulates are of lower significance. (G) sheep liver with cysts.

TABLE 1. Forms of echinococcosis in humans[a]

Name of disease (according to WHO/OIE; [223])	Cystic echinococcosis	Alveolar echinococcosis	Polycystic echinococcosis	
Causative agent	*E. granulosus*	*E. multilocularis*	*E. vogeli*	*E. oligarthrus*
Other names of the disease	Hydatid disease, hydatidosis	Alveolar hydatid disease	*E. vogeli* echinococcosis, neotropical echinococcosis	*E. oligarthrus* echinococcosis, neotropical echinococcosis
Adult parasite				
Length (mm)	2.0–7.0	1.2–4.5	3.9–5.6	2.2–2.9
No. of proglottids	3 (4–6)	5 (2–6)	3	3
Definitive hosts	Domestic dog, wild canids (coyote, dingo, red fox, etc.)	Red fox, arctic fox, raccoon dog, coyote, domestic dog, cat	Bush dog, domestic dog	Wild felidae: pampas cat, Geoffroy's cat, ocelot, jaguar, cougar, jaguarundi, puma, bobcat
Intermediate hosts	Primarily ungulates, also marsupials	Rodents, other small mammals	Rodents: paca and agouti	Rodents: agouti, spiny rat, paca
Geographic distribution of the parasite	Worldwide	North America, northern and central Eurasia	Central and South America	Central and South America
Larval parasite in humans				
Organ localization	Visceral, predominantly liver and lungs	Visceral, primarily liver, metastases in lungs, brain, bones, etc.	Visceral, mainly liver, abdomen, lungs	Orbita, heart
Morphology	Fluid-filled mostly solitary (and less frequently multiple) cysts, unilocular or multichambered, diam 1–>15 cm (Fig. 2); often with protoscoleces	Masses of numerous small cysts (diam microscopic up to 3 cm), often interconnected, surrounded by dense connective tissue, no cyst fluid, appearance of cheeselike mass, sometimes with central necrosis (Fig. 7); rarely a few protoscoleces	Polycystic; fluid-filled cysts, diam up to 4–6 cm, solitary, but often aggregated, interconnected and multichambered; thick laminated layer; protoscoleces frequently present	Fluid-filled cysts with tendency for multicystic development, less subdivision than in *E. vogeli*, and laminated layer thinner; protoscoleces formed.
Type of growth in humans	Concentric expansion	Exogenous proliferation, tumorlike, infiltrative	Exogenous and endogenous proliferation	Expansive, no indication of exogenous proliferation

[a] Data from references 156 to 158 and 194.

intermediate host spectrum, geographic distribution, adult and metacestode morphology, maturation time in definitive hosts, organ localization of metacestodes, and protoscolex production (59). It has to be emphasized that at least seven of nine *E. granulosus* genotypes are infective to humans. Globally, most human cases of CE are caused by the sheep strain (G1) of *E. granulosus*. Information on the infectivity of the lion strain and the buffalo strain is not available. Currently, there is no evidence that the horse strain is infective to humans (59,195). This strain is widespread and common in Ireland, but to date autochthonous cases of human CE have not been observed. However, definitive conclusions regarding the infectivity of the horse strain should not be drawn unless strain typing has been performed for a larger number of human CE cases. An example in this respect is the camel strain of *E. granulosus*. Earlier, it was assumed that humans may not be susceptible to the autochthonous camel strain in Kenya since all 42 *E. granulosus* isolates of human origin were typed by restriction fragment length polymorphism-PCR as the sheep strain (216). However, the camel strain has recently been identified in human CE cases in Argentina, Nepal, and Iran (64, 175, 195, 224). According to Thompson and McManus (195) and Le et al. (128), special features revealed by genetic comparisons and phylogenetic analyses would justify recognition of the horse and the cattle strain of *E. granulosus* as separate species, namely, *E. equinus* and *E. ortleppi*, respectively.

Cystic Echinococcosis in Humans

Course of infection. CE is caused by the metacestode stage of various strains of *E. granulosus*, which is a cystic structure typically filled with a clear fluid (hydatid fluid). About 5 days after ingestion of eggs, the metacestode is a small vesicle (60 to 70 μm in diameter) consisting of an internal cellular layer (germinal layer) and an outer acellular, laminated layer. This cyst (endocyst) gradually expands and induces a granulomatous host reaction, followed by a fibrous tissue reaction and the formation of a connective tissue layer (pericyst). The size of cysts in the human body is highly variable and usually ranges between 1 and 15 cm, but much larger cysts (>20 cm in diameter) may also occur (3, 148, 184) (Fig. 2). The exact time required for the development of protoscoleces within cysts in the human host is not known, but it thought to be more than 10 months postinfection. Protoscoleces can already be formed in cysts of 5 to 20 mm in diameter (149); on the other hand, a proportion of cysts do not produce protoscoleces and remain "sterile." Most of the cysts are univesicular (i.e., unilocular), but in some of them, smaller daughter cysts are formed within larger mother cysts. Mixed infections with metacestodes of *E. granulosus* and *E. multilocularis* are rare, although the two species occur simultaneously in large areas of endemic infection (149).

In the human host, cysts may develop in many anatomic sites following oral ingestion of *E. granulosus* eggs. This form of echinococcosis is known as primary CE. Secondary CE, predominantly in the abdominal cavity, results from spontaneous or trauma-induced cyst rupture and the release of protoscoleces and/or small cysts, which can grow to larger cysts. Approximately 40 to 80% of patients with primary CE have single-organ involvement and harbor a solitary cyst (3, 149). Examples of the organ sites of cysts in hospital patients are presented in Table 3.

TABLE 2. Strains of *E. granulosus*[a]

Strain or isolate[b]	Definitive and intermediate hosts[b]	Infectivity for humans	Probable geographic distribution
G1: common sheep strain	D: dog, fox, dingo, jackal, hyena	Yes	Europe, Middle East, Africa, Iran, India, Nepal, China, Russia, Australian mainland, Tasmania, New Zealand, United States, South America
	I: sheep, cattle, pig, camel, goat, macropods		
G2: Tasmanian sheep strain	D: dog, fox	Yes	Tasmania, Argentina
	I: sheep, cattle?		
G3: (buffalo strain)?	D: dog, fox?	?	Asia
	I: buffalo, cattle?		
G4: horse strain[c]	D: dog	No/?	Europe, Middle East, South Africa (New Zealand?, United States?)
	H: horse, other equines		
G5: cattle strain[d]	D: dog	Yes	Europe, South Africa, India, Nepal, Sri Lanka, Russia, South America?
	I: cattle, buffalo, sheep, goat		
G6: camel strain	D: dog	Yes	Middle East, Iran, Africa, China, Nepal, Argentina
	I: camel, goat, cattle		
G7: pig strain	D: dog	Yes	Poland, Slovakia, Ukraine, Russia, Argentina
	I: pig		
G8: cervid strain (G8)	D: wolf, dog	Yes	North America, Eurasia
	I: cervids		
G9: ?	?	Yes	Poland
Lion strain	D: lion	?	Africa
	I: zebra, wildebeest, warthog, bushpig, buffalo, various antelope species, giraffe?, hippopotamus?		

[a] Data from references 150, 194, and 195.
[b] G, genotype; D, definitive hosts; I, intermediate hosts.
[c] proposed species status, *E. equinus* (195).
[d] Proposed species status, *E. ortleppi* (195).

A literature review of 9,970 patients (originating from regions in South America, Africa, Europe, and Australasia where the sheep strain is common and infection is endemic) has revealed that the average liver-to-lung infection ratio was 2.5:1 (126). A different situation exists in infected but asymptomatic individuals. Ultrasonographic and chest X-ray surveys of approximately 10,000 apparently healthy individuals living in areas of Argentina and Uruguay with endemic infection revealed liver-to-lung ratios of 6:1 and 12:1, respectively (126). An explantation for the shift from the higher liver-to-lung ratios in asymptomatic individuals to lower values (2.5:1) in hospitalized patients is that lung cysts cause more frequently morbidity than hepatic cysts (126).

The initial phase of the primary infection is always asymptomatic. Small, well encapsulated, nonprogressive or calcified cysts typically do not induce major pathology, and patients may remain asymptomatic for years or permanently (3, 149). The induction of morbidity depends on the number, size, and developmental status of the cyst(s) (active or inactive), the involved organ, the localization of the cyst(s) within the organ, the pressure of cysts on surrounding tissues and structures, and the defense mechanisms of the infected individual. Ultrasonographic studies in South America have shown that the average diameter of cysts in asymptomatic carriers was significantly smaller (approximately 4 cm) than that in symptomatic patients (approximately 10 cm) (126). According to Perdomo et al. (151), approximately 88% of cysts detectable in asymptomatic carriers were <7.5 cm in diameter. An ultrasonographic

survey in Italy revealed that 60% of 424 individuals with CE were asymptomatic (21).

Cyst growth is generally slow. In 14 asymptomatic cyst carriers in Argentina, the diameter of liver cysts increased by <3 to 4 cm in 6 patients and showed no modification in 8 individuals during a 10- to 12-year observation period (72, 126). Low growth rates were also reported for hepatic cysts in another Argentinian study of asymptomatic patients (126). There is
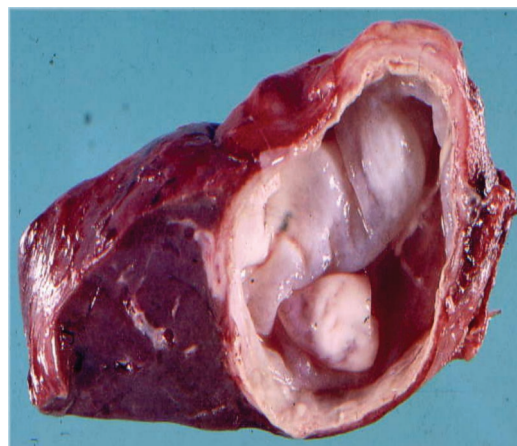

FIG. 2. Hepatic CE in a patient (endocyst removed; lesion size approximately 3 by 3.5 cm).

TABLE 3. Organ sites of *E. granulosus* cysts in humans[a]

Organ	Study A[b]: single-organ involvement in 459 patients		Study B[c]: single- and multiple-organ involvement in 15,289 Chinese surgical cases	
	No. of cases	% of cases	No. of cases[d]	% of cases
Liver	316	68.8	11,499	75.2
Lungs	79	17.2	3,432	22.4
Kidneys	17	3.7	68	0.4
Spleen	15	3.3	160	1.0
Muscles and skin	10	2.2	29	0.2
Abdominal and pelvic cavity	9	2.0	794	5.2
Mediastinum, heart	5	1.1	4	0.03
Brain	4	0.9	61	0.4
Bones	3	0.6	30	0.2
Ovarium	1	0.2	9	0.06
Other organs: skin, eye, spinal cord, pancreas, urinary bladder, testis, etc.				Each <0.1

[a] Adapted from reference 149.
[b] Data from reference 45. Single-organ involvement in 459 patients, originating predominantly from the Mediterranean region.
[c] Data from reference 140.
[d] The number of cases in this column exceeds the total of 15,289 since many patients had multiple-organ involvement; the same applies to the percentages.

evidence that liver cysts grow at a lower rate than lung cysts (126). However, the growth rates of cysts may vary between cysts in the same organ or in the same individual and between individuals in various regions. For example, in the Turkana district of Kenya, a region of high endemicity where CE caused high morbidity, higher growth rates of cysts were recorded. In an ultrasonography study of 66 patients, about 30% of the abdominal cysts grew slowly (1 to 5 mm per year), 43% showed moderate expansion (6 to 15 mm per year), 11% exhibited a more rapid increase (average of 31 mm and maximum of 160 mm per year), and 16% of the cysts did not expand or had collapsed (169,172). The latter finding shows that spontaneous involution of cysts is possible, which leads to changes in the ultrasonographic appearance of the cysts (see below).

Clinical signs may occur after a highly variable incubation period of several months or years. Frider et al. (72) observed that 21 (75%) of 28 carriers of liver cysts in Argentina remained asymptomatic during follow-up periods of 10 to 12 years after the initial diagnosis, while 7 (25%) developed symptoms related to their liver infection. Hepatic cysts can cause pain in the upper abdominal region, hepatomegaly, cholestasis, biliary cirrhosis, portal hypertension, ascites, and a variety of other manifestations (3, 149). Cysts may rupture into the peritoneal cavity, causing anaphylaxis or secondary CE, or into the biliary tree, leading to cholangitis and cholestasis. Abscess formation is possible after bacterial infection of cysts. Chronic cough, expectoration, dyspnea, hemoptysis, pleuritis, and lung abscess are selected symptoms caused by pulmonary cysts, and neurological disorders can be induced by cysts in the brain (3, 149). The modulation of T-lymphocyte responses plays an important role in the outcome of the infection. Th1 and Th2 responses have been associated with resistance and with susceptibility or severe forms of CE, respectively (215). The majority of patients produces various classes of serum antibodies which are not associated with protection but are valuable diagnostic indicators (28, 84).

CE occurs in age groups from younger than 1 to over 75 years. In some areas of endemic infection, most hospital cases are recorded in the age groups between 21 and 40 years, but the highest morbidity may also occur in younger individuals aged between 6 and 20 years (3, 149). An analysis of 8,596 individuals in areas of endemic infection in Uruguay has revealed a significant age-dependent increase of hepatic cysts detectable by ultrasonography from 0.33% in the age group from 0 to 9 years to 3.80% in the age group from 70 to 79 years (151). Similar observations were made in other areas of endemic infection (168). In most of the larger series of patients, there were no significant differences in the gender ratios of individuals with CE (25, 149, 151).

Diagnosis. The diagnosis of CE in individual patients is based on identification of cyst structures by imaging techniques, predominantly ultrasonography, computed tomography, X-ray examinations, and confirmation by detection of specific serum antibodies by immunodiagnostic tests (28, 84, 90, 114, 149, 192). For clinical practice it should be noted that the enzyme-linked immunosorbent assay (ELISA) using crude hydatid cyst fluid has a high sensitivity (over 95%) but its specificity is often unsatisfactory. If purified antigens (e.g., antigen B) or other techniques (immunoblot analysis, detection of immunoglobulin G4 (IgG4) antibodies, immunoelectropheresis, etc.) are used, specificity is improved but average sensitivity is much lower (Table 4). Furthermore, it should be remembered that approximately 10 to 20% of patients with hepatic cysts and about 40% with pulmonary cysts do not produce detectable specific serum antibodies (IgG) and therefore give false-negative results (3, 149). Cysts in the brain, bone, or eye and calcified cysts often induce no or low antibody responses (3). In routine laboratory practice, usually at least two different tests are used to get the most reliable results (for the differential diagnosis of CE and AE, see the discussion of diagnosis of AE, below). More details are given elsewhere (28, 84, 104, 168, 223).

