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Parasitocidal Effect of Chemotherapy in Alveolar Hydatid Disease: Review of Experience with Mebendazole and Albendazole in Alaskan Eskimos

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Evidence that the larval stage of *Echinococcus multilocularis* in humans is killed by chemotherapy is presented in a review of our 17-year experience with treatment of alveolar hydatid disease in Alaska. The efficacy of chemotherapy was assessed with use of an in vivo assay of parasite viability by means of inoculation of voles, immunohistochemical tests, and histopathologic findings. Of 14 tests performed for nine patients, 12 in vivo assays (86%) were negative after chemotherapy, while only two (17%) of 12 vole tests for seven untreated patients were negative. Regression or arrest of growth of metastatic and primary hepatic lesions, together with their partial-to-complete calcification and prolonged survival times has been observed among patients treated with the benzimidazole compounds. For six who received appropriate chemotherapy, treatment has been discontinued for an average of 4.6 years (range, 3–7 years) without an increase in lesion size or other evidence of reactivation.

Alveolar hydatid disease (AHD), caused by the larval stage of the cestode *Echinococcus multilocularis*, is a serious health problem among Eskimos in northwestern Alaska, as well as in various populations in Eurasia. *E. multilocularis* is indigenous to the arctic tundra, where arctic foxes and small rodents (voles and lemmings) serve as the final and intermediate hosts. The disease has an extensive distribution in the northern hemisphere, but in North America most autochthonous cases of AHD have been diagnosed in Eskimos in northwestern Alaska. Although good results have been achieved in cases of resectable lesions, before 1986 81% of patients in Alaska had nonresectable lesions at the time of diagnosis. In a report of 1,411 operations for AHD performed in the Commonwealth of Independent States, Zhuravlev [1] also found the resectability rate to be low (18%). These findings clearly reflect the need for an alternate method of treatment of AHD.

E. multilocularis was first identified in the Western Hemisphere on St. Lawrence Island, Alaska, in 1951 [2] (a few earlier cases of AHD were diagnosed retrospectively). Thus far 70 autochthonous cases of AHD have been diagnosed in North America, and all but two have occurred among Eskimos

from St. Lawrence Island and from a hyperendemic area on the mainland of northwestern Alaska.

Clinical evaluations of patients, surgeries, and autopsies were conducted at the Alaska Native Medical Center, which, since its establishment in May 1953 in Anchorage, has been the location of the patient-related work concerning AHD. This center is a facility of the U.S. Public Health Service and is the referring institution for a broad-based health delivery system serving the needs of all indigenous peoples in Alaska. The organization includes village clinics staffed by trained Native American health aides and supported by five small, regional field hospitals. Biological and epidemiological investigations concerning *E. multilocularis* were initiated at the Arctic Health Research Center of the U.S. Public Health Service in 1950 and later undertaken also at the Arctic Investigations Program of the Centers for Disease Control in Anchorage. Consequently, the investigations concerning *E. multilocularis* and AHD have continued without interruption for ~40 years, and some of the same personnel have been involved for all or most of that period. Aside from basic biological studies, major aspects of this study have included clinical chemotherapy trials and the development of screening and preventive programs [3].

During the early years of this experience, most of the patients with AHD were admitted to the hospital with an abdominal mass or symptoms related to the primary hepatic lesion. For some patients the initial diagnosis was made on the basis of a positive screening serology with use of the indirect hemagglutination method. In 1985 an improved serological technique with use of a specific antigen of *E. multilocularis* was introduced [4, 5]; and in 1988 field trials were initiated in which a portable ultrasonography (US) unit was used for screening in four high-risk villages, which resulted in

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the diagnosis of four active cases at an early stage of development. Another result of the improved method of screening was the identification of patients with a number of small, calcified hepatic lesions that on further study were found to represent lesions in which the larval cestode had died [6]. Five of these lesions were resected to confirm the diagnosis and to permit testing for viability. Thus far, 26 such cases have been identified and the patients received a clinical diagnosis of inactive AHD; in 12 cases serologies were positive and in 14 the diagnosis was based primarily on the results of computed tomography (CT) or US findings. All such inactive cases are still under investigation and will not be considered further here. The 44 locally acquired cases of active AHD diagnosed in North America form the basis for this review.

After publication of the report of Heath and Chevis [7], widespread interest developed in the use of benzimidazole compounds for the treatment of hydatid disease. Clinical trials of both mebendazole and albendazole have been conducted; however, the results have been inconsistent. Some authors have reported a poor outcome with these drugs in the treatment of cystic hydatid disease [8–11], while others have obtained more optimistic results with regard to the treatment of this condition or AHD [12–25]. The purpose of this paper is to review in detail our 17-year experience with chemotherapy for AHD in Alaska and to present the data that have led us to conclude that *E. multilocularis* can be eradicated by treatment with compounds of the benzimidazole group.

Methods

The records of all 44 patients with active AHD were reviewed. Tissues were obtained from 14 patients on 26 occasions for in vivo assays for viability. Chemotherapy has been offered to all patients since 1974 (mebendazole through 1984 and albendazole since 1985). Patients scheduled for surgery usually received two or three 28-day courses of albendazole before resection or biopsy of tissues that were to be tested for viability was performed. After a diagnosis of AHD was made and clinical and laboratory data were recorded, chemotherapy was initiated as follows: patients received 40 mg/(kg · d) of mebendazole (microcrystalline form [Vermox], Janssen, Piscataway, NJ) in three doses with fatty meals [12–14, 26]. Albendazole (Zentel), supplied as 200-mg tablets by Smith Kline & French Laboratories (Philadelphia), was used with the approval of the U.S. Food and Drug Administration after informed consent was obtained. An oral dose of 400 mg was taken b.i.d. with meals according to a protocol in which 28-day courses of therapy are alternated with 14-day drug-free intervals [27] (for convenience, such a course, although consisting of 28 days of therapy given during a 42-day period, will be referred to as 1 month of chemotherapy).

The efficacy of chemotherapy for AHD was assessed by a

combination of methods in addition to clinical findings. An in vivo test for viability of the larval cestode has been based on the intraperitoneal inoculation of membranes from patients into red-backed voles (*Clethrionomys rutilus* [Rodentia: Arvicolidae]). More recently, equally good results have been obtained with northern voles (*Microtus oeconomus*) and Mongolian gerbils (*Meriones unguiculatus*) (the red-backed and northern voles are natural intermediate hosts of *E. multilocularis* on St. Lawrence Island and in major regions of Europe and Asia endemic for AHD). We examined inoculated rodents 3–4 months postinoculation to determine results. The proliferation of vesicles confirmed that the larval cestode was viable.

