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Cryptosporidium spp. and Cryptosporidiosis

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INTRODUCTION

The genus *Cryptosporidium* identifies protozoan parasites that grow and reproduce within epithelial cells of the respiratory and digestive organs of vertebrates. Once thought to be rare and host specific, *Cryptosporidium* is now known to be ubiquitous and to have many hosts. Once thought to be nonpathogenic, some isolates are now known to cause severe illness. Although recognized and named in 1907, most information on its identification, clinical significance, epidemiology, and treatment has been obtained only within the past few years.

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TABLE 1. Named species of *Cryptosporidium*

Species	Author	Host
C. agni	Barker and Carbonell, 1974	*Ovis aries* (domestic sheep)
C. ameivae	Arcay de Peraza and Bastardo de San Jose, 1969	*Ameiva ameiva* (lizard)
C. anserinum	Proctor and Kemp, 1974	*Anser anser* (domestic goose)
C. baileyi	Current, Upton and Haynes, 1986	*Gallus gallus* (domestic chicken)
C. bovis	Barker and Carbonell, 1974	*Bos taurus* (ox)
C. crotali	Triffit, 1925	*Crotalus confluens* (snake)
C. ctenosauris	Duszynski, 1969	Costa Rican lizard
C. cuniculus	Inman and Takeuchi, 1979	*Oryctolagus cuniculus* (domestic rabbit)
C. felis	Iseki, 1979	*Felis catis* (domestic cat)
C. garnhami	Bird, 1981	*Homo sapiens* (man)
C. lampropeltis	Anderson, Dusynski, Marquardt, 1968	*Lampropeltis calligaster* (lizard)
C. meleagridis	Slavin, 1955	*Meleagris gallopavo* (turkey)
C. muris	Tyzzer, 1907	*Mus musculus* (domestic mouse)
C. nasorum	Hoover, Hoerr, Carlton, Hinsman and Ferguson, 1981	*Naso literatus* (fish)
C. parvum	Tyzzer, 1912	*Mus musculus* (domestic mouse)
C. rhesi	Levine, 1981	*Macaca mulatta* (rhesus monkey)
C. serpentis	Levine, 1981	Colubrid, crotalid, and boid snakes
C. tyzzeri	Levine, 1961	*Gallus gallus* (domestic chicken)
C. vulpis	Wetzel, 1938	*Vulpes vulpes* (European common fox)
C. wrairi	Vetterling, Jervis, Merrill, Sprinz, 1971	*Cavia porcellus* (guinea pig)

This review summarizes recent publications that have increased our knowledge about *Cryptosporidium* and its biology and its veterinary and medical importance.

THE ORGANISM

History

According to the American parasitologist E. E. Tyzzer (260), the first published description of a parasite resembling *Cryptosporidium*, in the gastric epithelium of mice, was by Clark in 1895. In 1907, Tyzzer (259) himself clearly described a protozoan he frequently found in the gastric glands of laboratory but not wild mice. He offered the name *Cryptosporidium muris* but did not provide characteristics for establishing a new genus until 1910 (260). Using a microscope with limited resolution, Tyzzer saw stages of asexual development, sexual development, and sporogony, all of which he interpreted to be extracellular; he noted that oocysts left the body via the feces (259). In 1910, Tyzzer (260) described *C. muris* in greater detail, extended the host range, and suggested that sporozoites liberated from oocysts that had matured in the gastric glands might be a source of autoinfection.

A second species, *C. parvum*, was identified and named by Tyzzer in 1912 (261). It was found in the small intestine (not the stomach) of laboratory mice and could be transmitted to other laboratory mice in which it also developed only in that location. He found similar organisms in the small intestine of a rabbit, but omitted the rabbit as a host in the species description.

Cryptosporidium sp. in cecal epithelia of chickens was reported by Tyzzer in 1929 to be identical to *C. parvum*, but in 1961 Levine named it *C. tyzzeri* to emphasize the chicken host and then synonymized it with *C. meleagridis* in 1984 (152). Morbidity and mortality in avian cryptosporidiosis was described by Slavin in 1955 in turkeys; he named this parasite *C. meleagridis* (240).

Between 1968 and 1981, other species of *Cryptosporidium* in fish, reptiles, birds, and mammals were named on the assumption that each host species harbored a separate species of *Cryptosporidium* (Table 1).

Recognition of *Cryptosporidium* associated with bovine diarrhea by Panciera et al. in 1971 (200) initiated veterinary interest that resulted in numerous case reports and surveys on a variety of domestic animals.

The first cases of human cryptosporidiosis were reported in 1976 (175, 195), but relatively few were subsequently diagnosed until cryptosporidiosis was reported to be a life-threatening infection in acquired immune deficiency syndrome (AIDS) patients. Medical interest in the epidemiology, diagnosis, and treatment of cryptosporidiosis increased dramatically from that time to the present.

Accumulation of veterinary and medical observations on clinical illness associated with severe cryptosporidiosis stimulated experimental studies, which seek to find a small animal model of disease, develop in vitro growth systems, and test potential disinfectants and chemotherapeutic agents.

Classification

All species of *Cryptosporidium* are taxonomically classified as shown in Table 2. Within the phylum *Apicomplexa* are several related genera referred to collectively as coccidia. These include *Besnoitia*, *Caryospora*, *Eimeria*,

TABLE 2. Taxonomic classification of *Cryptosporidium*[a]

Classification	Name	Biological characteristics
Phylum	*Apicomplexa*	Apical complex with polar rings, rhoptries, micronemes, conoid, and subpellicular microtubules
Class	*Sporozoasida*	Locomotion of mature organisms by body flexion, gliding, or undulation
Subclass	*Coccidiasina*	Life cycle with merogony, gametogony, and sporogony
Order	*Eucoccidiorida*	Merogony present; in vertebrates
Suborder	*Eimeriorina*	Male and female gametes develop independently
Family	*Cryptosporidiidae*	Homoxenous with development just under surface membrane of host cell; oocyst without sporocysts and with four sporozoites; microgametes without flagella

[a] From reference 154.