Ultrasonography-guided fine-needle puncture has been used in recent years as a diagnostic procedure in doubtful cases of CE, i.e., in the absence of detectable anti-*Echinococcus* antibodies, in patients with small lesions resembling hepatic cysts, and in patients with lesions which cannot be distinguished from liver abscess, neoplasms, or other conditions (149). Aspirated

TABLE 4. Tests for antibody detection in human CE and AE[a]

Echinococcosis form and test	Antigen[b]	Sensitivity (%)	Relative specificity[c] (%)	Cross-reactions
Cystic				
IgG ELISA	Crude EgCF	80–>99	61.7	Cestodes (89%), trematodes (30%), nematodes (39%)
	Antigen B (native or synthetic peptide)	63–92	85–93	AE
IgG4 ELISA	Crude EgCF	61–67	>99	AE only (see AE)
EITB[d]	Crude EgCF	71	>98[e]	*T. solium* cysticercosis only
	Antigen B fraction	92	100	None
	Antigen B subunits	34–36	>90	
Alveolar				
IgG ELISA	Crude EgCF	97.1	61.7	See above
	Em2PLUS	97.1	98.9	CE (25%)
	Em2/Em2G11	89.3	100	CE (5.6%)
	Em II/3–10	86.4	98.4	CE (6.5%)
IgG4 ELISA	Crude EgCF	48–67	>99	CE (see CE)
EITB	Em18	97	100	None
	Glycoproteins	70–90	>95	

[a] Data from references 84, 87, 90, 168, 186, and other sources.
[b] EgCF, *E. granulosus* cyst fluid; Em, *E. multilocularis*.
[c] Tested with panels of 80 to 184 sera from patients with different parasitic infections (excluding *Echinococcus*-infected patients).
[d] EITB, enzyme-linked immunoelectrotransfer blot.
[e] Including additional sera from patients with other diseases.

cyst fluid can be examined for protoscoleces, rostellar hooks, and *Echinococcus* antigens or DNA (186). To prevent secondary echinococcosis if a hydatid cyst is punctured, chemotherapy with albendazole is recommended for 4 days before the procedure. Chemotherapy should be continued for at least 1 month after puncturing a lesion that was diagnosed as an *E. granulosus* cyst (149), even after its immediate surgical removal.

Classification of cyst types is an important basis for decisions about treatment options. A highly informative review of imaging techniques for diagnosing human echinococcosis has been published by von Sinner and Lewall (213). Recently, the World Health Organization (WHO) Informal Group on Echinococcosis has published an international consensus classification of ultrasonograms of hepatic cysts (222, 223).

Ultrasonography with portable equipment is used for surveys in the field. This technique is well accepted by the population, explores abdominal sites, identifies cyst types, and can be performed at relatively low cost (25, 149, 151, 185). Differential diagnosis of other space-occupying lesions (tumors, liver abscesses, etc.) can be difficult or impossible and may require the use of additional diagnostic techniques. A disadvantage of ultrasonography is that cysts in other sites (lung, brain, etc.) cannot be readily detected. Several comparative field surveys have shown that ultrasonography is much more precise in detecting abdominal cysts than are immunodiagnostic tests since the latter exhibit relatively high rates of false-negative and false-positive results (22, 28, 35, 168, 179, 185).

Treatment. There are several major options for treatment of CE, including surgery, puncture aspiration injection reaspiration (PAIR), and chemotherapy. For asymptomatic individuals, a "wait-and-observe" approach may be considered with supervision of the patient (101, 102, 115, 149).

(i) Surgery. Surgery, using various technical approaches (3, 142, 149), has the potential to remove the cysts and lead to complete cure. It can be successfully performed in a high

proportion of patients with simple forms of CE (cyst number and organ involvement limited, cysts not in risky locations, disease not too far advanced). However, surgery may be impractical in other cases, predominantly in patients with multiple cysts in several organs, in patients with a high surgical risk, and if facilities for advanced surgery are inadequate. In such situations, PAIR or chemotherapy can be considered as alternative options of treatment.

The effect of pre- or postoperative chemotherapy for preventing secondary CE after spillage of cyst fluid during surgery is still unclear. For the PAIR technique (see below), experts recommend chemotherapy with albendazole 24 to 4 h before intervention and 15 to 30 days afterwards (222). The number of *E. granulosus* cysts developing from intraperitoneally inoculated protoscoleces in rodents could be reduced by 80 to 90% if albendazole treatment (10 mg/kg of body weight/day) for 1 week was initiated immediately after inoculation, but treatment starting 15 days after inoculation was ineffective (143). Data on praziquantel treatment are contradictory. In a previous study (165), the drug reduced protoscolex viablity by 65 to 82% when applied in vitro at a concentration of 0.1% for 10 min. According to a recent publication, a 0.1% praziquantel solution had no marked protoscolicidal effect in vitro after 1 h but was strongly effective at 1% after 30 min (100). In mice, treatment with high doses of praziquantel (600 mg/kg of body weight/day on 5 days per week) for 4 months did not significantly influence established *E. granulosus* cysts. When the same treatment was initiated 43 h after intraperitoneal application of protoscoleces, a high prophylactic effect was achieved, as indicated by a 99% reduction in cyst numbers (208). However, the drug doses used in this experiment are much higher than those used in humans (e.g., for a *Schistosoma mansoni* infection, a single dose of 40 mg/kg of body weight was recommended).

(ii) Puncture-aspiration-injection-reaspiration. PAIR was introduced in the mid-1980s (14, 67, 69, 73, 117). It is a minimally invasive technique and includes the following steps: (i)
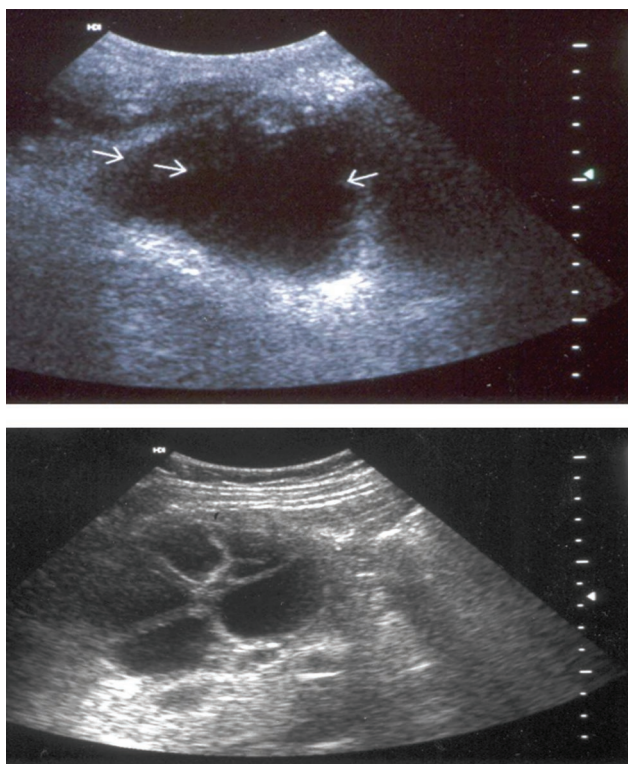
FIG. 3. Ultrasonograms of hepatic cysts of *E. granulosus* (Top) Type CL of WHO-IGWE classification (see text): lesion (arrows) with uniform anechoic content, not clearly delimited by an hyperechoic rim (cyst wall not visible). (Bottom) Type CE2: multivesicular cysts. Reprinted with permission from P. Kern and Dr. W. Kratzer, University Hospital and Medical Center, University of Ulm, Ulm, Germany.

percutaneous puncture of the cyst under ultrasonographic guidance, (ii) aspiration of a substantial portion (for example, 10 to 15 ml) of the cyst fluid, (iii) injection of a parasitocidal solution (95% ethanol; approximately an equivalent of one-third of the amount aspirated), and (iv) reaspiration of the fluid content after 5 min (222). Hypertonic NaCl solution (at least 15% [final concentration] in the cyst fluid) can also be used as a parasitocidal solution, but its action is slower, so that reaspiration is performed only after 15 to 20 min (116, 222).

A guideline for the performance of PAIR has recently been published (222). PAIR should always be performed by skilled and experienced physicians well prepared to deal with complications. According to expert recommendations, PAIR should be accompanied by chemotherapeutic coverage to minimize the potential risk of secondary echinococcosis (149, 221, 222). In this indication, albendazole is applied in daily oral doses of 10 mg/kg of body weight 24 to 4 h before and 15 to 30 days after the intervention (222). More studies are needed to evaluate the efficacy and optimize this treatment schedule.

PAIR is indicated for univesicular hepatic cysts of ≥5 cm in diameter (types CEL and CE1 according to the international classification [222]), for cysts with daughter cysts (type CE2) (Fig. 3), for cysts with detached membranes (type CE3), and also for multiple cysts if accessible to puncture (222). The main contraindications for PAIR are cysts communicating with the biliary tree, cysts in a risky or inaccessible location in the liver,

cysts free in the abdominal cavity, and cysts in the lungs, heart, brain, or spine (149, 222).

Great care must be taken to detect cysts with biliary communications in order to prevent an influx of parasitocidal solution into the biliary tree and the risk of chemical cholangitis. Therefore, it is a basic requirement to examine aspirates from liver cysts for traces of bilirubin. Furthermore, endoscopic retrograde cholangiopancreatography is used to rule out cyst-biliary communications (222). If bilirubin is present in the cyst fluid, the PAIR procedure must be discontinued.

PAIR interventions in more than 2000 patients had a high rate of efficacy and generally a low rate of complications (67, 116, 137, 209, 222). There are indications that PAIR has several detrimental effects to the parasite, including (partial) detachment of endocyst membranes from the pericyst and/or damage of the germinal layer and protoscoleces by the parasitocidal solution. A recent international survey of PAIR treatments performed in various hospitals showed the following results (68). Treatment of 765 abdominal cysts, mostly hepatic, almost always resulted in various degrees of size reduction (at least 50%) and involution of the cysts, except for two failures (0.26%). A >5-year follow-up of approximately 10% of the cysts and a <5-year follow-up of 90% revealed 12 recurrences (1.6%). Major complications occurred in four patients (0.52%), with one death (0.13%) and spillage of hydatid fluid in four patients (0.52%); 13.7% of the patients had minor complications. Ustunsoz et al. (209) have reported a 97% cure rate of PAIR in 70 Turkish patients with a mean follow-up of 37 months and only two (3%) recurrences.

(iii) Percutaneous thermal ablation. A new approach of treatment involves percutaneous thermal ablation (PTA) of the germinal layer in the cyst by using a radiofrequency ablation device. Brunetti and Filice (18) have used PTA for treating two patients with hepatic cysts; more experience with this technique is needed. PTA would have the advantage that injection of parasitocidal substances into the cyst is unnecessary.

(iv) Chemotherapy. Chemotherapy with benzimidazoles (albendazole or mebendazole) is indicated for patients with inoperable CE and for those with multiple cysts in two or more organs. Cysts located in bones are less susceptible to chemotherapy. According to WHO recommendations, albendazole is given in daily doses of 10 to 15 mg/kg of body weight in two divided doses postprandially for 3 to 6 months. The usual dose of mebendazole is 40 to 50 mg/kg of body weight per day for at least 3 to 6 months (115, 221, 222). Results for over 2,000 well-controlled cases treated with benzimidazoles and evaluated for up to 12 months have shown that cysts disappeared in 10 to 30% of the patients (cure), there was objective evidence of response in 50 to 70% (degeneration or size reduction of cysts), and 20 to 30% did not exhibit morphological changes of the cysts (101, 102, 149, 197, 198). Relapses after chemotherapy have been observed in 14 to 25% of patients, but are usually sensitive to retreatment (149). In a comparative study with 448 patients, Franchi et al. (70) assessed the efficacy of mebendazole and albendazole treatment (3 to 6 months) and found degenerative changes in 82% of the cysts in the albendazole group and in 56% in the mebendazole group ($P < 0.001$). Relapses were observed in 25% of the cysts. Side effects of chemotherapy are generally mild and rarely treatment limiting (3, 101, 221, 223). Although the efficacy of chemotherapy is not

TABLE 5. Options for the diagnosis of *E. granulosus* in animals

Animal group	Material required	Test, sensitivity and specificity[a]	Reference(s)
Live animals			
Individual dogs	Feces in buffer	Screening: coproantigen ELISA. S, 65–77%; SP, >90%.	28, 40
		Secondary[b]: copro-PCR. S, under evaluation; SP, close to 100%.	Mathis and Deplazes, unpublished
Dog populations	Fecal material discharged by dogs after arecoline treatment	Standard option: macroscopic examination of discharged material. S, 65% after single-dose arecoline, 78% after second dose; SP, close to 100%.	179
	Feces in buffer	New option. Screening: Coproantigen-ELISA. S and SP, as for individual dogs.	28, 40
		Secondary: copro-PCR. S and SP as for individual dogs.	Mathis and Deplazes, unpublished
Intermediate hosts: sheep, goat, cattle, horse etc.		No reliable in vivo method for detecting the infection in individual animals, except rare cases in which cysts can be identified by ultrasonography in conjunction with antibody detection, for example in individual horses.	54
		A new ELISA might be useful for the detection of *E. granulosus* in sheep flocks (sensitivity, 50–60%).	120
Dead animals			
Dogs and other carnivores	Small intestine	Standard option: Parasite detection at necropsy by direct examination of the intestine or by sedimentation technique (S and SP, close to 100%).	54
	Feces from rectum or content from intestine in buffer	New option: coproantigen ELISA in conjunction with copro-PCR (details as for small intestine).	
Intermediate hosts	Viscera	Cyst detection at meat inspection or necropsy; in doubtful cases histology and/or PCR.	54

[a] S, sensitivity, SP, specificity.
[b] Secondary test for confirmation or exclusion.

satisfactory and the costs are high, it is an option of treatment, predominantly for inoperable cases.

E. granulosus Infection in Animals

Definitve hosts. The domestic dog is the principal definititive host of *E. granulosus*, but in certain regions wild canids may be involved in the life cycle of the parasite (Table 1). Although *E. granulosus* penetrates deep between the villi of the small intestine of a definitive host, there are no pathogenic effects even in animals with a heavy infection (54). Therefore, infected definitive hosts are typically asymptomatic carriers of the parasite.

The diagnosis of intestinal *E. granulosus* infection in living dogs is difficult because the small proglottids spontaneously discharged with feces are usually overlooked and eggs detected by routine coproscopic techniques cannot be differentiated by light microscopy from the eggs of other *Echinococcus* species or of *Taenia* species. ELISAs for detecting parasite antigens in fecal samples (coproantigens) have been used in specialized laboratories for the last few years (29, 40). Recently, a PCR for specific detection of DNA from *E. granulosus* eggs has been developed (A. Mathis and P. Deplazes, unpublished data) (Table 5). The coproantigen ELISA has a reasonable sensitivity and a high specificity and can be used as a screening test for individual dogs or for dog populations (Table 5). One of the advantages of this test is that about 200 samples can be examined by one person per day (41). The more sophisticated PCR can be used as a highly sensitive and specific secondary test for confirming or excluding an *E. granulosus* infection (Table 5). Postmortem examination of definitive hosts for *Echiococcus*

species requires special techniques (Table 5), which are described elsewhere in detail (54). Praziquantel is the drug of choice for treating infected dogs (reviewed in reference 54) (see "Control options and prevention" below).