Tissues for bioassay were obtained by means of surgical or needle biopsy on 14 occasions from nine individuals who had received at least 2 years of therapy with mebendazole or 2 months of therapy with albendazole (table 1). These parameters were based empirically on results of bioassays performed before 1985 (for all patients treated for ≥ 24 months, with one exception, the results were negative) [26]. Since vesicles of the larval cestode in host tissue remain infective for >1 week when stored under refrigeration, vesicles obtained at autopsy 2–3 days postmortem were suitable for testing. Untreated patients for whom in vivo tests were performed served as historical controls. Patients who received insufficient chemotherapy, as defined above, are for present purposes described as undertreated. Twelve tests were performed for 10 untreated or undertreated individuals.

The reliability of the in vivo test depends on whether an adequate quantity of membranes from the patient's tissues has been obtained. Material obtained by needle biopsy is the least reliable, since few, if any, membranes may be present. In contrast to tissues of *E. multilocularis* that are used for maintaining isolates in the laboratory, also transferred by intraperitoneal inoculation, those obtained from patients are difficult to quantify for in vivo tests. Fully developed larval cestodes from rodents consist of a dense aggregation of microcysts with abundant protoscolices and little or no host tissue. Consequently, uniform 0.1-g samples are readily obtainable. In humans, however, sterile vesicles (lacking protoscolices) that are usually of small size are dispersed in a dense matrix of collagen that has replaced hepatic tissue. In collecting material for inoculation, slices of the lesion are examined for cavities containing membranes (figure 1), which are translucent and often folded [28]. The membranes are removed by means of fine-pointed forceps and placed in saline, after which aliquots are prepared for inoculation into the rodents (three rodents were routinely inoculated, unless the quantity of membranes was insufficient).

When normally developed larval *E. multilocularis* consists of great numbers of closely apposed, interconnected vesicles, each made up of an external nonviable layer, the laminated membrane, and an internal layer of germinal tissue from which brood capsules and protoscolices arise. When found

Table 1. Efficacy of chemotherapy determined by in vivo assay of parasite viability in voles for untreated and treated patients with alveolar hydatid disease.

Treatment	Patient no.*	Source of tissue	Date tissue obtained	No. of months of chemotherapy	Results of assay (no. of voles)		No. of negative tests (%)	
					Growth	No growth		
Untreated	26	Resection	10/71	0	2	1	1 (14)	
	30	Resection	8/73	0	2	1		
	4	Surgical biopsy	11/74	0	1	2		
	W†	Resection	10/77	0	3	2		
	35	Surgical biopsy	11/80	0	0	2		
	38	Resection	6/84	0	2	0		
	51	Surgical biopsy	5/87	0	2	0		
Undertreated								
Mebendazole (<2 y)								
	5	Needle biopsy	2/77	6	1	0	1 (10)	
	5	Surgical biopsy	2/77	6	1	1		
	34	Surgical biopsy	2/82	15	1	3		
Albendazole (<2 mo)								
	42	Surgical biopsy	10/85	1	0	2	2 (17)	
	42	Surgical biopsy	2/88	1	1	1		
Treated								
Mebendazole (≥2 y)								
	4	Needle biopsy	11/78	48	1	1	10 (91)	
	1	Surgical biopsy	12/78	37	0	1		
	1	Surgical biopsy	2/80	62	0	3		
	34	Surgical biopsy	11/82	24	0	1		
	1	Autopsy	4/84	108	0	2		
	34	Autopsy	10/84	37	0	2		
	3	Autopsy	3/85	123	0	3		
	30	Autopsy	9/85	42	0	3		
	4	Surgical biopsy	11/86	143	0	2		
	35	Surgical biopsy	—/86	72	0	2		
	35	Surgical biopsy	3/90	74	0	2		
Albendazole (≥2 mo)								
	39	Surgical biopsy	5/85	2	0	2	11 (79)	
	42	Surgical biopsy	3/90	9	1	5		
	60	Surgical biopsy	5/91	3	1	2		

NOTE. For seven untreated patients, seven tests were performed; for nine undertreated patients who received mebendazole, 10 tests were performed; for 10 undertreated patients who received albendazole, 12 tests were performed; for six treated patients who received mebendazole, 11 tests were performed; and for nine treated patients who received albendazole, 14 tests were performed.

* Patient no. corresponds with that in text [13].

† Patient from Wisconsin.

in humans, however, the organism's germinal layer is very thin and usually not discernible by light microscopy. In active lesions of AHD, all germinal tissue in the peripheral zone of proliferation is presumably viable; it is from that zone that surgical and needle biopsy specimens are obtained. Vesicles in such tissues consist of laminated membrane, presumably with a thin layer of germinal tissue which, when inoculated into rodents, undergoes proliferation and ulti-

mately produces protoscolices. We have routinely inoculated 10–15 small vesicles, judged from experience to be adequate for producing vesicles in an individual rodent (figure 2). The minimal number of cells required for proliferation is unknown, but Furuya [29] determined that growth occurred when 10^7 undifferentiated (germinal) cells from tissue cultures were inoculated into cotton rats (*Sigmodon hispidus*).

The germinal membrane in paraffin sections is stained by

Figure 1. Cut surface of a typical lesion of AHD in the liver (case 60). Arrows indicate cavities filled by membranes of the larval *E. multilocularis*. The scale bar has a value of 5 mm.

means of the avidin-biotin immunohistochemical (ABC) method [30]. With this technique active lesions can be distinguished from those in which the larval cestode has died spontaneously, but it appears to be of limited value in assessing the effect of long-term mebendazole therapy. In such cases, positive staining has been observed for scattered vesicles which, as indicated by other evidence, were nonviable [30].

It is often difficult to determine whether the larval cestode in lesions is dead or alive when it is assessed by means of the usual histopathologic methods. The laminated membrane may persist even in totally calcified lesions in which the larval cestode was evidently nonviable for 10–30 years [6]. Nonetheless, such membranes in decalcified tissues stain strongly when the periodic acid–Schiff method is used and often do not differ in staining characteristics from membranes taken from active lesions. The presence of the laminated membrane in nonactive lesions may account for a persistent antibody response. Since protoscolices are very rarely produced in humans (they were found in a metastatic lesion in the brain in only one of our cases), viability cannot be established on the basis of observation of flame cells or by less reliable methods of staining [31]. Signs of degenerative changes in laminated membranes and the characteristics of the cellular response are useful in distinguishing nonviable vesicles.

Clinical Experience

The effect that chemotherapy has had on the clinical course of the disease was also evaluated. Among 31 patients for whom the diagnosis was made before 1974, six were cured with surgical resection and two underwent incomplete resections. Twenty-three patients with nonresectable disease initially received no chemotherapy. Early in this experience five cases were excluded from analysis because clinical data were insufficient for assessment (data on these five cases were included only with regard to survival). Two cases in which incomplete resections were performed and one recent case (case 42 in which severe undertreatment occurred be-

cause of noncompliance with therapy) are added to the remaining 18 untreated cases to give a total of 21 patients who had active untreated or undertreated lesions and who were observed over time. They serve as the historical controls to be compared with 13 patients who received chemotherapy (table 2). (Eleven active cases were diagnosed after 1974 when chemotherapy trials were initiated; of these, data from three are not included because the patients died of causes unrelated to AHD before they had received 2 years of mebendazole therapy.) Five patients in the untreated group eventually received chemotherapy (cases 1, 2, 3, 30, and 42), and data from these cases appear in both the treated and untreated categories, resulting in analysis of 34 cases.

In this study the sizes of untreated hepatic lesions were largely determined during physical examination by measuring the palpable liver edge or hepatic mass below the costal margin. Before 1975 the only means for monitoring the progress of lesions was by physical examination, and thus it was customary for the physician to conduct thorough examinations and to record results at the time of each clinic visit. Most of the examinations were performed by one of the authors over the period of 1961 to the present. Data from physical examinations represent, in nearly all cases, the average measurements derived from several cases. Lesions of treated cases were more precisely monitored by CT and US, imaging techniques not previously available. Overall progression was assessed by measuring the change in lesion size as determined by physical examination or imaging methods or on the basis of extension of disease, the development of end-stage disease or metastases, and other clinical criteria.

Figure 2. Appearance of vesicles of *E. multilocularis* taken from tissue shown in figure 1. The quantity shown was sufficient for inoculating three voles and inducing proliferation. Each space has a value of 1 mm.

Table 2. Summary of clinical data on patients with untreated and treated alveolar hydatid disease.

Case no./age (y)	Date	Years observed	Initial size	Final size*	Status of lesion over time					Summary of progression	Clinical findings
					Progression						
					Growth†	Extension‡	Metastases	ESD			
Untreated and undertreated patients											
1/34§	12/66	8	5	12	+	—	Lung, mediastinum, lymph nodes	+	OP	Hepatic abscess (20 × 25 cm); then mediastinal and pulmonary mets and ESD	
2/67§	12/69	5	0	1.4	+	—	—	+	OP	Rapidly enlarging widespread pulmonary mets; ESD	
3/56§	6/71	4	4	13	+	+	Brain, retina	+	SP	Lesion (26 cm) with extension through diaphragm; ESD, 1969	
30/65§	3/73	7	0	5 × 8.4	+	—	—	—	OP	Lesion (2 cm) “resected for cure”; increasing serum antibody titers and diagnosis of a recurrent 5 × 8-cm lesion on CT, 10/80	
42/20§	4/85	2.7	7.7	9.8	+	—	—	—	OP	Lesion (8 cm) inadequately treated, 1985–1988; noncompliance with chemotherapy and low serum level of ALBZ led to reactivation	
23/52*	1/47	11	2	10	+	+	—	+	SP	Duodenal mass and mets to liver on surgery, 1947; massive hepatic abscess; marsupialization	
10/30*	1/50	2.5	ND	ND	+	—	Brain	+	SP	Mets to brain; craniotomy, 11/50; protoscolices found in microcysts of brain; died	
25/30*	1950	13	15	ND	+	+	—	+	SP	Lesion (15 cm) partially excised, 1950; pain and jaundice, 1954; hepatocolic fistula and fatal hemorrhage, 1963	
24/54*	7/57	1	10		+	—	Brain	+	SP	Hepatomegaly, abdominal mass (10 cm); CNS symptoms; fatal brain mets	
17/74*	5/58	0.1	7 × 10		+	+	Lung	+	SP	Jaundice; abdominal mass diagnosed as cancer; massive ESD with extension into duodenum; mets to lung and fatal hemorrhage, 1963	
19/53§	2/59	13	0	8	+	+	—	+	SP	Large hepatic mass with extension into IVC; anasarca; death 13 y after diagnosis	
33/22§	2/60	3	0	14 × 16**	+	+	—	+	OP	Jaundice; stony-hard mass (8 × 12 cm) of left lobe resected; recurrence within 3 y with massive lesion (14 × 16 cm) extending through diaphragm; biliary obstruction; death	

Table 2. (Continued)

Case no./age (y)	Status of lesion over time									Clinical findings
	Date	Years observed	Initial size	Final size*	Progression				Summary of progression	
					Growth†	Extension‡	Metastases	ESD		
11/65§	1960	4.5	6	17	+	+	—	+	SP	Diagnosis by serosurvey; progression to ESD; liver enlarged (from 6 cm to 17 cm below costal margin); IVC obstruction; anasarca and death
14/51§	11/60	10.4	3	8	+	—	Brain	+	SP	Diagnosis by serology; increasing liver size for 11 y; fatal brain mets
16/81††	6/62	8.6	10	0††	—	+	—	—	R	Spontaneous drainage of large abscess by fistula to skin (persisted 8 y); died of other causes
12/53§	8/62	0.2	10 × 7		+	+	—	+	SP	Jaundice (3 mo); surgical exploration for ESD; central lesion (10 × 7 cm) with obstruction of IVC
15/28§	10/67	0.1	ND	ND	+	—	Brain	+	SP	Seizures, craniotomy for “brain abscess”; died 1 mo later
9/62§	12/67	7	0	8	+	—	—	—	OP	Liver scan (negative), 1967; repeated, 1972 (multiple hepatic lesions); died with advanced AHD
7/53††	12/63	11	3	13	+	—	—	+	SP	Nodular liver on physical examination; increasing size of liver; died of pneumonia
8/82§	1970	5	2	10	+	—	—	+	SP	Diagnosis by serosurvey; increasing liver size; died of ESD; lesion (16 cm) at autopsy
6/74§	2/71	6	4	12	+	+	—	+	SP	Diagnosis by serology; progressed to ESD; IVC obstructed; anasarca
Treated (mebendazole)										
1/42§§	12/74	17.3	21	8††	—	—	—	—	OR	Regression of substernal mets (26–8 mm); clinically improved for 10 y; died of late complications of AHD
2/62	1/75	21.9	1.4	1.4	—	—	—	—	OR	Rapid growth of pulmonary mets arrested by MBZ (1/75 to 3/86); 27 of 30 pulmonary nodules and primary hepatic lesions totally calcified, appear inactive on CT (5/89); clinically well
3/61§§	1/75	13.7	26	8††	—	—	Brain, retina	—	R	See table 3
30/72	10/80	12.1	5 × 8.4	2 × 4**	—	—	—	—	OR	See table 3
4/43	12/74	16.9	20	10.5	—	—	—	—	OR	See table 3
5/65	4/76	15.5	7 × 10	7 × 10	—	—	—	—	U	Diagnosed by serology; vole assay positive after chemotherapy (5 mo); no increase in lesion size for 8.5 y; therapy with MBZ (8/78 to 2/85); strongly positive serology now negative for 5 y