Intermediate hosts. Infections with *E. granulosus* cysts in intermediate hosts (sheep, goat, cattle, horses, etc.) are typically asymptomatic, except a few cases of long-standing and heavy infections, for example in horses (Fig. 4). There are no reliable methods for the routine diagnosis of the infection in living animals, but in rare cases cysts have been identified by ultrasonography alone or in conjunction with serum antibody detection (54). A new ELISA with a high specificity and a sensitivity of 50 to 60% might be useful for detecting *E. granulosus* cysts in sheep on a flock basis but cannot be used for reliable diagnosis of infected individual animals (120) (Table 5). The most reliable diagnostic method is cyst detection during meat inspection or at postmortem examination (Table 5). CE in farm animals causes considerable economic problems due to loss of the edible liver. Significant loss of meat and milk production and value of the fleece from infected sheep may also occur. These losses are of especial significance in countries of low economic output where sheep production is of particular importance (201).

Epidemiology

Life cycle patterns. The life cycles of *E. granulosus* strains (Table 2) can be classified as domestic, involving the domestic dog as the principal definitive host and various species of domestic ungulates as intermediate hosts, or as sylvatic, involving wild carnivores and ungulates as hosts (the wildlife cycle).
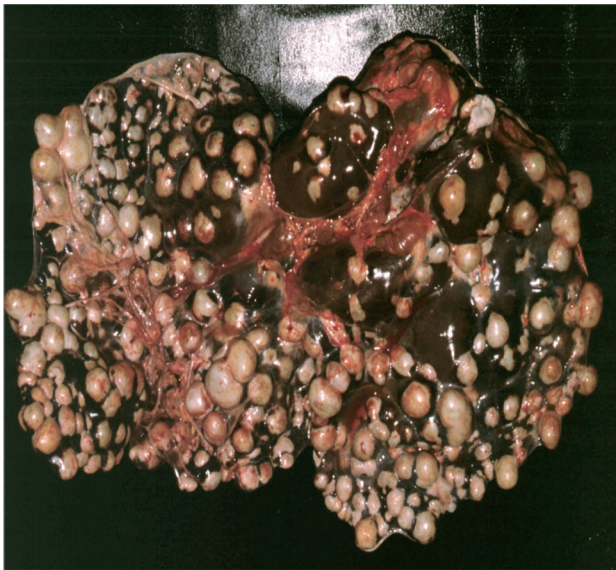
FIG. 4. Horse liver with multiple cysts of *E. granulosus* (cyst diameters approximately 1 to 10 cm). The horse exhibited clinical signs of the disease.

Within the cycles, the specific role of various host species may differ considerably between regions of endemic infection. In many areas of endemic infection, domestic and sylvatic life cycles coexist or overlap (155). For example, the dog-sheep strain is globally the most widespread and important strain of *E. granulosus* and exists in its domestic form (dog-sheep/goat) in many regions. However, in Australia this strain is transmitted between domestic animals (dog/sheep) and wild-animal hosts (definitive hosts are dingoes [*Canis lupus dingo*], dingo-domestic dog hybrids, less frequently red foxes [*Vulpes vulpes*]; intermediate hosts are mainly macropod marsupials, also feral pigs [*Sus scrofa*] and wombats [*Vombatus ursinus*]) (105). On the other hand, the cervid strain of *E. granulosus* in the Arctic is transmitted almost exclusively between wolves and wild Cervidae (elk [*Alces alces*], reindeer [*Rangifer tarandus*], and red deer [*Cervus elaphus*]) but domestic dogs and domesticated reindeer can replace the wild hosts (155). Complex situations of coexisting or overlapping domestic and sylvatic cycles also exist in other regions (for example, in Africa and Eurasia) and represent special problems in echinococcosis control (105, 132, 133, 155).

Transmission dynamics. During the past four decades, considerable advances have been made in understanding the epidemiological key factors and the transmission dynamics of *E. granulosus* and other members of the family Taeniidae (notably *Taenia hydatigena* and *T. ovis*). A mathematical model was developed which allows us to quantify various factors contributing to the regulation and stability of the parasite populations and to draw conclusions for control (74, 78, 85, 166, 167, 199, 200). For *Taenia* species, the following key factors have been identified (78): (i) biotic potential of the parasite, (ii) immunity acquired by the intermediate host as a density-dependent constraint, and (iii) environmental factors as density-independent constraints in the free-living egg-phase.

T. hydatigena and *T. ovis* have high biotic potentials with the production of large numbers of eggs and large numbers of metacestode cysts developing in sheep. In contrast, the biotic potential of *E. granulosus* is relatively low, representing less than 5% of the potentials of *T. hydatigena* and *T. ovis* (75). Results of previous studies have suggested that the degree of immunity acquired by definitive hosts during natural infections with *E. granulosus* is negligible and does not play a role in regulating the intestinal parasite population (75). Experiments to stimulate strong immunity against intestinal stages of *E. granulosus* in dogs have failed so far (92). Recent observations from Tunisia and Kazakhstan, where young dogs are more heavily infected than older dogs, should stimulate new basic studies of the immune responses of dogs to intestinal cestode infections (199).

On the other hand, acquired immunity in intermediate hosts has clearly been identified as a density-dependent constraint reducing the parasite (metacestode) population of *Taenia* species. A considerable degree of immunity against *T. hydatigena* and *T. ovis* is acquired by sheep within about 2 weeks after ingestion of small numbers of eggs (as few as 10 eggs per animal); it persists life-long in the presence of eggs in the environment but is lost between 6 and 12 months in the absence of eggs, and it does not depend on the presence of metacestodes from a previous infection (74, 75). Strong immunity can also be experimentally induced against *E. granulosus*, but it requires much larger numbers of eggs (approximately 50,000 eggs per animal) (199). Consequently, sheep populations do not develop strong immunity against *E. granulosus* under natural infection pressure, as indicated by the fact that both the prevalence and intensity of the infection with cysts of *E. granulosus* increase with age of sheep (123, 124, 206).

Environmental temperature and humidity influence egg survival and infectivity but do not regulate the parasite population. *E. granulosus* eggs can survive under humid conditions for several weeks or months in areas of warm and cold climates, but they are sensitive to desiccation (55, 75). Several factors play a role in egg dispersal (75, 78) (see also "Eggs in the environment" below).

Infection risk for humans. Humans acquire primary CE by oral uptake of *E. granulosus* eggs excreted by infected carnivores. The infection may be acquired by handling infected definitive hosts, egg-containing feces, or egg-contaminated plants or soil followed by direct hand-to-mouth transfer. It has been shown that *Echinococcus* eggs adhere to the coat of dogs, particularly to the hairs around the anus and on the thighs, muzzles, and paws. The same applies to dogs infected with *Taenia* species and to foxes infected with *E. multilocularis* (55). Eggs can also be ingested with vegetables, salads, uncooked fruits, and other plants which have become contaminated. Foodstuffs or surfaces may possibly be secondarily contaminated with *Echinococcus* eggs via wind, birds, beetles, and flies (55). Also, drinking water contaminated with *Echinococcus* eggs by the feces of infected carnivores is a potential source of infection (see below). Prenatal transfer of *E. granulosus* does not play a role (26).

Very little is known about the relevant modes of *E. granulosus* egg transmission to humans. Campos-Bueno et al. (20) in Spain have evaluated several risk factors in a case-control study involving 127 patients with proven CE cases and 127
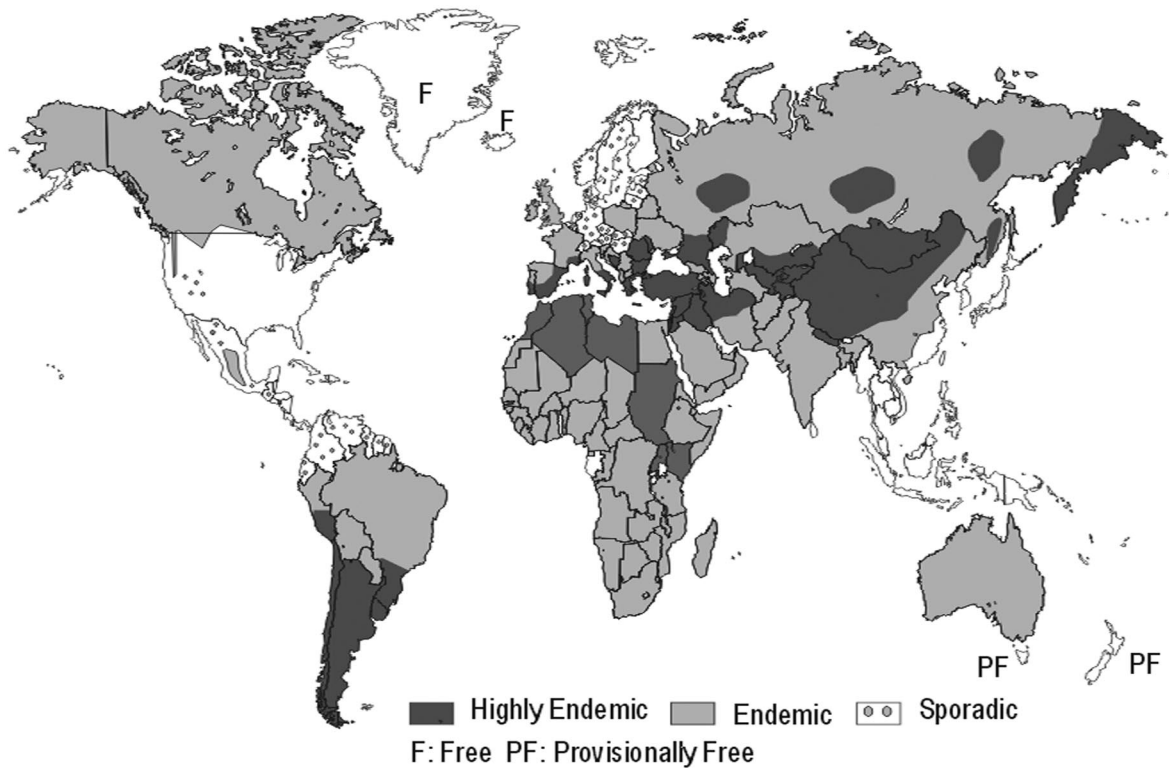
FIG. 5. Approximate global distribution of *E. granulosus* (as of 2002). The exact identification of areas of normal and high endemicity is difficult because of incomplete or lacking data. Modified from WHO/OIE 2001 (223) with permission.

controls matched by sex, age, and residence. The risk of infection was highest in small places with up to 500 inhabitants and increased with the number of dogs in the family and the number of years of coexistence with them. Further important risk factors were dogs having access to raw viscera of slaughter animals and dogs kept loose and able to enter dwellings. Surprisingly, the ingestion of products from family vegetable gardens over prolonged periods was not associated with an increased risk for CE. In a case-control study in Argentina, one of the risk factors for CE was spending the first years of life surrounded by a large number of dogs (125). In Tibetan aeras of China (Sichuan), increased risks for CE were associated with nomadic life, age, playing with dogs, not protecting food from flies, and raising yaks or sheep (217). In studies in Jordan (43) and Kyrgystan (204), multivariate analysis revealed the use of potentially contaminated water as the only statistically significant risk factor for humans, but confounding factors could not be excluded. Water wells were also suspected as sources of infection with *E. granulosus* in arid areas of Africa where humans and carnivores frequently use the same water points (132). In a cross-sectional survey in an area of endemicity in mid-Wales (United Kingdom), no significant association could be found between treatment of humans for CE and many of the well-established risk factors, such as dog or farm ownership (44). The identification of risk factors is generally difficult for various reasons, such as small sample sizes, long time interval between infection and diagnosis of CE, and high mobility of patients and migration of definitive hosts. Molecular approaches allowing the species-specific identification of *Echi-*

nococcus eggs in the environment will open up new opportunities for the study of transmission routes (see "*E. multilocularis* infection in animals" below).

Global distribution of *E. granulosus* and CE in humans. Due to the lack of well-documented data from many countries, the global picture of the current situation is incomplete. However, a recent review (58) has shown that *E. granulosus* is known to occur on all continents and in at least 100 countries (Fig. 5). High parasite prevalences are found in parts of Eurasia (for example, the Mediterranean region, the Russian Federation and adjacent independent states, and China), Africa (northern and eastern regions), Australia, and South America. In some European countries or regions, the annual incidences (AI) of hospital cases of human CE vary between <1 and >8 per 100,000 population. In China, CE is regarded as one of the major public health problems (220). In Xinjiang, the average AI was 8.7 per 100,000 in 1990 but the AI was up to 42 per 100,000 in one of the counties (140). In Sichuan province, human CE had a prevalence of 2.1% (85/3,998) in 1997 to 1998 (217). High incidence rates or prevelances have also been recorded from countries in northern and eastern Africa (prevalences of >3%) and South America (for example; an AI of 9.2 per 100,000 population in Uruguay in 1995). A few islands are free of *E. granulosus* (Iceland and Greenland), and in some islands only very sporadic, cases have been detected in domestic animals in recent years ("provisionally free") (New Zealand, Tasmania, southern Cyprus). The occurrence of *E. granulosus* is sporadic or has not been reported from other regions, including countries or regions in northern and central

Europe, in North and Central America, in the Pacific Region, and in the Caribbean.

Factors associated with persistence, emergence, or reemergence. Key factors associated with persistence, emergence, or reemergence of CE have recently been described in Bulgaria (196) and the Mediterranean region (12). They include (i) the presence of large numbers of dogs (especially stray dogs) infected with *E. granulosus*, (ii) easy access of dogs to organs of livestock infected with *E. granulosus* cysts, (iii) insufficient facilities for slaughter and destruction of infected viscera, (iv) illegal or uninspected home slaughter, (v) a close association of dogs and other animals on small rural lots of land, (vi) uncontrolled animal trade and movements within and between countries, (vii) poor living conditions (especially lack of tap water), (viii) lack of adequate health education, and (ix) economic instability and financial restrictions in control and prevention. In central Asian countries (Kazakhstan and Kyrgystan), the reemergence of CE is clearly associated with the transition from a planned to a free-market economy since their independence from the former Soviet Union and its several consequences, such as a decline of the economy and living standards, deterioration of veterinary and medical services owing to the lack of adequate funding, and reforms in agriculture with increase of smaller livestock enterprises, uncontrolled slaughter, and offal disposal (183, 203, 204, 205).