Table 2. (Continued)

Case no./age (y)	Date	Years observed	Status of lesion over time							Summary of progression	Clinical findings
			Initial size	Final size*	Progression						
					Growth†	Extension‡	Metastases	ESD			
34/50 ^{§§}	11/80	3.9	7 × 10	9.7	—	—	—	—	OR	Therapy with MBZ (11/80 to 12/83); growth of two central lesions arrested for 4 y; obstruction of common bile duct; external tube drainage for 10 mo; biliary cirrhosis and portal hypertension; died	
35/56 ^{††}	10/80	9.5	5.4 × 6.6		4.7 × 6	—	—	—	OR	See table 3	
Treated (albendazole)											
42/20	4/85	6.6	9.8	11	+	—	—	—	P	See text	
39/51	2/85	6.7	4.3	S	—	—	—	—	OR	Diagnosis by serosurvey; after therapy with ALBZ (2 mo) lesion resected; in vivo viability assay negative; postoperative serologies negative for 6.5 y	
51/67	2/87	4.7	3.4 × 4.5	3.5 × 3.9	—	—	—	—	U	Lesion (4 cm) found incidentally on CT, 2/87; open biopsy specimen gave positive vole viability results; therapy with ALBZ (3.7 mo); severe dermatitis; ALBZ discontinued (see table 4)	
53/33	6/88	3.3	2 × 4	1.5 × 3.2	—	—	—	—	OR	Lesion (2 × 4 cm, mixed density) found on US; therapy with ALBZ (7 mo) tolerated; resection offered, declined (see table 4)	
60/53	2/91	0.7	3 × 3	S					OR	Suspicious finding on screening US, 6/88; US negative when repeated 6/89; serum antibody titers elevated, lesion (3 cm, mixed density) found on CT; ALBZ therapy for 3 mo; lesion resected 5/91; weakly positive results in one of three voles; 12 mo of therapy with ALBZ scheduled	

NOTE. ESD = end-stage disease; + = occurred; — = did not occur; OP = objective evidence of progression; mets = metastases; SP = severe progression; CT = computed tomography; ALBZ = albendazole; ND = not determined; IVC = inferior vena cava; R = regression; AHD = alveolar hydatid disease; OR = objective evidence of regression or negative in vivo assay; MBZ = mebendazole; U = unchanged; P = progression; S = no evidence of recurrence; and US = ultrasonography.

* Lesion size or hepatomegaly determined on physical examination, CT, or roentgenography.

† If patient died of brain metastasis or overwhelming AHD, growth is presumed.

‡ Obstruction of vena cava or portal vein or fistula to the skin, bowel, or pleura.

§ Patient eventually treated.

|| Pulmonary metastases (average of five nodules).

* Death directly related to AHD.

** Size of lesion measured at autopsy.

†† Died of unrelated causes.

‡‡ Change in size due to drainage of abscess.

§§ Died of late complications of AHD; viability assay negative.

||| Alive.

End-stage disease was defined as that involving a massive lesion (diameter, >15 cm or liver edge >11 cm below the costal margin), and extension of disease was defined as that causing obstruction of the inferior vena cava, major hepatic bile ducts, or portal vein or the development of fistulae or distant metastases [26]. Progression of disease is severe and unequivocal: if a patient had end-stage disease before the start of chemotherapy and died of late complications of AHD, the case was not described as showing severe progression or as developing end-stage disease while receiving chemotherapy.

Results

Long-term mebendazole therapy. Eight patients were treated with mebendazole for ≥ 2 years. Of these, tissues were obtained for viability studies from six. A needle biopsy specimen from one patient (case 4) was positive in 1978, 48 months after therapy was initiated. Tissues were evaluated on 10 other occasions from these six patients. Five specimens were obtained at autopsy and five during surgical exploration. The autopsy findings and in vivo results for two of the patients have been previously reported [26]. Table 3 presents a summary of data for the remaining four patients (see also figures 3 and 4).

Short-term albendazole therapy. Five patients were treated with albendazole. Two lesions measuring 4.3 cm and 3 cm were resected after 58 and 84 days of therapy, respectively. The in vivo assay of resected tissues was negative for the first patient. For the second patient, whose case was recently diagnosed (case 60), proliferation of the larval cestode was observed in one of three voles that were injected. However, the extent of proliferation was very limited—the weight of the metacestode tissue was <0.1 g, as compared with the usual weight of 5–15 g when untreated membranes are injected. These findings suggest reduced viability of the larval cestode, with growth from only one of the many microcysts injected. Two patients with 4.5- and 4-cm lesions were treated with only albendazole for 3.75 months and 7 months, respectively. No increase in lesion size has been observed with CT during 4.7 and 3.3 years of follow-up.

The fifth patient (case 42) was a 20-year-old woman who had an 8-cm nonresectable lesion and who was treated for 10 months with albendazole (400 mg b.i.d.) from June 1985 to July 1986 [27]. Although the initial in vivo test performed after 3 months of therapy with albendazole was negative, the case was complicated by both noncompliance and low serum albendazole levels of 310 ng/mL. She had received no more than 1.5 months of appropriate therapy when reactivation with growth of the lesion to 10 cm occurred. A second series of treatments for 9 months (600 mg b.i.d.) arrested growth for 16 months, and peak serum albendazole levels of 1,320 and 2,120 ng/mL were attained. However, the lesion then increased in size to 11 cm, and results of an in vivo assay

were positive. A third series of treatments with albendazole for 9 months was started in February 1990, followed by long-term mebendazole therapy. The size of the lesion has been stable for 21 months and the patient remains asymptomatic, but the long-term prognosis is not clear. Although we believe that this patient has been taking her drugs as directed since 1988, she, very unlike the other patients, has been quite unreliable in many ways. In addition, other factors such as possible drug resistance or inadequate host immunity must be considered as contributing to this delayed treatment failure. This is the only case, in our experience, in which the larval cestode grew during administration of chemotherapy. While it is too early to fully assess this case, we will consider it at this time as one in which inappropriate therapy was administered.

Vole-inoculation studies. Data from our experience with the vole-inoculation method for assessing the viability of the larval cestode of *E. multilocularis* are presented in table 1. Among 12 viability assays of tissue from 10 untreated or undertreated patients, 10 (83%) were positive, while only two (17%) were negative. Of nine treated patients, an assay performed in 1978 of a needle biopsy specimen from one who had received 48 months of mebendazole therapy was positive. Since that time, 11 of 13 consecutive in vivo tests for nine treated patients failed to show growth of the larval cestode (79% negative). Ten of these negative tests involved specimens from patients who had received ≥ 2 years of mebendazole therapy, and one involved specimens from the patients who had received 2 months of preoperative albendazole therapy.

Untreated vs. treated cases. The clinical course of the 29 study cases is summarized in table 2. Twenty of these were diagnosed before 1974, when mebendazole was introduced. Four cases were diagnosed by serological screening, while 16 patients presented with a mass or symptoms. Among 21 untreated patients, increasing severity of hepatomegaly or lesion size, as determined by physical examination, CT, or direct measurement, was demonstrated in each of the 14 patients that could be assessed (figure 5). Seven patients were excluded: six in whom the size of the lesion could not be determined and one (case 16) in whom a large abscess drained spontaneously, resulting in a decrease in the degree of hepatomegaly. In two cases the disease recurred after performance of what were believed to have been complete surgical resections. The recurrent lesions presumably arose from microscopic, residual material that was not discernible at the time of surgery; the size of the lesions was considered to be zero immediately after surgery. These lesions progressed in size to reach diameters of 14 cm and 8 cm within 3 and 7 years, respectively (cases 33 and 30).

Drainage procedures or surgical intervention resulted in marked reduction in the size of the hepatic abscess in three cases (cases 1, 3, and 4). However, these changes were unrelated to the effect of chemotherapy and have been excluded

Table 3. Clinical findings and evidence of nonviability of *E. multilocularis* for patients receiving mebendazole therapy.

Case no.	Clinical findings	Pathological findings	Evidence of nonviability
3	End-stage disease at diagnosis (1971); hepatic abscess (7–8 L, 18 × 25 cm); marked clinical improvement with MBZ therapy, 1975–1985; pyogenic infection of hepatic abscess (1977) requiring external drainage for 2 y; retinal metastasis (3.25 mm) diagnosed (1980); seizure (1984) led to diagnosis of a brain met; led active life until 1/85; hospitalized, died of sepsis and renal failure	Extensive AHD of right lobe of liver and RLL of lung at autopsy; brain met (2.5 cm) and subretinal met (10 mm); vesicles of <i>E. multilocularis</i> abundant; inoculation of three voles	Negative vole (× 3) and ABC test results; weak PAS staining; extensive necrosis of brain lesion; degenerative changes in retinal met
4	Diagnosis by positive serology and enlarged liver; 12 × 20-cm central lesion treated with MBZ (12/74 to 4/87); abscess decreased from 20 cm to 10 cm without drainage; biliary obstruction requiring choledochoduodenostomy and partial resection (11/86) (wall of lesion was thin, fibrotic with no matrix); biliary stent requires changing every 2–4 mo; patient remains active and asymptomatic 17 y after diagnosis	Considerable necrosis of tissue around laminated membranes; large proportion of vesicles not taking up PAS stain; great majority of membranes gave negative ABC test results with rare scattered membranes positive	Negative vole test results (× 2); decrease in lesion size without drainage and loss of matrix; no recurrence 4.5 y after MBZ therapy discontinued
30	Lesion (12 cm) “resected for cure” (1973); increasing serum antibody titers led to diagnosis of a recurrent lesion (5 × 8 cm); MBZ therapy 42 mo (discontinued 1/85); died of cancer of breast, 9/85	Metastatic cancer and <i>E. multilocularis</i> lesion (2 × 2 × 4 cm) on autopsy	Very weak PAS stain uptake, negative ABC and vole test results (× 3); decrease in lesion size (10/80 to 9/85, from 5 × 8 cm to 2 × 4 cm)
35	Positive serology; CT revealed a 6.5-cm central hepatic lesion (10/80); MBZ therapy (10/80 to 12/86); biliary stricture required internal drainage with stent (11/86 and 12/86); maintained active life and full employment, then died of cerebrovascular accident (4/90)	Gelatin-like and friable laminated membranes in autopsy tissue	Degenerative changes in laminated membranes, negative vole test results of surgical and autopsy tissues (1990)

NOTE. MBZ = mebendazole; met = metastasis; AHD = alveolar hydatid disease; RLL = right lower lobe; ABC = avidin-biotin immunohistochemical test; PAS = periodic acid-Schiff; CT = computed tomography.

from assessment of change in lesion size. In nine treated cases the size of the hepatic lesion has been assessed over time (figure 6), and in three cases metastatic lesions have been monitored by roentgenography, CT, or US (figure 7). The arrest of growth following institution of chemotherapy is well illustrated in cases 1 and 2. The continued growth of the retinal metastasis in case 3 is possibly explained by poor penetration of mebendazole through the blood-retina barrier. Viability tests of membranes from other lesions in this case were negative. Among the 13 treated patients, eight are living. The lesions in two were resected (cases 39 and 60), and in another (case 42) the status of the lesion is uncertain. In

the remaining five, chemotherapy has been discontinued for an average of 4.8 years (range, 3–7 years) without evidence of any increase in lesion size on semiannual or annual CT and US.