Examples of emergence or reemergence. Reports from several countries provide documented evidence for the emergence or reemergence of *E. granulosus* and CE in recent years. For example, in Bulgaria the annual incidence of CE in children has increased from 0.7 per 100,000 in 1971 to 1982 to 5.4 in 1995 (196). Other reports indicate an alarmingly high prevalence of *E. granulosus* in humans and animals in some countries of the Mediterranean region (12). In Kazakhstan the annual surgical incidence of CE over the whole country was below 1.4 per 100,000 inhabitants from 1988 until 1995 but has increased to approximately 2.5 in 1997 and to 5.9 in 2000; 29% of the cases were in children younger than 14 years, indicating recent transmission (182, 183, 203). In the South Kazakhstan Oblast, the prevalence of *E. granulosus* cysts was 13.6% in 5,968 sheep prior to independence and 37.0% in 917 sheep in the same area in 1999 to 2000 (203). A similar trend has been identified in Kyrgystan (203, 204), where the annual incidence of CE per 100,000 inhabitants has increased over the whole country approximately threefold from 5.4 cases in 1991 to 18 in 2000. Hospital admissions due to CE in the capital, Biskek, have increased 5.9-fold from 21 cases in 1990 to approximately 124 in 1999; the increase of pediatric cases was 41 times higher in 2000 (82 cases) than in 1990 (2 cases) (204). These data are supported by ultrasonography cross-sectional surveys of 8,777 persons between 1989 and 1994 and 1,486 subjects between 1991 and 2000; in this period, the prevalence had increased significantly, from 0.42 to 1.35% (204).

The data from Bulgaria, Kazakhstan, Kyrgystan, and some other regions provide strong evidence for a real increase or reemergence of the incidences and prevalences in recent years, which is not attributable to improved diagnosis or reporting.

Control Options and Prevention

Several options for the control of *E. granulosus* have been thoroughly evaluated and are described in detail elsewhere (13, 61, 62, 74–77, 153). One option (type I) emphasizes long-term measures of public health education with primary health care (147) and veterinary public health activities, such as the improvement of slaughter hygiene and meat inspection, dog registration and sanitation measures (77). Experience from several countries has shown that this option alone may not be sufficient and may be too slow for effective *E. granulosus* control (77). Another option (type II) is based on legislation and includes specific measures targeted to interruption of parasite transmission. Prior to the "attack phase" of the program, baseline data are collected to serve as references for measuring control progress. Important base-line data are the prevalence of *E. granulosus* in dog populations, the age-dependent prevalences of cysts in sheep and other domestic ungulates, and human cases of CE. Modern techniques can now be used for surveys; for example, the coproantigen ELISA can be used to detect *E. granulosus* in dog populations (instead of arecoline testing) and ultrasonography alone or in combination with serology can be used for mass diagnosis of CE in humans (24, 28, 71, 168, 179, 223). Specific control measures include stray-dog control, registration of all owned dogs, spaying of bitches, and treatment of all (or most) dogs with praziquantel at predetermined intervals, for example every 6 or 8 weeks. These measures are complemented by upgrading of meat inspection, slaughter hygiene, slaughter offal disposal, public health education, and other measures. Control programs in various countries have shown that the attack phase can be successfully concluded in less than 15 years if the necessary measures can be performed without major constraints and financial restrictions (76–78). Under suboptimal conditions, the attack phase can last much longer. For example, in the Rio Negro Province of Argentina, a control program including dog treatment with praziquantel (5 mg/kg of bodyweight) at 2-month intervals has, within about 20 years (1979/1980 to 1999), reduced the prevalence of cysts in sheep from 61 to 18% and of intestinal stages in rural dogs from an estimated 40 to 2–3% (124). After the parasite has been driven close to extinction during the attack phase, further measures are necessary in the following consolidation and maintenance phases (76, 77). Major problems of control programs against *E. granulosus* are long-term funding and perturbations due to political and administrative reasons. Control options of type II were predominantly successful in island situations (New Zealand, Tasmania, Falkland Islands, and Cyprus), and partially effective in continental regions (Argentina, Chile, Uruguay, Bulgaria, Spain, parts of China, and some other areas) (24, 61, 62, 76, 77, 124, 219).

Great efforts have been made in Australia and New Zealand to develop vaccines which can protect sheep or cattle against infections with metacestode stages of taeniid cestodes. A recombinant vaccine against *Taenia ovis* in sheep has been successfully developed by using antigens derived from oncospheres (108, 129). Similar vaccines were developed against *T. saginata* in cattle, *T. solium* in pigs, and *E. granulosus* in sheep and cattle (93, 129). Large controlled studies with sheep have shown that vaccination with a recombinant oncospheral *E. granulosus* an-

tigen (EG95) induces high degrees of protection, reducing the cyst numbers in vaccinated animals by approximately 90 to 100% (93, 95, 107, 129, 130). A high degree of immunity (about 80%) persists for 6 months (in the absence of reinfection), and pregnant ewes vaccinated before lambing transfer high levels of antibody to their lambs (94).

A recent mathematical simulation suggests that a combination of regular dosing of dogs with praziquantel and vaccination of intermediate hosts would destabilize the system more rapidly than other control options (200). Regrettably, the vaccine is not yet commercially available.

Problems of safety precautions and disinfection have been neglected in research. A review of the current state of art has been published in the *WHO/OIE Manual on Echinococcosis* (55). Essential precautions are summarized as follows. (i) Personnel involved in handling animals infected with mature intestinal stages of *Echinococcus* spp. or egg-contaminated materials should weare protective clothing (cap, face mask, safety glasses, single-use overall, plastic apron, rubber gloves, and boots). (ii) For work with infected definitive hosts (for example, treatment of dogs), their intestines, fecal matter, or other materials possibly containing infective *Echinococcus* eggs, special rooms or sterile bench systems should be used. In some countries, a BL-3 biohazard safety level is required. (iii) Whole carcasses of carnivores, intestines, or fecal sample possibly containing infective *Echinococcus* eggs can be decontaminated by deep-freezing at −70 to −80°C. Care should be taken that the effective temperature reaches all parts of the material and is maintained for at least 96 or 48 h, respectively. The temperatures of household deep-freezers are too high to inactivate eggs. *Echinococcus* eggs are killed within 5 min at +60 to 80°C and instantly at +100°C. (iv) Persons who have had a single exposure to infected final hosts or egg-contaminated materials or who have ingested apparently contaminated food should receive serological screening for specific antibodies at the following intervals after the suspected contact: 4 weeks and 6, 12, and 24 months. Individuals with repeated infection risk (for example, laboratory personnel, field workers in echinococcosis control) should be serologically examined twice a year.

In areas which are free of *E. granulosus* or have only sporadic occurrence of the parasite, special measures should be taken in order to prevent the introduction of the parasite by living definitive or intermediate host animals.

E. MULTILOCULARIS AND ALVEOLAR ECHINOCOCCOSIS

The Parasite and Its Life Cycle

The adult stage of *E. multilocularis* is characterized by its small size (length of up to 4.5 mm), a mean number of five segments, a sack-like uterus, and other morphological features, allowing its differentiation from *E. granulosus* and other *Echinococcus* species (193, 223) (Table 1). Transmission of *E. multilocularis* occurs in a sylvatic cycle, which is sometimes linked via infected small mammals to domestic dogs and cats (Fig. 6). In the sylvatic cycle, foxes (mainly the Arctic fox [*Alopex lagopus*] and the red fox [*Vulpes vulpes*]) play a key role as definitive hosts and small mammals, mainly rodents, are the intermediate
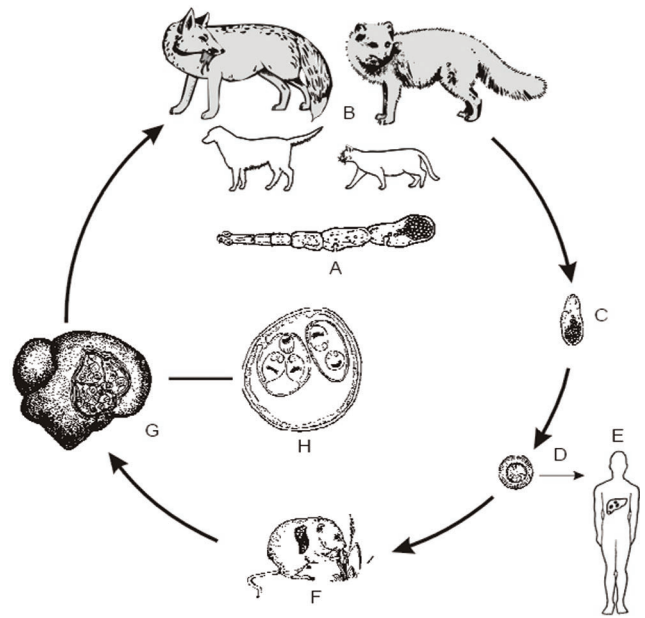

FIG. 6. Life cycle of *E. multilocularis.* (A) Adult parasite. (B) Foxes (left, red fox; right, Arctic fox) as principal definitive hosts; dogs, other canids, and cats can be involved in the cycle. (C) Proglottid with eggs. (D) Egg with oncosphere. (E) Infection of humans. (F) Rodent infected with metacestodes. (G) Rodent liver with metacestodes. (H) single metacestode cyst with protoscoleces.

hosts. In some areas, other wild canids, such as coyotes (*Canis latrans*), raccoon dogs (*Nyctereutes procyonoides*), and wolves (*Canis lupus f. familiaris*), or wild felidae (wild cats) can also serve as definitive hosts. Among the many species (>40 species) of small mammals that are susceptible to *E. multilocularis* under natural conditions, members of the family Arvicolidae (voles and lemmings) and Cricetidae (hamsters, gerbils, and related rodents) are most important (79, 155, 165). Aberrant host animals and humans can also become infected with the metacestode stage, which has the potential to cause AE, one of the most lethal helminthic infection in humans. Although some variation between *E. multilocularis* isolates from North America and Eurasia has been described, there is no evidence for distinct genetic strain differences (91). This is in accordance with the fact that *E. multilocularis* in various regions, including large areas of the northern hemisphere (Asia, Europe, and North America), is infective to humans.

Alveolar Echinococcosis in Humans

Course of infection. The metacestode stage of *E. multilocularis* in natural intermediate hosts or aberrant hosts is characterized by an alveolar structure, composed of numerous small vesicles (<1 mm to 3 cm in diameter). A characteristic feature of this stage is its exogenous tumour-like proliferation, which leads to infiltration of the affected organs and, in progressive cases, to severe disease and even death (Fig. 7). The single vesicle has a wall structure similar to that of the metacestode of *E. granulosus* (germinal and laminated layer) (48). In intermediate or aberrant hosts, the metacestodes can proliferate from
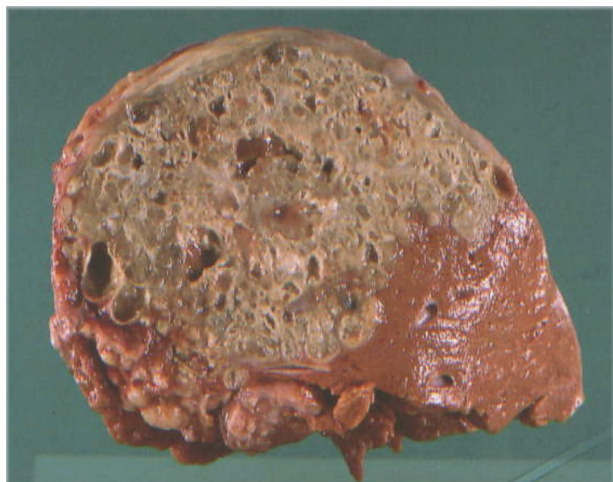
FIG. 7. Hepatic alveolar echinococcosis in a 62-year-old Swiss patient (maximum diameter of single cysts approximately 1.5 cm).

initially minor lesions (microscopic up to a few millimetres) to diameters of 15 to 20 cm (in the human host) (3, 48). Data from patients with single-organ involvement indicate that metacestodes initially establish themselves almost exclusively in the liver (approximately 99% of the cases) and are rarely found in extra-hepatic sites (48). Later in the infection, metastases may spread from the liver to adjacent locations (abdomen, retroperitoneum, etc.) or to distant organs (lungs, brain, bones, etc.). In a Swiss series of 70 patients with advanced AE, the liver alone was involved in 67% of patients, the liver and adjacent organs were involved in 20%, and the liver and distant organs were involved in 13% (48). Recently, a new clinical classification system has been proposed (related to a similar system used for malignant tumour diseases) that is based on imaging and clinical parameters and takes into account the parasite mass (and hepatic localization of the parasite), the extrahepatic involvement of neighbouring organs, and the absence or presence of distant metastases (122, 223). This system provides a defined basis for decisions about therapeutic options, for follow-up studies after treatment, and for prognostic considerations.

In humans, several main phases of the infection (initial, progressive, advanced, stability, abortive course) and several pathological entities can be distinguished. The initial phase is always asymptomatic and may be cured spontaneously or turn to a progressive course. Estimates of the incubation period vary between less than 5 and up to 15 years (3, 178); the shortest period between oral uptake of E. multilocularis eggs and seroconversion is unknown. In the progressive phase, symptoms occur when the metacestode has infiltrated larger parts of the liver or influences important functions. Initial symptoms include abdominal pain, jaundice, hepatomegaly, sometimes fever and anaemia, weight loss, and pleural pain (3, 48, 178). The advanced stage is characterized by severe hepatic dysfunction, often associated with portal hypertension. The duration of the disease is variable between weeks and years. Mortality rates in untreated or inadequately treated AE patients can be very high; in three groups of such patients (a total of 107 individuals), the average survival rate 10 years after

diagnosis was 29% (range, 0 to 23%) and the survival rate after 15 years was 0% (reference 3 and references therein). The reported ages of patients at diagnosis ranged from 5 to 89 years, with means of 45 ± 15 years in a Japanese series (178) and 52 ± 17 years in a Swiss series (56). The most frequent ages at diagnosis are usually between 35 and 65 years, and the gender ratio is often close to 1:1 (48). A stable phase of the infection can occur in patients undergoing long-term chemotherapy, and this phase inhibits further parasite proliferation (see below). Abortive cases have been observed in asymptomatic patients, when the parasite dies out and is mineralized (9, 89, 149, 162).

During the infection with E. multilocularis metacestodes, parasite-specific humoral and cell-mediated immune responses are both progressively established. The latter may play a crucial role in host defense (86). Immunological studies of mice experimentally infected with E. multilocularis have revealed an initial Th1 dominant cytokine secretion, including interleukin-2 (IL-2) and gamma interferon. This is associated with slow parasite proliferation. Rapid growth of the parasite was associated with secretion of Th1- and Th2-type cytokines including IL-5 and IL-10. Finally, in animals with advanced AE, suppression of immunity was observed associated with almost complete inhibition of cytokine secretion by lymphocytes on specific or unspecific in vitro stimulation, (63, 214, 215). A varying, spontaneous cytokine secretion was also observed in patients in different phases of AE. In patients with progressive disease, IL-10 secretion by peripheral mononuclear cells was more pronounced and IL-10 levels in serum were higher than in individuals with abortive forms (82, 83, 218).