Extension of the disease into adjacent structures was observed in 10 of 21 untreated cases (48%) and consisted of penetration of the diaphragm, formation of a fistula to the skin or bowel, or blockage of the inferior vena cava. No extension of disease was observed in any of our cases after chemotherapy was started. Distant metastases were observed in eight of the 29 cases summarized in table 2 and in one patient not in the study group. Among untreated patients, four

Figure 3. *Left*, PA chest roentgenogram taken in 1971 of a 58-year-old Eskimo man with a massive hepatic lesion after 3,600 mL of fluid was aspirated from the lesion and air was injected. Note air-fluid level and elevated diaphragm. *Right*, flat plate of abdomen after instilling contrast medium (abscess measured 25 × 18 × 17 cm). (Reprinted with permission from [12]).

developed symptomatic brain metastases and survived, on average, only 0.9 years (range, 1–12 months) after diagnosis; for two patients incidental autopsy findings of pulmonary or pulmonary and brain metastases were noted. Three patients with metastases received chemotherapy and survived an average of 17.3 years after diagnosis. In cases 1 and 2 there was objective evidence of regression of widespread metastases after mebendazole therapy was started (figure 6). In case 3 brain and retinal metastases were discovered during the period of chemotherapy. However, it is not clear when these metastases actually developed. The brain metastasis in

this case behaved very differently from those of untreated patients. No growth was apparent during the year after diagnosis was made by CT, and it did not cause further symptoms or contribute to the patient's death. Tissues from metastases in cases 1 and 3 were not submitted for vole inoculation, but results of periodic acid–Schiff staining of histologic sections and ABC tests were consistent with severely damaged or nonviable larval cestodes. Growth in the retinal lesion, however, suggests at least that the metastasis was active.

In untreated cases objective evidence of severe progression was observed by roentgenography, CT, or US in six (43%) of

Figure 4. *Left*, Surgical specimen from internal drainage and unroofing procedure in 1986 after a 43-year-old man presented with a 20 × 12 × 12-cm nonresectable hepatic lesion in 1974, for which he received mebendazole (3 g daily for 12 years [case 4]). The thin (2–3 mm) fibrotic wall of the abscess is held in the forceps. *Right*, the absence of residual matrix contrasts with the characteristic thick matrix of an untreated lesion (autopsy specimen, case 14).

Figure 5. Increase in lesion size or hepatomegaly over time in untreated or undertreated alveolar hydatid disease.

14 patients who could be assessed, and the infection advanced to end-stage disease in 81% (17 of 21 cases). Considering all parameters, severe progression was confirmed in 95% of untreated cases. On the basis of the same criteria, none of the 13 treated cases showed severe progression. There was objective evidence of a favorable response in 10 patients (77%) as indicated by regression in lesion size in five patients and negative *in vivo* viability assay for five. On the basis of each of these parameters, striking differences are observed between treated cases and the untreated controls.

Survival. In assessing the clinical effect of chemotherapy, we had an early favorable impression that survival time was extended through its use [13, 14, 26]. Among 21 patients who were never treated, the average survival time was 5.3 years postdiagnosis, and all of those patients have died.

Figure 6. Size of the larval *E. multilocularis* (EM) lesion as determined by roentgenography or CT over time in treated alveolar hydatid disease. Note chemotherapy has been discontinued in each case except case 42.

Figure 7. The effect of mebendazole therapy on the size of metastatic lesions of alveolar hydatid disease. The reduction in the size of the substernal metastasis of case 1 and the arrest of growth of the rapidly enlarging pulmonary metastases in case 2 are attributed to mebendazole therapy. AP = anteroposterior.

Among eight treated patients for whom AHD was diagnosed before 1981, survival time now averages 13.6 years (figure 8). Three patients who had advanced disease when chemotherapy was started are living, with survival time now averaging 18 years. Survival after the onset of end-stage disease was 0.6 years in the untreated cases and 15.7 years among patients in the treated group (figure 9). Because diagnosis has been made recently for most patients and their disease was identified at an earlier stage when the lesion was smaller, so

Figure 8. Comparative survival rates for 33 patients with alveolar hydatid disease. All untreated patients have died (average survival time, 5.3 years). The average survival time for eight treated patients who received the diagnosis before 1981 is 13.6 years and three of these are alive.

Figure 9. Survival after the onset of end-stage alveolar hydatid disease. Nine untreated patients survived only 0.6 years after onset of end-stage disease while four treated cases have survived 15.7 years, and two are alive.

little is known regarding the natural history of AHD that it is difficult to speculate on what the eventual survival time will be among the treated patients. Nevertheless, since all have remained asymptomatic and, with the exception of the one noncompliant patient, no enlargement of the lesion has been discerned for a period averaging nearly 5 years, we believe that they, as a group, can be expected to survive well beyond the untreated patients. The 5-year survival rate was 56% for the untreated group and 90% for the treated groups. The 10-year survival rate among untreated patients with a diagnosis of AHD before 1981 was 31% (five of 16) and 75% (six of eight) in the treated groups. Ammann et al. [23] also reported improved survival among 60 patients treated with long-term mebendazole therapy. The 5-year survival rate for these patients was 96%, and at 10 years, 84%. For untreated historical controls the 10-year survival rate was <10%.

Discussion

The natural clinical course of untreated AHD has a wide spectrum of presentations. Some lesions appear to respond to host defenses and are spontaneously cured [6]. More charac-

teristically, however, the course of untreated AHD is that of relentless growth with invasion of vital structures, resulting in obstruction of the inferior vena cava, major bile ducts, or portal blood flow; terminal anasarca often develops. A massive liver or a greatly distended abdomen due to ascites characteristically develops. Before we conducted our first chemotherapy trial in late 1974, 67% (16 of 24) of our cases developed along this dreadful course (three of the first four patients treated with mebendazole had marked hepatomegaly when treatment was initiated). In others, fatal brain metastases or extensive pulmonary metastases occurred. One may consider this progressive but lingering fatal course to be the "classic" clinical course of active, untreated AHD.

The untreated AHD lesion consists of extremely dense fibrous tissue in which microcysts of the larval *E. multilocularis* are scattered [13]. The matrix is so dense that, as the lesion enlarges, blood vessels within the lesion are obliterated and a central zone of avascular necrosis characteristically develops (figures 3 and 4). In such lesions, the volume of parasite tissue is low, and all but a minute fraction of such tissue consists of nonliving, laminated membranes. Because the nonliving membranes as well as the dense fibrous tissue associated with AHD lesions would not be affected by a parasitocidal agent, reduction in lesion size, especially in the liver, may be minimal or may not occur at least during the first few years posttreatment. Where the larval *E. multilocularis* is rapidly proliferating and where less scar tissue develops, as in metastatic lesions, reduction in lesion size might be more likely to occur, as indeed was observed in each of two such patients (cases 1 and 2) who could be evaluated. Consequently, the arrest of growth of hepatic AHD lesions may well be all that is observed, even when the larval cestode is killed with therapy. Reduction in the size of the lesion should not necessarily be expected.