Other studies suggest that the formation of the laminated layer by the metacestode inhibits or prevents immunological control of parasite proliferation. In recent studies of a laminated layer-associated antigen (Em2G11), a high-molecular-weight mucin-type glycosylated protein could be identified (103). This protein stimulates antibody production in the absence of major histocompatibility complex class II- restricted T-cell help. In addition, it does not stimulate cell proliferation in vitro. Therefore, it is claimed to be a relevant factor contributing to the lack of protection against the metacestode in vivo (31). The mouse model has provided much useful information; however, due to the rapid parasite development in mice, it might not be an appropriate model for the study of all mechanisms involved in human AE.

Diagnosis. Essentially the same procedures are used for diagnosing AE in human patients as for diagnosing CE (3, 112, 149). Among the imaging techniques, ultrasonography is the method of choice for screening; it is usually complemented by computed tomography, which detects the largest number of lesions and characteristic calcifications. Magnetic resonance imaging may facilitate the diagnosis in unclear cases (164). Immunodiagnostic tests (for primary diagnosis or confirmation of imaging results) are more reliable in the diagnosis of AE than of CE since more specific antigens are available (Table 4). For example, the Em2plus-ELISA, using a mixture of affinity-purified E. multilocularis metacestode antigens (Em2-antigen) and a recombinant antigen (EmII/3-10), exhibited a diagnostic sensitivity of 97% in 140 patients with confirmed AE and an overall specificity of 99% for infections due to other helminths (87). However, the use of this test in a broader spectrum of

patients has revealed lower sensitivity (approximately 85%) and specificity (>95%) (168). Immunoblot tests using the EM18 antigen are reported to have sensitivities between 50 and 90% and specificities of >95% (168) (for further details, see references 84, and 104).

The diagnosis can be confirmed by parasite identification in surgical or biopsy material. In most of the cases, histological examination is sufficient, but recognition of characteristic structures in fine-needle biopsy specimens or calcified samples may be difficult or impossible. In such cases, the specific Em2G11 antigen can either be detected immunhistologically or in an ELISA using a monoclonal antibody (39). This antigen persists in calcified lesions within fragments of the laminated layer even after the death of the parasite. Furthermore, specific PCRs targeting the U1 small nuclear RNA gene or the mitochondrial 12S rRNA gene (16, 42) can be used. The viability of the parasite can be assessed by transplanting metacestode tissue samples to laboratory rodents (50). Another option is the use of reverse transcription-PCR (111). The sensitivities of both techniques depend on the amount and quality of the sample material. Puncture of the liver of a human with AE includes a risk of dissemination of parasite material and may require postinterventional chemotherapy.

Immunodiagnostic tests (alone or in combination with ultrasonography) have been used for screening human populations for AE in various countries, for example in Alaska, Austria, China, France, Germany, Japan, and Switzerland (10, 17, 30, 81, 88, 174, 189). In view of the low prevalence of the infection in most areas of endemic infection, it is essential to use highly sensitive and specific test systems. The largest mass-screening program was carried out in Japan (55, 178, 189). In Hokkaido (population of 5.8 million), 715,841 individuals received serological primary screening during 1984 to 1993. Overall, 5,159 individuals had a positive ELISA reaction, 1,272 persons underwent secondary ultrasonographic screening, and, finally, 60 persons (0.008% of the total) were shown to have asymptomatic AE (189). Eearly detection of AE by mass screening can be cost-effective and reduces morbidity, suffering, and mortality (55). In Hokkaido, the rate of complete surgical excision of liver lesions in the group of screened individuals was 100%, in contrast to a resectability rate of only 20% in nonscreened patients in whom AE was detected at a later stage (55).

Treatment. There are several options for treatment, including surgery, chemotherapy, and interventional procedures (2, 3, 113, 149, 221). Liver transplantation is rarely indicated and has a relatively high risk of postoperative metastasis formation (149). This is due to minor parasite remnants, which cannot be resected and proliferate under immunosuppression. Recommendations for treatment have been published by the WHO Working Group on Echinococcosis (221, 223).

(i) Surgery. The first-choice treatment in all operable cases is radical resection of the entire parasite lesion(s) from the liver and other affected organs by using procedures of radical tumour surgery (3, 113, 149, 221). Radical surgery is possible in virtually all cases diagnosed in an early stage but in only 20 to 40% of the advanced cases (3, 113, 178, 221). It may lead to complete cure, but resection is often incomplete because of diffuse and undetected parasite infiltration into host tissues. Therefore, according to WHO recommendations, postsurgical chemotherapy should be carried out for at least 2 years, with

monitoring of the patients for a minimum of 10 years for possible recurrence (221, 223). In one case, despite postoperative medication with mebendazole for 2.5 years, a recurrence was observed in a patient 14 years after radical surgery (3).

(ii) Chemotherapy. Chemotherapy is recommended for a limited period (at least 2 years) after radical surgery (see above) and for long-term periods (from many years to lifelong) after incomplete resection of lesions in inoperable cases and after liver transplantation (see the above remarks on liver transplantation) (221, 223). Chemotherapy of infected laboratory rodents with mebendazole and albendazole, applied at high oral doses over at least 2 months, causes destruction of protoscoleces, damage of the germinal layer, inhibition of metacestode proliferation, and metastasis formation but does not usually kill the parasite (46).

For chemotherapy of AE in humans, mebendazole is given at daily doses of 40 to 50 mg/kg of body weight in three divided doses. Albendazole is given at daily doses of 10 to 15 mg/kg of body weight in two divided doses (149, 221). Albendazole is licensed for cyclic treatment, i.e., 28 days of treatment followed by 14 days without chemotherapy, but continuous treatment is also practised (see below). Both drugs should be taken with a fat-containing meal (221, 223). The evaluation of treatment success in human AE is difficult because there are no methods allowing a direct assessment of the parasite's activity status (alive or dead). The most reliable indirect criteria are (i) longterm survival rates of patients, (ii) lack of disease progression and improvement of the clinical status, (iii) decrease or arrest of parasite proliferation, and (iv) lack of recurrence. The size and structure of the parasite lesions are evaluated at regular intervals (approximately 6 to 12 months) by ultrasonography and computed tomography. Serology using specific tests has only some value in cases after radical operation. In a Swiss study, 110 patients with nonresectable AE had received longterm chemotherapy (mainly with mebendazole) for 9.4 ± 5.8 years and were under follow-up observation for 12.8 ± 6.9 years (4). This therapy resulted in an increased 10-year survival rate of approximately 80% (versus 29% in untreated historical controls) and a 16- to 20-year survival rate of approximately 70% (versus 0% in historical controls) (4). The optimal duration of treatment has not yet been determined. In a group of 19 patients with nonresectable AE, long-term mebendazole therapy (average duration, 4.3 years) was ceased because there was no evidence of parasite activity (6). Recurrence occurred in seven patients (37%) within an average of 1.6 years after discontinuation of chemotherapy. On the other hand, there is evidence that in some cases long-term chemotherapy can be parasiticidal rather than merely parasitostatic (5).

Recently, Reuter et al. (163) have compared the efficacies of mebendazole and albendazole in 35 AE patients, 12 of whom had extrahepatic lesions. The average time of treatment was 24 months for mebendazole, 25 months for cyclic albendazole (see above), and 28 months for continuous albendazole. The duration of treatment and the average follow-up period (3.2 years) were relatively short compared with long-term treatment (see above) but were sufficient for the purpose of the study. The criteria for success of treatment were lack of disease progression (i.e., stability or regression of AE lesions) for >1 year and lack of effects necessitating a change of treatment (progression of disease or intolerable side effects). There was

TABLE 6. Options for the diagnosis of *E. multilocularis* in animals

Animal group	Material required	Test, sensitivity and specificity[a]
Live animals		
Dogs and cats: individual animals and populations	Feces in buffer	Screening: coproantigen ELISA. S, 84–95%; SP, 96–99%
		Secondary[b]: copro-PCR. S, 89–94%; SP, ~100%.
Population of foxes	Feces collected in the environment	Screening: coprogantigen ELISA. Secondary: copro-PCR. S and SP similar to above.
Aberrant hosts: dogs, monkeys, pigs	Serum, fine needle biopsy	Abdominal ultrasonography, other imaging techniques, serology possible but not validated for all species detection of specific antigens and DNA in liver biopsy samples
Dead animals		
Dogs, cats, foxes, etc.	Small intestine	Standard option: parasite detection at necropsy by intestinal smear technique (S, 78%; SP, ~100%) or by sedimentation technique and counting technique (S, ~100%; SP, ~100%).
	Feces from rectum or contents from intestine in buffer	New option: coprogantigen ELISA and/or copro-PCR can also be used for routine screening.
Aberrant and intermediate hosts	Internal organs	Normal necropsy procedures, histology, in conjunction with PCR in doubtful cases.

[a] Average values of various studies. Data from references 36, 37, 41, 49, and 134. S, sensitivity; SP, specificity.
[b] Secondary test for confirmation or exclusion.

no significant difference between initial treatment with mebendazole, which was successful in 71% of cases (12 of 17), and albendazole therapy, which was successful in 78% (14 of 18). Four of five progressive cases could be stabilized by changing the treatment regimen (change from mebendazole to albendazole or vice versa or from cyclic to continuous albendazole). The overall success was 97% (34 of 35). Continuous albendazole treatment of seven patients for >12 months was successful and well tolerated. In this study, the use of albendazole has reduced costs considerably (approximate costs in Germany per patient per year are $4,300 to $6,350 for albendazole and $8,200 to $16,300 for mebendazole) (163). Furthermore, the authors (163) have summarized data from 19 published studies involving approximately 500 AE patients treated with mebendazole or albendazole. Most of the patients were treated for >20 months. The success rates were over 74% (up to 100%) in 18 trials and lower (55%) in only one study.

E. multilocularis Infection in Animals

Definitive hosts. Like *E. granulosus*, infection with *E. multilocularis* is typically asymptomatic in definitive hosts (54). The repertoire for the diagnosis of the infection in living dogs, cats, and foxes (Table 6) has been considerably improved in recent years and includes the coproantigen ELISA and PCR techniques for the specific detection of DNA in *E. multilocularis* eggs and/or in parasite tissue fragments released into the intestinal contents (see references 36, 49, 53, and 134 and references therein). These techniques can also be used for the examination of fecal samples collected in the environment (154, 188, 207). Praziquantel is highly effective against intestinal stages of *E. multilocularis* in definitive hosts, but chemotherapy of dogs and cats infected with the parasite requires a careful risk assessment and special safety precautions (55) (see "Control options and intervention" above).

Intermediate and aberrant hosts. A relatively high proportion of the natural intermediate hosts (small mammals), in-fected with the metacestode of *E. multilocularis*, will die of the infection if not previously captured by a carnivore. According to earlier reports, metacestodes of *E. multilocularis* can be found under natural conditions in various mammalian hosts that do not play a role in the transmission cycle, such as horses, domestic and wild pigs, nutria (*Myocastor coypus*), several species of monkeys in captivity, and some others (references 54 and 118 and references therein). In Japan, *E. multilocularis* lesions were diagnosed in 0.82% of 1,100 horses and 0.14% of 1 million slaughtered pigs during 1993 to 1994 (145). In our Institute in Zurich, 15 cases of AE were diagnosed in monkeys and 10 cases were diagnosed in dogs during the period from 1987 to 2000 (37). A finding of peculiar interest was that the domestic dog, a natural definitive host of *E. multilocularis*, can also harbor the metacestode stage, which causes severe lesions in the liver or other organs and produce symptoms very similar to human AE (Fig. 8). In two of these cases it was observed for the first time that dogs can be simultaneously infected with adult stages in the intestine and metacestodes in the liver. Furthermore, lesions caused by *E. multilocularis* metacestodes were detected in the liver of 10% of 90 slaughter pigs which had been kept outdoors, and severe pathology and disease were observed in several genera of monkeys in capitivity (*Hylobates*, *Macaca*, *Miopithecus*, and *Lemur*) (37). These infections in aberrant host animals are important indicators for the existing infection risk for humans.

Epidemiology

Transmission dynamics of *E. multilocularis* are based on the predator-prey relationship between carnivores and small mammals and depend on a large number of interacting factors. Some of the major factors are presented in Table 7. Since only a few of these factors have been studied in detail, our understanding of the whole epidemiological system is still limited.

Parasite-host assemblages. In various regions of endemic infection, different definitive and intermediate host assem-
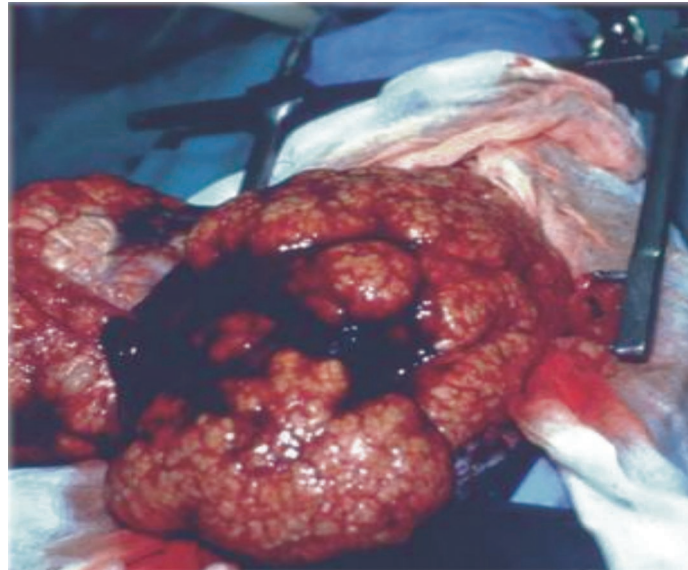
FIG. 8. Hepatic alveolar echinococcosis in a dog.

blages are involved in the transmission cycles. This is exemplified by an outline of two different epidemiological situations in the Arctic tundra region and in sub-Arctic regions.

(i) Arctic region. On St. Lawrence Island, Alaska, the epidemiological situation is characterized by rather uniform biotope conditions. The Arctic fox is the sole definitive host of *E. multilocularis* in a wildlife cycle (155, 160, 180). Arctic foxes are highly susceptible to *E. multilocularis*, as indicated by high parasite pervalences (overall prevalence, approximately 77%) and heavy worm burdens (burdens in excess of 100,000 in an individual fox were not uncommon) (160). Voles, predominantly the northern vole (*Microtus oeconomus*), are intermediate hosts and represent the major prey of foxes. Prevalences of *E. multilocularis* metacestodes in these voles increase with age and can reach approximately 40% (160). In villages, the Arctic fox is replaced by the domestic dog as definitive host. In previous years, large numbers of dogs were kept in the villages and had access to voles living in these synanthropic habitats. Up to 83% of the voles and 12% of the dogs were found to be infected with *E. multilocularis.* This synanthropic cycle represented the major risk factor for humans (160).

(ii) Sub-Arctic regions. In sub-Arctic regions of North America and Eurasia, the situation is more complex than in the Arctic tundra. Landscape characters, biotopes, and climatic conditions are more diverse, populations of small mammals often consist of several species susceptible to *E. multilocularis*, and sometimes more than one carnivore species is suited as the definitive host of the parasite. For example, in central Europe, red foxes play the key role as definitive hosts. They have a wide geographic range in European countries but fox densities per square kilometer are highly variable. In larger regions of the area of endemicity, the average prevalences of *E. multilocularis* in foxes vary from approximately 1 to >60% (51, 52, 79, 131, 170, 172). Information on parasite prevalences in foxes is available from several central European countries, but exact data on infection intensities are scarce. Some data show that the distribution of parasite numbers in a given fox population is rather heterogeneous, with a small number of foxes carrying

TABLE 7. Variable factors in the epidemiology of *E. multilocularis*

Key factors	Selected contributing factors (defined or suspected)
Definitive hosts and the adult parasite	Animal species: geographic and spatial distribution, population size and dynamics, interactions with prey animals, feeding habits, behavior, landscape characters of the habitat, relation to human habitats
	E. multilocularis: prevalence, intensity, and duration of the infection; intensity of egg production and release; host immunity
Parasite eggs in the environment	Dispersal and survival of eggs, conditions of climate and weather
Intermediate hosts and the metacestode stage	Animal species: biology and longevity, geographic and spatial distribution, population size and dynamics, feeding habits, role as prey animals of carnivores, interactions with other small mammals, landscape characters of the habitat
	E. multilocularis: prevalence, intensity, and duration of the infection; intensity of protoscolex production; host immunity
Humans and other aberrant hosts	Exposure to eggs, behavior, relationship to carnivores, susceptibility, resistance, and immunity

most of the parasite biomass. For example, in a Swiss study the average worm number in 133 adult and subadult foxes was approximately 3,000, ranging between 1 and approximately 57,000; 69% of the foxes had worm burdens below 1,000 per animal and 31% had burdens above this number. Only 7.5% of the foxes (10 of 133) harbored more than 10,000 worms, corresponding to 72% of the total biomass (99). Previous data on differences of *E. multilocularis* prevalences and infection intensities in young and older foxes were contradictory. It has now been documented in several studies that juvenile foxes are more frequently and/or intensively infected than are adult foxes (99, 190). These findings suggest that older foxes acquire partial immunity under high-endemicity conditions but that under low infection pressure immunity may not be expressed.

Domestic dogs and cats have been found infected with *E. multilocularis* in several European countries (19, 47, 51, 152). In a previous study in France, 5.6% of 36 dogs were identified as carriers of *E. multilocularis*, and in a further five studies in Germany and France, 0.5 to 3.7% of cats (58 of 498) were identified (by necropsy) as carriers (51). In an area of endemic infection in eastern Switzerland with an average prevalence of *E. multilocularis* in foxes of approximately 33%, only 0.30% of 660 dogs and 0.38% of 265 cats from "normal" populations were parasite carriers (36). In a model calculation, these data were referred to the population sizes of these hosts in a given area (Canton of Zurich), and it was estimated that 1,551 foxes, 145 dogs, and 552 cats could have hypothetically been carriers of the parasite (52). Besides prevalence and population sizes, further factors have to be considered in assessing the relative risks posed by the various definitive hosts. These include the duration of the *E. multilocularis* infection, worm burdens, capacity of egg production, habitat and behavior of the hosts, and their relationships with humans.

Dogs are highly susceptible to *E. multilocularis*, but cats appear to have a lower and a more variable degree of susceptibility, as observed both in several older and in more recent experimental studies (60, 106). However, naturally infected cats can harbor small numbers of *E. multilocularis* worms containing fully developed eggs and are therefore potential sources of infection (48).

In areas of endemic infection in central Europe, the average prevalences of *E. multilocularis* metacestodes in rodents are generally low (<1%) (48), but they may be higher locally. For example, prevalences up to 21 and 39% have been recorded in two studies of water voles (*Arvicola terrestris*) in high-endemicity foci in Switzerland (89, 188) and prevalances of 12 to 14% have been recorded in *Microtus arvalis* in a focus in France (79). These data are indicative for a heterogeneous ("patchy") spatial distribution of infected rodents. Different rodent species differ in their susceptibility to the meacestode stage of *E. multilocularis* (215) and capacity for protoscolex production (see below). Typically, the prevalences of *E. multilocularis* metacestodes in rodents increase with age (79, 160, 188).

Influences of landscape characters and rodent populations. In view of the wide distribution of foxes and the ubiquity of susceptible small mammals in most European habitats, one could anticipate that virtually all regions might be suitable for *E. multilocularis* transmission. However, in some European regions, the parasite has so far not been recorded.

(i) Factors related to larger regions. Based on observations in Alaska, China, Japan, and France, a group of authors has put forward the hypothesis that on a regional scale intensive transmission of *E. multilocularis* occurs if one or two species of rodents are dominant, their populations reach high densities for several months or years, and foxes use these rodents as main prey animals (79, 212).

Studies in France have shown that prevalences of *E. multilocularis* in foxes are higher in areas of medium altitude (600 to 900 m) where permanent grassland is prominent (79). In such areas, the field vole (*M. arvalis*) and the water vole (*Arvicola terrestris*), the two most important intermediate hosts in central Europe, undergo multiannual cyclic population outbreaks which lead to high population densities (79). During the high-density phase of *M. arvalis* and *A. terrestris*, several kilograms per hectare of biomass is available as prey for foxes. In this phase, foxes prey mainly on these species. For example, in the Swiss Jura and in Franche-Comté, *A. terrestris* represented 87% of the mammalian prey items, and 54% of all dietary items of foxes (79). During the cyclical decline of the dominant rodent species, the diet of foxes is more diversified. In spite of annual and cyclic fluctuations of rodent populations, a high level of transmission is maintained in certain areas which provide favorable conditions for dominant rodent species. Such conditions also exist on permanent grassland of suburban recreation areas, vegetable gardens, orchards, and similar habitats.

(ii) Factors related to macro- and microfoci. Evidence has accumulated in recent years that a heterogeneous spatial distribution of definitive and intermediate hosts is a particular epidemiological feature of *E. multilocularis*. This heterogeneity can lead to highly variable parasite prevalences and the formation of larger foci (macrofoci) or small foci (microfoci) of intensive transmission ("hot spots"). For example, within an area of endemicity of approximately 4,450 km^2 in northern Germany, two high-endemicity macrofoci have been identified, with an *E. multilocularis* prevalence in foxes of 23.8%, which was significantly higher than the prevalence of 4.9% in the surrounding area (190).

Microfoci of some 10 m^2 have been identified in France in which *E. multilocularis* prevalences in *M. arvalis* exceed 12 to 14% (79). Such foci were found in places where the density of deposits of fox feces was high and the parasite eggs could be covered with soil by ploughing (79). In Zurich, Switzerland, high contamination with fox feces was found in the recreational area, and it was observed that foxes deposit their feces directly on ground systems of *A. terrestris* (38). In Hokkaido, Japan, foxes breed and defecate predominantly in areas where *Clethrionomys rufocanus* is abundant (79). These data indicate that several factors contribute to the formation of macro- and microfoci.

Eggs in the environment. Exact knowledge of the intensity and dynamics of *E. multilocularis* egg excretion by definitive hosts is lacking. The method by which the eggs are dispersed in the environment has not been adequately investigated, mainly because morphological differentiation of eggs from *E. granulosus* and other taeniids is not possible. Recent developments of new techniques for detecting *E. multilocularis* antigens or DNA in fecal samples of foxes and other definitive hosts have opened new options for transmission studies. In one study in

Switzerland a coproantigen ELISA was used as a screening method and a PCR (134) was used as a confirmation assay. It was found that 10 to 60% of 647 fecal samples from foxes in an urban area were coproantigen positive and that the spatial distribution of these samples was in accordance with *E. multilocularis* prevalences found in necropsied foxes (188).

Eggs of *E. multilocularis* remain infective for approximately 1 year in a suitable, moist environment at lower temperatures, but they are sensitive to desiccation and high temperatures (211). Their high resistance to low temperatures is a precondition for their survival in Arctic regions. These eggs can survive at $-50°C$ for 24 h but are killed at $-70°C$ within 96 h and at -80 to $83°C$ within 48 h. Deep-freezing at $-70°C$ for at least 4 days or at $-80°C$ for at least 2 days is recommended for inactivating *E. multilocularis* eggs in carcasses or intestines of final hosts or in fecal material before examination in the laboratory (55).

Infection risk for humans. It is generally assumed that humans can become exposed to the eggs of *E. multilocularis* by handling infected definitive hosts or by ingesting food or water contaminated with eggs (55, 180). However, studies of the epidemiological significance of the various potential methods of transmission are lacking.

Biostatistical studies of suspected risk factors are scarce. Stehr-Green et al. (187) have assessed risk factors on St. Lawrence Island, Alaska, and found that people who have owned dogs, kept dogs around dwellings, and have houses built on the tundra were at higher risk from AE. In an area of endemicity in Austria, Kreidl et al. (121) found cat ownership and hunting to be independent risk factors for AE and rejected the hypothesis that eating of mushrooms or certain wild berries is a main risk factor. Such conclusions are difficult to prove, mainly because of the long incubation period of AE and possible data corruption by undetected confounding factors.

Exposure of humans to eggs may be influenced by occupational and behavioral factors. Hunters, trappers, and people working with fur may frequently be exposed to the eggs of *E. multilocularis*, but there is no evidence that these groups are at increased risk (98, 160). Older data from Austria, Germany, France, and Switzerland have indicated that persons working in agriculture were at increased risk of infection (57, 110). Living in the countryside in close proximity to infected foxes (dogs or cats) and/or frequent contacts with egg-contaminated soil or plants may be reasons for a higher infection risk. Egg-contaminated plants were obviously the infection source for monkeys in a zoo in Switzerland. The monkeys suffering from AE had been regularly fed with grass harvested from a meadow in an area of high endemicity accessible to foxes (37). There are some hints that higher incidences of AE in humans might be associated with high *E. multilocularis* prevalence in foxes (57, 66, 79, 144). A high proportion of grassland can result in high rodent populations over prolonged periods, favoring disease transmission (79). According to studies in France, high densities of *A. terrestris* yielded a 10-fold-higher risk for AE in humans (212).

Both the wide distribution and high prevalences of *E. multilocularis* in wild carnivores and the low incidence of human AE suggest that the infection risk for humans is limited by unknown factors. There is evidence that humans have a relatively high degree of innate resistance to infection with eggs of *E. multilocularis*, as indicated by the slow development of the metacestode stage in internal organs, the reduced capacity of protoscolex formation, and the type of histopathological reaction. Further factors may include low exposure rates of humans and immunogenetic factors of the human population (215).

Global distribution in humans. *E. multilocularis* in carnivores is widely distributed in the northern hemisphere, including regions of central Europe, most of northern and central Eurasia (extending eastward to Japan), and parts of North America (Fig. 9). Currently, the parasite is found in at least 30 countries, including large territories, for example in Russia, Kazakhstan, China, parts of Europe, and North America (51, 58, 180).

The annual incidence of human AE is not documented in most of the countries where infection is endemic (58). Reliable data from central Europe (Austria, France, Germany, and Switzerland) and Japan (from 1970 to 1992) have indicated low annual incidences of new AE cases of between 0.02 and 1.4 per 100,000 population for entire countries or larger regions of endemicity (52). In Switzerland, the countrywide annual incidences showed only minor variation between 0.10 and 0.18/100,000 for the 37 years between 1956 and 1992 (52). Much higher incidences have been reported from St. Lawrence Island, Alaska (180), but these data refer only to villages where AE cases have been diagnosed and are local group incidences. Ultrasonographic and immunodiagnostic surveys (1991 to 1997) have revealed a very high prevalence within a focus in Gansu, China, where 135 (4%) of 3,331 persons examined had documented AE (30). Although generally rare, AE deserves public health attention due to the high fatality rate of untreated patients and the high costs of treatment.

Emergence and spread of *E. multilocularis*? The question of the emergence and spread of *E. multilocularis* is of actual public interest and has been addressed in recent reviews (51, 52, 79, 80, 131, 170). In this context, some key questions are discussed here.

(i) Risk areas and spreading. According to Rausch (155), *E. multilocularis* has been indigenous since post-glacial times in the Arctic tundra zone of North America and has spread southward. The genetic homogeneity of *E. multilocularis* isolates originating from North America, Europe, and Japan (91) has been interpreted as an indication that an invasion of the parasite from the Arctic to sub-Arctic and temperate regions may have occurred relatively recently (170). Indeed, there are indications from various regions for the spreading of *E. multilocularis*.

In Japan, *E. multilocularis* is thought to have been introduced into the northern part of the country in 1924 to 1926 in red foxes translocated from one of the Kurile Islands to Rebun Island (northwest of Hokkaido) for the purpose of controlling the vole population. Another outbreak occurred in about 1960 in eastern Hokkaido (180), followed by the spread of the parasite between 1981 and 1991 from approximately 8 to 90% of the area (189). In North America, *E. multilocularis* occurs in the Northern Tundra Zone (NTZ) of Alaska and Canada and further south, in the North Central Region (NCR). It is assumed that prior to the 1960s, *E. multilocularis* spread from the NTZ and became established in central North America, including parts of three Canadian provinces (Alberta, Saskatchewan, and Manitoba) and 13 contiguous U.S. states (Fig. 9).
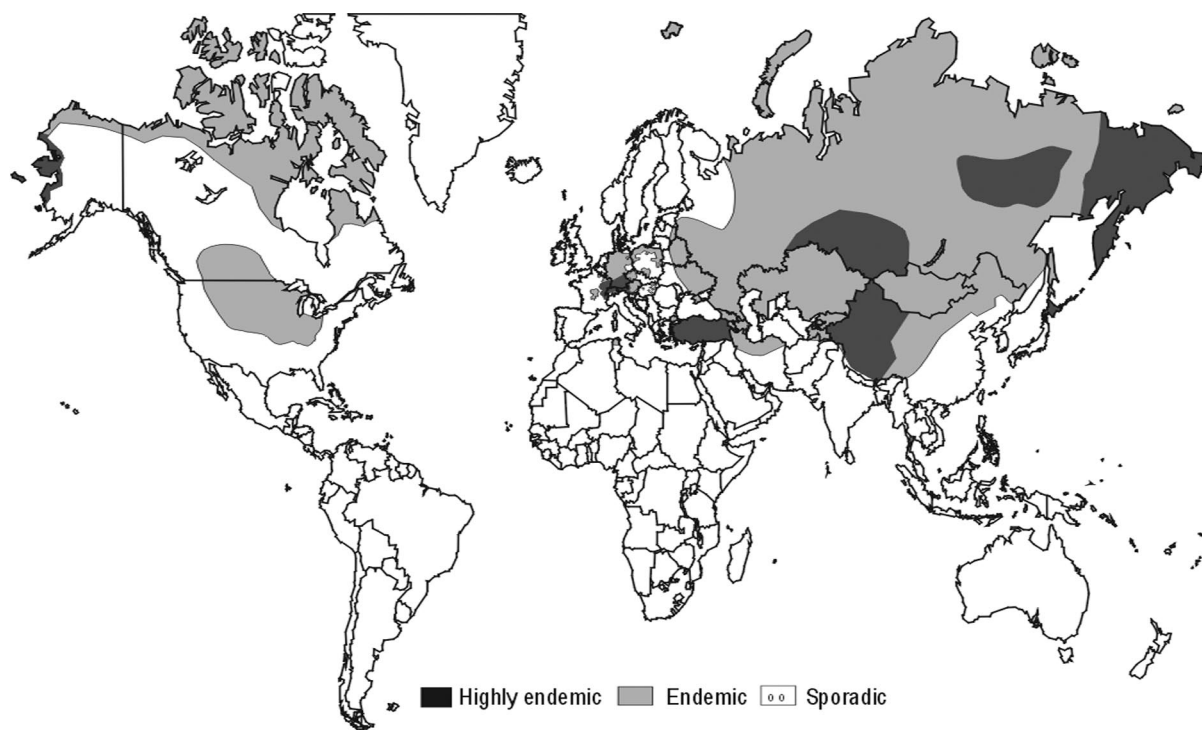
FIG. 9. Approximate global distribution of *E. multilocularis* (as of 2002). Exact identification of areas of normal and high endemicity is difficult becaue of incomplete or lacking data. Modified from WHO/OIE 2001 (223) with permission.