Distant metastases appear to be associated largely with advanced disease. Seven of the eight cases with metastases had advanced or end-stage disease when metastases were first observed. In Alaska, only two (20%) of the last 10 new active cases of AHD diagnosed since 1975 occurred in patients who presented with symptoms, compared to 78% before that time. It appears that improved diagnostic and surveillance techniques have led to the diagnosis of AHD when the lesion is smaller (5 cm vs. 13 cm) and at an earlier average age (43 years vs. 59 years), thus permitting diagnosis and treatment before an advanced stage of disease has developed (which perhaps explains what appears to be a lower incidence of distant metastases in recent years).

The clinical course of the first four patients to receive chemotherapy in 1974 was significantly altered. Two of these patients eventually died 14 and 17 years after the diagnosis of late complications of AHD was made, but their course did not follow the classic course described above. Two patients are living 15 and 22 years after diagnosis with what we believe are dead lesions. These patients (nos. 2 and 5) have not

received chemotherapy for an average of 6.2 years. Their CT studies have shown no growth of the lesions for 10 years and there has been extensive or complete calcification of their primary lesions. In case 2, 27 of 30 pulmonary metastases are totally calcified; no growth has been observed in the remainder for 17 years [12]. In case 5, the EM₂ ELISA serology was strongly positive from 1975 to 1986 and on each of seven tests has been consistently negative since 1986. Although serologies are often positive for patients with nonviable lesions because of retained laminated membranes, we believe the conversion to negative in this case is highly significant. These findings strongly suggest that the larval cestode is dead in each case.

After an intense study of the first nine inactive cases diagnosed [6], differentiation between an active AHD lesion and an inactive lesion in which the larval cestode has died has thus far not been difficult. Active lesions have been, without exception, of mixed density on CT [32]. They have been much larger in size and often were associated with symptoms, end-stage disease, or metastasis, whereas none of the inactive lesions have presented in association with these features. Among 26 cases identified as dead or inactive, all have had very densely calcified lesions and no demonstrable hypodense areas on CT. Of the lesions, 22 (85%) were ≤ 2 cm in diameter, only one (3.8%) was > 3 cm in diameter [6], and none was associated with symptoms; no patients developed end-stage disease or metastases. There is no evidence to suggest that any of the 13 treated cases presented in table 2 had inactive disease at the time of diagnosis: the average lesion size was 9.8 cm (range, 3 cm–26 cm); the viability of the cestode was demonstrated by a positive viability assay with voles for six; three others had symptoms or end-stage disease; and viability was also evaluated in two cases by histopathologic examination of surgical tissue. The determination of viability was based on CT findings for only two of these patients (cases 5 and 53), and each had a typical mixed-density lesion, 4 cm and 10 cm in diameter, respectively. The lesion in case 53, discussed below, was the only one for which viability of the cestode could be seriously questioned. Thus far we have seen little reason to consider a lesion with typical mixed densities on CT as anything other than active. As improved screening methods permit diagnosis of active cases when the lesion is quite small, this issue may become difficult and require more study.

Vole-inoculation studies. We believe the vole-inoculation test represents the best and the only direct means of assessing viability of larval *E. multilocularis*. It is the standard by which other viability methods are measured. In animal studies Eckert [33] demonstrated extensive destruction with necrosis of larval *E. multilocularis* after administration of mebendazole therapy. Yet inoculations into animals with use of tissue from these severely damaged and apparently necrotic vesicles resulted in regrowth of the larval cestode, a finding that demonstrated that residual, viable parasitic tissues were

present. Schantz et al. reported that albendazole (as with mebendazole) was not parasitocidal against *E. multilocularis* in animal hosts even when the hosts were medicated continuously for up to five months [34]. The failure of mebendazole to kill the parasite in such in vivo studies in laboratory animals is in part the basis for the widespread view that mebendazole may be parasitostatic but not parasitocidal [15, 16, 35].

However, humans have a much more active immunologic response to *E. multilocularis* than do rodents, as evidenced by the absence of protoscolices together with the marked degree of necrosis and scarring associated with the lesion that develops in humans. The not-infrequent occurrence of spontaneous cure with death of the larval cestode also indicates a good host defense in humans [6]. Thus, the combination of an active immunologic response and the effect of chemotherapy could result in death of the parasite in humans but not in rodents.

The appearance of a typical *E. multilocularis* lesion on CT or an abdominal roentgenogram has been described as being of mixed density, with areas of calcification interspersed with radiolucent or hypodense areas [32, 36]. This finding suggests that these lesions continue to proliferate peripherally, with healing in deeper tissues, death of the larval cestode, and increasing calcification. The laminated membranes in the microcysts are durable. In autopsy specimens, as well as in old, calcified, inactive lesions [6], the membranes have been observed in abundance despite the fact that the results of all viability assays indicated that the parasite was dead. When membranes are collected for viability assay, the percentage of microcysts that contain viable germinal tissue is not known but could be quite low. It is possible that among entire aliquots of membranes prepared for injection into voles there may be none with viable germinal cells. This may, in part, explain why proliferation fails to occur in some voles injected with membranes from viable lesions, as observed in cases 26, 30, 4, W, 5, and others (table 1), and is the reason why three voles are routinely injected. Proliferation occurred in nine (60%) of 15 voles injected with tissues from untreated patients, while it occurred in only three (9%) of 34 voles injected with tissues from treated patients.

The favorable results among Alaskan patients, as reflected by the results of viability tests with voles, were not achieved in an important investigation by Eckert and Jacquier (unpublished). In vivo viability tests in gerbils were performed with use of tissue from 14 untreated Swiss patients. Positive results were obtained in 11 (79%). Of tests on tissue from 12 patients who had been treated from 1 to 108 months with mebendazole (11 patients) or albendazole (one patient), 10 (83%) were positive. The difference in the numbers of positive assays in the Swiss and Alaskan groups is striking but may be attributable largely to the duration of chemotherapy. The average period of treatment in Alaska was 70 months but was only 19 months in the Swiss experience. We seldom obtained negative test results unless the treatment had been

Table 4. Albendazole therapy: results of in vivo viability assays and clinical assessments among compliant patients.