Previous surveys of endoparasites of canids and rodents in the NCR had failed to reveal *E. multilocularis* (180).

Recent surveys in central Europe have revealed that *E. multilocularis* has a much wider geographical distribution than previously thought. By the end of the 1980s, areas of endemic infection with *E. multilocularis* were known to exist in only four countries (Austria, France, Germany, and Switzerland), but by the end of 2001 the parasite was known to occur in red foxes in at least nine further central European countries (Belgium, Czech Republic, Denmark, Italy, Liechtenstein, Luxembourg, Poland, Slovak Republic, and The Netherlands) (references 51, 58, and 173 and references therein). Findings of *E. multilocularis* metacestodes in rodents have been reported from several countries (Slovenia, Bulgaria, Romania, etc.) and more recently from Spitsbergen (Norwegian Svalbard Island group in the Barents Sea). Since surveys were not conducted in previous years, it cannot be determined if the new records reflect a recent extension of the parasite's range or only the first identification of hitherto unnoticed areas of endemic infection.

(ii) AE in humans as a risk indicator. The real infection risk for humans in areas of endemic infection is reflected by AE cases in the human population. Such cases have been diagnosed in many Eurasian areas and in Alaska, but only two cases are known from the NTZ in North America (58, 180). Apparently, the infection risk can differ considerably between and within various regions. For example, since the middle of the 19th century, most AE cases in central Europe have been recorded from regions in western Austria, southwestern Germany, eastern France, and northern Switzerland, where recent surveys have revealed high prevalences of *E. multilocularis* in

foxes (58, 66, 110). Since 1993, human cases of AE have been recorded from at least 8 (61%) of 13 countries with endemic infection, namely, from Austria, Belgium, France, Germany, Slovak Republic, Switzerland, Liechtenstein, and Poland (51, 119) but most of the human cases have been reported so far from Switzerland, France, Germany, and Austria (58, 110). Between 1982 and 2000, 559 human cases of AE were reported on a voluntary basis from nine European countries to the European Echinococcosis Registry (110) and 202 new cases were diagnosed in Turkey between 1980 and 1998 (1). These data probably do not include all cases, but they do indicate a considerable and persistent infection risk for humans in certain Europen regions. In France, cases of human AE are found predominantly in areas of intermediate altitudes (600 to 900 m) where grassland is dominant and the *E. multilocularis* prevalence in foxes is high (40 to 60% in winter) (79). In Japan, with the spread of *E. multilocularis* in Hokkaido, the number of human cases of AE had increased in that area from only 6 new cases between 1937 and 1964 to a total of 110 cases between 1985 and 1994 (118).

(iii) Increasing fox populations and parasite prevalences. Evidence is accumulating that in parts of Europe the fox population densities have increased in recent years (23), possibly due to reduced fox mortality after the introduction of antirabies vaccination. For example, in Baden-Württemberg, southwestern Germany, the number of foxes sampled by hunting has increased approximately 2.7-fold between 1975/1976 and 1997 (data extracted from a graph) (170). In several other Federal States of Germany, increasing fox populations have

been observed in recent years, associated with increasing prevalences of *E. multilocularis* (15, 109, 136, 170, 173).

(iv) Invasion of urban areas by foxes. Invasion of urban areas by foxes has been observed in the United Kingdom since the middle of the 1940s; in recent years it has also been observed in continental Europe (reference 38 and references therein) and Japan (207). Such foxes have been identified as carriers of *E. multilocularis* in several European cities, for example in Copenhagen, Geneva, and Zurich. The number of foxes shot or found dead in Zurich increased 20-fold between 1985 and 1997. Ecological studies in this area revealed high fox population densities, small home ranges, formation of family groups, and a low immigration rate. The overall prevalence of *E. multilocularis* in urban foxes was found to be 47% (99). Furthermore, the highest contamination with fox feces positive for *E. multilocularis* coproantigens was found in adjacent recreational areas. In such places, *A. terrestris* and *Clethrionomys glareolus*, common voles of the urban periphery, were infected with *E. multilocularis* metacestodes. The average prevalences of infection in these two species were 9.1 and 2.4%, respectively (188). Metacestode prevalences in *A. terrestris* did not show significant seasonal variation. An average of 3.5% of voles were infected with metacestodes containing between 14 and 244,400 protoscoleces per animal. These data have provided the first evidence of an urban cycle of *E. multilocularis*. Hence, the contamination of a densely populated urban environment, including recreational areas, with *E. multilocularis* eggs by foxes represents a potential new risk factor for humans. Moreover, dogs preying on metacestode-infected rodents in the urban area can acquire the *E. multilocularis* infection and may pose a further infection risk, especially due to their close contacts with humans.

(v) Potential modes of spreading. There is little knowledge about the modes and dynamics of *E. multilocularis* spreading, but epidemiological evidence suggests that migration of infected foxes can play a role. In the Arctic region of North America, *E. multilocularis* may be transported and dispersed by foxes migrating on the sea ice or on land (155). In Japan, the parasite evidently became established on Hokkaido by migrating foxes from the Kurile Islands (reference 180 and references therein). In Europe, the spreading of *E. multilocularis*, if it happened at all, could be associated with spatial migration of red foxes out of areas of endemic infection. Most foxes migrate less than 5 to 10 km, and only a few migrate more than 50 to 70 km (190). There are good reasons to assume that the establishment of urban cycles of *E. multilocularis* (see above) was initially caused by the invasion of infected foxes. If rodents populate new habitats, they normally migrate short distances. For example, *A. terrestris* migrates 30 to 50 m (97). However, a wider extension of rodent habitats, induced by human activities or other factors, may well contribute to a long-term dissemination of the parasite. Furthermore, dislocation of hosts infected with *E. multilocularis* may result in parasite spreading. Evidently, *E. multilocularis* has been imported to northern Japan by dislocation of foxes from one of the Kurile Islands to Rebun Island. In the United States, foxes and coyotes have been moved from areas of endemic infection to other areas without infection for hunting purposes, posing the risk of disease spreading (180). Parasite dispersal by dislocation of infected domestic dogs and cats has also to be considered, but its

significance is unknown. On the Arctic Norwegian island of Svalbad (Spitsbergen), *E. multilocularis* apparently became endemic after the accidental introduction of a suitable intermediate host, *Microtus rossiaemeridionalis* (170). Transportation of *E. multilocularis* eggs sticking to people's shoes and mechanical dispersal by flies and birds could be other modes of dispersal which are proven for *E. granulosus* and *Taenia* species (127, 202).

Control Options and Prevention

Control in definitive hosts. Currently, there is no reliable and cost-effective method for sustainable control or eradication of *E. multilocularis* in the sylvatic cycle. Large field trials have been conducted since 1995 in Germany for mass treatment of red foxes with baits containing 50 mg of praziquantel. The baits are repeatedly distributed by light aircraft (171). According to first reports, it is possible to reduce the prevalence of *E. multilocularis* in the fox population significantly (181). These and other trials (171, 191) suggest that long-term control of *E. multilocularis*, in the sylvatic cycle in large areas, is extremely difficult and costly. Since the urban cycle of *E. multilocularis* seems to depend on locally restricted factors, we assume that a reduction of the infection pressure in distinct risk areas should be feasible. This hypothesis was tested in Zurich by distributing praziquantel-containing baits every month for 2 years in six areas of 1 km^2 inhabited by foxes. Preliminary results indicate a significant decrease of the environmental contamination with *E. multilocularis* eggs and of parasite prevalences in voles in baited areas compared to those in control areas (96).

In areas of endemic infection with low prevalences of *E. multilocularis* infection in dog and cat populations, mass treatment of these animals may currently be neither indicated nor feasible. The effect of such a strategy for preventing human cases of AE has not been evaluated, and cost-benefit considerations were not made. In these circumstances it may be appropriate to give regular praziquantel treatment every 4 weeks only to dogs and cats having access to infected rodents. New options should be considered: for example, mass screening of dog and cat populations by using the coproantigen ELISA with the aim of obtaining better baseline data for control strategies, or the development of a new scheme for regular drug treatments directed against *E. multilocularis* and other endoparasites of domestic carnivores.

Precautions for individuals. For persons at especial risk (for example, laboratory personnel working with *E. multilocularis* eggs or handling infected definitive hosts, children after exposure to feces of infected foxes, etc.), repeated serological screening for anti-*E. multilocularis* antibodies by using highly sensitive and specific tests (if necessary in conjunction with ultrasonography) is recommended, with the aim of detecting an infection in an early stage or excluding it with a reasonable degree of probability (52, 55) (see "Control options and prevention" above). In our experience, such precautions can help to reduce the anxiety of exposed persons in fear of having contracted a severe disease. Special safety precautions are recommended for laboratory and field workers possibly exposed to infective *E. multilocularis* eggs (55).

Measures to reduce morbidity and mortality. Mass screening of populations with the aim of detecting human AE cases at an early stage have been discussed above. The stepwise introduction of regular screening programs could be considered for areas of endemic infection with relatively high incidence rates of human AE or high prevalence rates of the parasite in definitive hosts (52, 55).

Surveillance. In view of the current lack of effective measures for control and prevention and the seriousness of AE in humans, long-term epidemiologic surveillance is extremely important as a basis for continuous risk analysis and the development of countermeasures. Furthermore, spreading and emergence of AE can be detected or excluded only on the basis of adequate surveillance. Until recently, the prevalence of *E. multilocularis* in foxes, dogs, and cats was determined only by parasite identification at necropsy. The use of the recently developed coproantigen ELISA allows mass screening of populations of living foxes, dogs, and cats (36, 52, 141, 188). Long-term monitoring of the parasite prevalence by ELISA should be carried out with selected and representative populations of foxes and, if necessary, of other definitive hosts. PCR for detecting parasite DNA in fecal samples may be used as a confirmation test in selected cases. Surveillance should also include mandatory reporting and centralized analysis of all cases of AE in humans and of *E. multilocularis* infections diagnosed in animals. A first step in this direction was recently made in Europe within the framework of a research program, initially sponsored by the European Union, by the establishment of European Echinococcosis Registry centers for AE patients and *E. multilocularis*-infected definitive hosts (110).

E. VOGELI, *E. OLIGARTHRUS*, AND POLYCYSTIC ECHINOCOCCOSIS

Human polycystic echinococcosis, caused by *E. vogeli* or *E. oligarthrus*, is confined to Central and South America and is therefore also denoted as neotropical echinococcosis.

Life Cycles of the Parasites and Epidemiology

E. vogeli is perpetuated in a life cycle with the bush dog (*Spoethos venaticus*) as the natural definitive host and pacas (*Cuniculus papca*) and agoutis (*Dasyprocta* spp.) as intermediate hosts (Fig. 10). Adult cestodes have also been found in one naturally infected domestic dog, and dogs could be experimentally infected (158). Intestinal stages of *E. vogeli* apparently do not develop in cats or in other felids. In a survey in Columbia, 30% of 325 pacas were infected with the metacestode stage of *E. vogeli* (34). Since the bush dog is a shy and rarely observed wild animal, its role as source of human infections remains obscure. It is assumed that domestic dogs may play a role in the transmission of parasite eggs to humans. Dogs are probably unable to capture pacas, but they may become infected with metacestodes when fed viscera of pacas at the hunting site or at home (11, 158). As shown in a recent study in which the Mongolian gerbil was used as an experimental host for *E. vogeli*, this parasite can be detected by the coproantigen ELISA developed for the detection of *E. multilocularis* (135). This would open the possibility for large-scale examinations of domestic dogs.
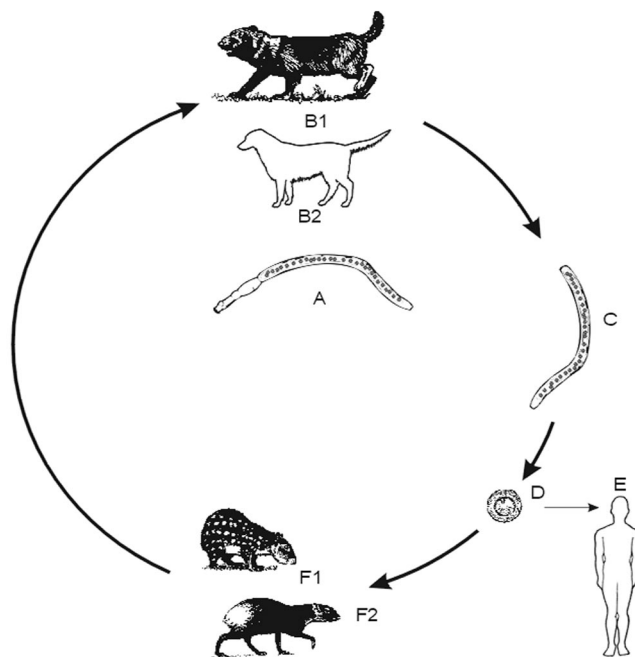

FIG. 10. Life cycle of *E. vogeli*. (A): Adult parasite. (B) Bush dog (*Speothos venaticus*) as principal definitive host (B1); domestic dogs are rarely infected (B2). (C) Proglottid with eggs. (D) Egg with oncosphere. (E) Infection of humans. (F) Intermediate hosts: paca (*Cuniculus paca*) (F1) and agouti (*Dasyprocta* spp.) (F2). Data from reference 180.