Case no.	Albendazole therapy (mo)	Follow-up	Vole test	Initial size	Serial CT examinations ($\times 5$)		Results of clinical assessment
					Final size of lesion (cm)	Changes in CT image	
39	2	6.6	—	4.3	...*		Excellent
51	3.75	4.7	ND	3.4×4.5	3.5×1	Much-reduced hypodense areas; calcifications more confluent and dense	Very good
53	7	3.3	ND	2×4	1.5×3.2	Reduced hypodense areas; calcifications more confluent and dense; decrease in size	Very good
60	3 + 9	0.7	+ (very weak)	3.3	...*		Excellent

NOTE. CT = computed tomography; ND = not done.

* Lesion surgically resected.

given for ≥ 2 years. Only three patients in the Swiss study had been treated for this long, and the test was negative for one of them.

The number of in vivo tests for which consistently negative results were obtained for mebendazole-treated patients (table 1), together with supporting clinical observations, offers convincing evidence that long-term mebendazole therapy has been parasitocidal. The limited number of vole tests performed for albendazole-treated patients and the shorter time of follow-up make the interpretation of the results for this group more difficult. However, in assessing these results, the following considerations should be kept in mind. The objective of these chemotherapy trials was, and continues to be, to learn as much as we can as quickly as possible about the therapeutic dosage of albendazole. We were aware that while patients were receiving mebendazole therapy, the parasite had survived as long as 48 months and that albendazole was often hepatotoxic; thus it was important to determine the shortest duration of administration of the drug for effective therapy. The first two vole tests gave negative results after only 2 and 3 months of therapy. More recent results indicate that the parasite, at least in case 60, survived 3 months of treatment. The positive vole tests in cases 42 and 60 should not be viewed so much as reflecting the failure of albendazole therapy but rather that the minimum treatment time should be >3 months.

In view of the in vivo results together with the clinical observations on the four compliant patients who received albendazole, very impressive results were obtained that suggest that the long-term prognosis for these patients is excellent (table 4). In case 39 the negative vole test and negative postoperative serologies over 6.6 years are significant. The

apparent reduced viability of the larval cestode with growth in only one of three injected voles in case 60 suggests that 3 months of chemotherapy had severely injured the parasite. In cases 51 and 53, no posttreatment tissue was available for in vivo studies. The clinical results, as reflected in the results of five serial CT studies, however, are very encouraging. In both cases, not only was there no growth of the lesion, but there has been a significant reduction in the amount of hypodense tissue; the calcifications have become more confluent and solid during the 3.3 and 4.7 years of observation. We are certain that in each case the lesion was active at the time chemotherapy was started because the pretreatment vole test in case 51 was positive and, in both cases, changes in the appearance on computed tomograms were observed over time. Had the lesion been dead, no change in appearance would have been expected. The advantages of a drug that is effective over months rather than years are so great that we feel continued emphasis on clinical trials with albendazole is justified.

We have presented our experience with albendazole for the treatment of AHD as well as evidence that it may be hepatotoxic in some cases [27]. Certainly, the need for close monitoring of all patients who receive the drug must be clearly recognized. There continues to be an urgent need to learn as much as possible from each new case of AHD. Our experience with this disease has persuaded us that postponing surgery adds little risk provided the patient is receiving appropriate chemotherapy. It is suggested that for all newly diagnosed cases, both of resectable and nonresectable lesions due to *E. multilocularis*, 4–6 months of preoperative therapy with albendazole be administered and be followed by viability studies on subsequent biopsy specimens or resected tis-

sues. A drug-free interval of 1 week before surgery is suggested so that residual drugs in the tissue do not give false in vivo assay results (this precaution was taken in case 60 but not in previous studies). Although the therapeutic serum level of albendazole is not known, the dose should be adjusted to assure an albendazole sulfoxide serum level of $\sim 1,000$ ng/mL. Until therapeutic parameters are better defined, we feel that, following biopsy or resectional surgery, additional chemotherapeutic coverage with albendazole for a total of at least 12 months is advisable.

Summary

Most of these data suggest that the outcome of chemotherapy extends well beyond that of a favorable or parasitistatic effect. Some of the most convincing evidence for the successful killing of the larval *E. multilocularis* as a result of chemotherapy includes the following findings.

(1) Among 11 in vivo tests in six mebendazole-treated cases, the results of 10 consecutive tests performed since 1978 have been negative (table 1).

(2) In case 1 regression of the enlarging substernal metastasis from 26 mm to 8 mm (with negative results of a vole test on three occasions) occurred, with extended survival of the patient for 17 years.

(3) The abrupt arrest of growth of numerous pulmonary metastases in case 2 was associated with this patient's survival for 22 years, and recent CT studies showed complete calcification of 27 of 30 pulmonary metastases as well as of the primary hepatic lesion.

(4) In case 4 the size of the hepatic abscess decreased without drainage, the surgical specimen appeared benign with loss of all matrix (figure 3), and the results of a vole test on the surgical tissue were negative. This patient is still living 17 years after the diagnosis was made, and mebendazole therapy has been discontinued for 4.5 years without evidence of recurrence.

(5) In case 5, followed for 15 years, a 7×10 -cm hepatic lesion, initially proven to be active by the vole test, has demonstrated decreasing hypodense areas, increasing calcifications, and no growth on serial CT studies over a 10-year period. The EM₂ serologies, consistently strongly positive for 10 years, have been negative on each of seven occasions since 1986 even though the patient has received no chemotherapy for 6.7 years.

(6) Among five patients treated with albendazole, vole viability assays were negative after 2 months of therapy for one patient; in two patients there was evidence of significant damage to the larval cestode after 1.5 and 3 months of therapy, respectively. For two other patients with resectable lesions who were treated with only albendazole, serial CT studies showed a decrease in the extent of radiolucent areas, an increase and confluence of calcifications, and no growth over 4 years. Although more time is required to fully assess this

group of patients, the findings are consistent with a lethal effect of albendazole therapy.

(7) A comparative review of treated vs. untreated cases revealed striking differences. Among 21 untreated cases there was severe progression of disease in 95%, end-stage disease developed in 81%, and all patients have died after an average survival time of only 5.3 years. Among 13 treated cases, excluding the noncompliant patient, none showed severe progression or developed end-stage disease; in 77% there was objective evidence of a favorable response to therapy, and survival time is now 13.6 years (eight patients are still living and asymptomatic).

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