Definitive hosts of *E. oligarthrus* are wild felids (Fig. 11). Of 10 species indigenous to Central and South America, 6 have been identified as definitive hosts of this species: pampas cat (*Felis colocolo*), Geoffroy's cat (*F. geoffroyi*), ocelot (*F. pardalis*), jaguarundi (*F. yagouaroundi*), jaguar (*Panthera onca*), and puma (*Puma concolor*). In addition, *E. oligarthrus* was found in one bobcat (*Lynx rufus*) in northern Mexico. The parasite reached maturity in experimentally infected cats (158). Agoutis (*Dasyprocta* spp.), spiny rats (*Proechimys* spp.), and pacas (*Cuniculus paca*) are the documented intermediate hosts. The metacestode prevalences found in several studies and countries were 18% (7 of 39) in agoutis (*Dasyprocta punctata*) (Panama), 0.17% (2 of 1168) in spiny rats (Colombia), and 0.92% (3 of 325) in pacas (Colombia) (158). The mode of transmission to humans is unknown.

Geographic Distribution and Prevalence

According to information published in 2002 (158), 99 human cases of PE have been diagnosed in 11 countries including a region from Nicaragua in Central America to Chile, Argentina, and Uruguay in South America (32, 158). Of 72 cases diagnosed by August 1996, the majority were from Brazil (24 cases), Colombia (16 cases), Ecuador (11 cases), and Argentina (11 cases); 1 to 3 sporadic cases were identified in seven other countries).

PE occurs predominantly in rural, sylvatic areas where *E. granulosus* is not endemic (32). *E. oligarthrus* has been found in natural intermediate or definitive hosts in a wide range as far
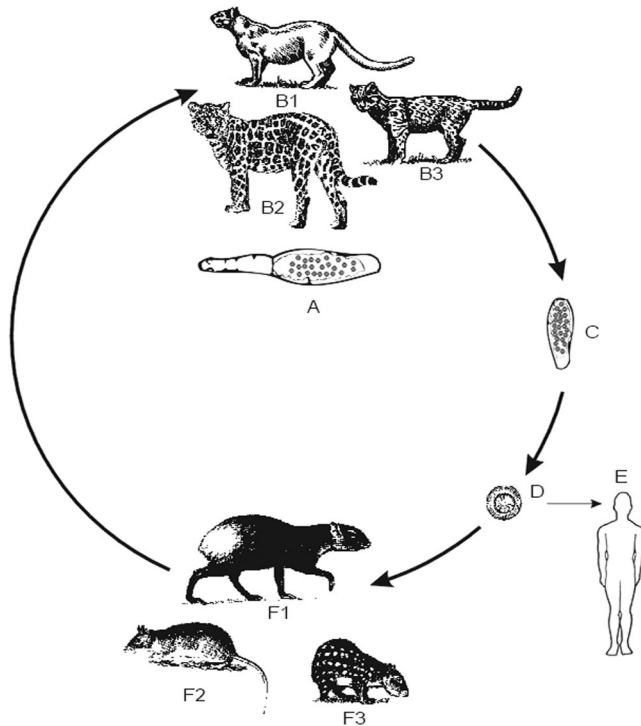
FIG. 11. Life cycle of *E. oligarthrus.* (A) adult parasite. (B) Wild felids as definitive hosts: cougar (*Felis concolor*) (B1), jaguar (*Panthera onca*) (B2), and ocelot (*Felis pardalis*) (B3) as examples. (C) Proglottid with eggs. (D) Egg with oncosphere. (E) Infection of humans. (F) Intermediate hosts: agouti (*Dasyprocta* spp.) (F1) spiny rat (*Proechimys* spp.) (F2), and paca (*Cuniculus paca*) (F3). Data from reference 180.

north as Costa Rica and far south as La Pampas Province in Argentina (180). Furthermore, this parasite was found in a bobcat in northeastern Mexico, approximately 100 km south of the border with Texas (177). As far as is currently known, *E. vogeli* occurs in the range of the bush dog, i.e., from Panama in the north to Paraguay and southern Brazil in the south. The distribution of these two species overlaps in some areas where suitable hosts are present (32).

Polycystic Echinococcosis in Humans

In 39 of the 99 diagnosed human cases, *E. vogeli* was identified as the causative agent, and in 3 further cases *E. oligarthrus* was identified; no species diagnosis was made in the remaining 57 cases (158). Although human infections with these parasites are summarized under the term "polycystic echinococcosis," it should be considered that we have to deal with two disease entities characterized by distinctive features of adult and larval parasite morphology, epidemiology, and manifestation in the human host (see also Table 1).

Course of the infection. (i) *E. vogeli* echinococcosis. In the natural intermediate host, the paca, the metacestode stage of *E. vogeli* usually develops in the liver and consists of subspherical, fluid-filled cysts, up to 3 cm in diameter, which are often interconnected and multichambered. The cysts may occur singly or in aggregations. The thin internal germinal layer is surrounded by a thick laminated layer (159, 161). In contrast to

cysts of *E. granulosus*, the metacestode stage of *E. vogeli* has the capacity for exogenous proliferation, which does not occur in the natural intermediate host but is pronounced in accidental hosts such as primates. Endogenous proliferation leads to multichambered cysts and endogenous daughter cyst formation (157, 159).

In a group of 59 patients with PE, the liver was involved in 78%, either alone (41%), with other abdominal organs (29%), or with chest organs (8%). The second most frequently affected organ was the lungs alone (14%) or with the liver and other organs (32). After growth and proliferation in the liver, cysts may penetrate the liver capsule and continue exogenous proliferation in the peritoneal cavity, eventually affecting various abdominal and chest organs such as the omentum, spleen, pancreas, diaphragm, intercostal muscles, pericardium, and lungs (32, 157). Penetration of the diaphragm, with subsequent cyst development in the pleural cavity and in the lungs, has been observed in experimentally infected gerbils (157). The exogenous proliferation of the *E. vogli* metacestode accounts for its considerable pathogenicity in other hosts than natural intermediate hosts, including humans and nonhuman primates (157). Single cysts usually vary in diameter between 0.5 and 6 cm, but larger cysts (>15 cm) may also occur (146). Cyst aggregates can attain much larger dimensions: in one case, a total of 2 kg of cysts was surgically excised (32). Caseous degeneration, partial necrosis, and calcifications of cyst masses have been observed in several patients (32).

Clinical manifestations of *E. vogeli* infection in humans are similar to those of AE. Typically, *E. vogeli* infection is a chronic disease lasting for long periods. In a group of 59 patients, the duration of illness reported at the first consultation ranged between 1 month and 22 years; the median age of 51 patients was 44 years (range, 6 to 78 years) without gender specificity (32). The main clinical manifestations include abdominal pain, palpable abdominal masses, loss of weight, jaundice, hepatomegaly, anaemia, fever, hemoptysis (in cases of lung involvement), and, in about 25% of patients, signs of portal hypertension and biliary obstruction. In some cases laboratory tests revealed high serum levels of blirubin, gamma-globulin, and liver enzymes, eosinophilia, and low levels of albumin (32, 65, 138, 139, 146). In advanced cases, mortality is high. According to one report, 22% of 46 patients with PE died during liver lobectomy or from postsurgical complications (32).

(ii) *E. oligarthrus* infection. In experimentally infected natural intermediate hosts (agoutis), the metacestode of *E. oligarthrus* consisted of subspherical, fluid-filled cysts located in muscles and subcutaneous tissues, in the heart, and in the lungs, with a tendency to become multichambered. However, *E. oligarthrus* has less subdivision into secondary chambers, the germinal layer is thicker, and the laminated layer is much thinner than in cysts of *E. vogeli*. Exogenous proliferation has not been observed (157).

To date, only three human cases have been diagnosed, two orbital (in Suriname and Venezuela) and one cardiac (in Brazil) (32). In the patient in Suriname (a 6-year-old boy), a large fluid-filled cyst (2.7 by 3.2 cm, filled with 10 ml of fluid) surrounded by a thick fibrotic capsule was located at the apex of the orbit and had caused exophthalmus, extensive chemosis, mydriasis, other symptoms, and blindness of the affected eye (11). In two patients with submandibular cysts reported from

India (158, 176), *E. oligarthrus* was described as causative agent, but there are doubts about the correctness of the diagnosis.

Diagnosis. Typically, polycystic structures can be detected by ultrasonography or computed tomography of the liver and abdomen or by X-ray examination of the chest. Antibodies against *Echinococcus* antigen could be detected in 12 of 16 patients by the indirect hemagglutination test (32, 138), but this test does not discriminate between *Echinococcus* species. In one study, discrimination between PE and CE was achieved by using a purified antigen of *E. vogeli* in the ELISA (85). The current standard technique for diagnosis of the involved *Echinococcus* species is the isolation of protoscoleces at surgical intervention or postmortem and the identification of rostellar hooks by the shape and dimensions (159). A new option for diagnosing the *Echinococcus* species is DNA analysis by PCR using protoscoleces. Four genetic sequences from *E. oligarthrus* (three mitochondrial and one nuclear) are published in data banks. Although the corresponding sequences are known for *E. vogeli*, differing, e.g., by 13.8% in the identified 471 bp of the mitochondrial ND1 gene, we are not aware of published reports exploiting the genetic difference for diagnostic species identification.

Treatment. Because of the high risk of surgical intervention in advanced cases of PE (see above), it has been recommended to consider chemotherapy with albendazole as the first treatment option. Surgery should be performed when the lesions are small, when biliary drainage is required, or when chemotherapy has failed (32). Experience with albendazole treatment of PE is limited but has shown some promising results. In one study, six patients were treated with 10 mg/kg of body weight per day, either continuously for 3 to 8 months or in several cycles. Reduction in cyst size or disappearance and clinical improvement were observed in four patients and clinical improvement alone was observed in two patients after a follow-up period of 10 to 30 months. Side effects were generally minor (32, 139). Studies of inoperable cases of AE have shown that long-term treatment over several years or life-long with mebendazole (or albendazole) is needed to achieve improvement or stabilization of the disease in the majority of cases (4).

Emergence or Spreading of Polycystic Echinococcosis?

By the end of the 1970s, human PE was recognized as a distinct disease entity. In 1979, D'Alessandro et al. (33) reported 13 human cases from four countries. By 2002, a total of 99 cases of human PE had been diagnosed in 11 countries (158), but some experts think that the published cases probably represent only a small proportion of the actual number (146). Although the recent increase in case numbers may at least partially reflect improved awareness of the disease and the results of better diagnostic methods, it is indicative of an infection risk existing in a larger area than was previously acknowledged.

The first report of *E. oligarthrus* in a bobcat in Mexico (177), where human cases of PE have not been observed so far, may be an indicator of a hitherto unknown area of parasite endemicity. The distribution of the bush dog, the only natural definitive host of *E. vogeli*, includes tropical sylvatic areas from Panama to Paraguay and southern Brazil (32). Interestingly, human cases of PE, in which the causative *Echinococcus* species could not be determined, were also found in regions outside the range of the bush dog, for example in Nicaragua, Chile, and Argentina. There are indications that some of these cases may have been caused by *E. oligarthrus*. However, it cannot be excluded that other, unidentified canids may be involved as definitive hosts in transmission of *E. vogeli*. According to reports from areas of endemic infection, viscera from hunted pacas are often fed to domestic dogs (hunting dogs) (158). This behavior increases the risk that dogs may become carriers of *E. vogeli* and infection sources for humans. In view of the gaps in our current epidemiological knowledge, further studies and continuous surveillance is needed.

CONCLUSIONS

During the last three decades, considerable progress has been achieved in various fields of echinococcosis research as described in this review. For example, various strains of *E. granulosus* have been identified and characterised; imaging and immunological techniques for diagnosing CE and AE in humans could be improved and have achieved high degrees of sensitivity and specificity; mass screening of human populations for abdominal CE or AE is now possible by ultrasonography alone or in conjunction with serum antibody detection; the coproantigen ELISA is a new tool for the identification of *E. granulosus* or *E. multilocularis* carriers in populations of carnivores (dogs, foxes, and cats); PCR techniques are now available for detecting DNA of *E. granulosus* and *E. multilocularis* in faecal samples of definitive hosts; and new options for treatment of human CE and AE have been developed. These options include improved surgical techniques, chemotherapy with albendazole or mebendazole, and PAIR as a minimally invasive technique for treating various forms of human CE. Although not fully satisfactory, chemotherapy is an option, predominantly in inoperable cases, and can be life saving, especially in patients with advanced AE. Praziquantel, a drug highly effective against intestinal stages of *E. granulosus* and *E. multilocularis* in carnivores, is now available in various formulations, improving the modes of drug application. A research highlight was the development of a recombinant vaccine which induces high degrees of protection against the establishment of *E. granulosus* cysts in domestic ruminants. Furthermore, excellent studies of transmission dynamics of *E. granulosus* and *Taenia* species have resulted in the development of a mathematical model of transmission and improved strategies for *E. granulosus* control. The long-term evaluation of various control strategies against *E. granulosus* has produced a large amount of data, providing a scientific basis for the improvement of control schemes. Our knowledge of polycystic echinococcosis, which occurs in Central and South America, has significantly increased in recent years, and has shown that this form of echinococcosis is apparently of increasing importance. Progress has also been made in some other fields, including our understanding of host immuninty to the metacestode stage.

Nevertheless, there are many open questions and unresolved problems waiting for further research. For example, there is a need to improve the chemotherapy of human echinococcosis, to better understand immunology, and to evaluate the potentials of immunotherapy or immunoprophylaxis. Since our

knowledge of the epidemiological key factors of *E. multilocularis*, *E. vogeli*, and *E. oligarthrus* is insufficient, further research is urgently required. Reliable parameters for measuring the actual infection risk posed by *Echinococcus* species for humans are needed. Furthermore, surveillance and monitoring systems are required which can detect changes in the risk of infection and which can monitor parasite spreading. The large-scale use of the recombinant vaccine for immunizing domestic ruminants against *E. granulosus* should be supported. The lack of methods for effective and feasible control of *E. multilocularis* and prevention of human AE requires special research efforts in a broad spectrum of relevant fields.

Recent publications (see, for example, references 7, 8, 12, 27, 51, and 223) have shown that human CE is persisting with high incidences in many parts of the world and that it is an emerging problem in some areas. AE, although rare in most of the regions of endemicity, represents a considerable public health burden since the infection is lethal in most untreated patients and treatment is very costly (223). Moreover, the risk that the causative agent of AE, *E. multilocularis*, might spread to further regions of the northern hemisphere cannot be excluded. In Central and South America, PE appears to be an emerging problem. Therefore, WHO and the public health authorities in the affected countries should make every possible effort to develop and establish countermeasures.

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