Frenkelia, *Isospora*, *Sarcocystis*, *Toxoplasma*, and *Cryptosporidium*. Twenty species of *Cryptosporidium* were named according to the host in which the parasite was found (Table 1). These recently have been reviewed by Levine (152) and by Upton and Current (280). Several *Cryptosporidium* species must be considered invalid because the oocyst stage which was the basis for speciation has recently been identified as the sporocyst stage of *Sarcocystis*. These include *C. ameivae*, *C. ctenosauris*, *C. lampropeltis*, *C. crotali*, and *C. vulpis*. Recent cross-transmission studies (Table 3) have invalidated the criterion of host specificity and thus have invalidated the species *C. agni*, *C. bovis*, *C. cuniculus*, and *C. felis*. Levine (152, 153) concluded that there were four valid species, one for each vetebrate class. Upton and Current (280) concluded that only two species of *Cryptosporidium* infecting mammals, *C. muris* and *C. parvum*, were valid. There appear to be two valid species infecting birds, *C. meleagridis* and *C. baileyi* (71, 240). Obviously there is a need for clear documentation regarding how many or which species infect fish, reptiles, birds, and mammals.

Host Specificity

Cryptosporidium, like the related genus *Eimeria*, has historically been assumed to be host specific. However, cross-transmission studies (Table 3) indicate that isolates of *Cryptosporidium* spp. from mammals are generally infective for other mammals; isolates from avians are infective for other avians. Transmission from mammals to avians is not well documented. Transmission from avians to mammals has not been successful. Transmission among other vertebrate classes has not been reported. In some cross-transmission studies authors indicate inability to transmit *Cryptosporidium* spp. from one host to another (128, 261, 284; D. S. Lindsay, B. L. Blagburn, and C. A. Sundermann, J. Parasitol., in press), but data on factors which affect the success or failure of transmission, including the age and condition of the oocysts as well as the age and immunologic status of the recipient host, were not well documented.

Life Cycle

The life cycle of *Cryptosporidium* resembles that of other coccidia and is depicted diagrammatically in Fig. 1. The sporulated oocyst is shed (see Fig. 7, 12, 13, and 14) in the feces of an infected host. Through contamination of the environment, food, or water, oocysts become ingested by other suitable hosts. In the gastrointestinal or respiratory tracts of such hosts, sporozoites excyst from the oocyst and parasitize epithelial cells. The sporozoites and subsequent developmental stages are found at the lumenal surface of the epithelium (see Fig. 8 to 11). Although organisms often appear to be attached superficially to a cell, all stages are actually intracellular, surrounded by host cell membrane but extracytoplasmic. The sporozoite differentiates into a spherical trophozoite with a single prominant nucleus (Fig. 3). Asexual multiplication (merogony or schizogony) results from nuclear division. Two types of meronts (schizonts) develop asexually. Type I meronts contains six to eight nuclei which become incorporated into six to eight merozoites when the meront is mature (Fig. 4). Each merozoite (Fig. 2) may invade a new host cell where it

TABLE 3. Transmission of *Cryptosporidium* infection among host species via oocysts

Oocyst source	Recipient species	Infection of recipient[a]	Citation(s)
Cat	Cat	+	128
	Human	(+)	144, 155
	Mouse	−	128
	Guinea pig	−	128
Cattle	Cat	+	27
	Cattle	+	83, 182, 266, 277
	Chicken	+, −	262; Lindsay et al. (in press)
	Dog	+	27
	Goat	+	109
	Guinea pig	+	266
	Human	(+)	10, 69, 70, 228
	Mouse	+	109, 204, 234, 266
	Pig	+	111, 182, 274, 278
	Rabbit	+	109
	Rat	+	109, 234, 266, 269
	Sheep	+	19, 109, 266, 269, 275
Chicken	Chicken	+	131; Lindsay et al. (in press)
	Cotton rat	−	Lindsay et al. (in press)
	Duck	+	Lindsay et al. (in press)
	Gerbil	−	Lindsay et al. (in press)
	Guinea pig	−	Lindsay et al. (in press)
	Hamster	−	Lindsay et al. (in press)
	Mouse	−	Lindsay et al. (in press)
	Pig	−	Lindsay et al. (in press)
	Quail	−	Lindsay et al. (in press)
	Rat	−	Lindsay et al. (in press)
	Turkey	+	Lindsay et al. (in press)
Deer	Mouse	+	267
Human	Cat	+	70
	Cattle	+	70, 266
	Dog	+	70
	Goat	+	70
	Human	+	34, 44, 143
	Mouse	+	70, 234, 265
	Pig	+	184
	Rat	+	234
	Sheep	+	265, 266
	Chicken	−	284
Guinea pig	Guinea pig	+, +	17, 284
	Mouse	−, +	17, 284
	Rabbit	−	284
	Turkey	−	284
Mouse	Cattle	+	277; Klesius et al. (in press)
	Mouse	+	260; Klesius et al. (in press)
	Pig	+	274
	Rat	−	260
	Goat	+	109
Pig	Cattle	+	277
	Pig	+	139
	Human	(+)	106
Rat	Sheep	+	266
Sheep	Mouse	+	267
	Pig	+	274
	Rat	+	266, 267
	Sheep	+	4, 267

[a] Parentheses indicate circumstantial evidence.

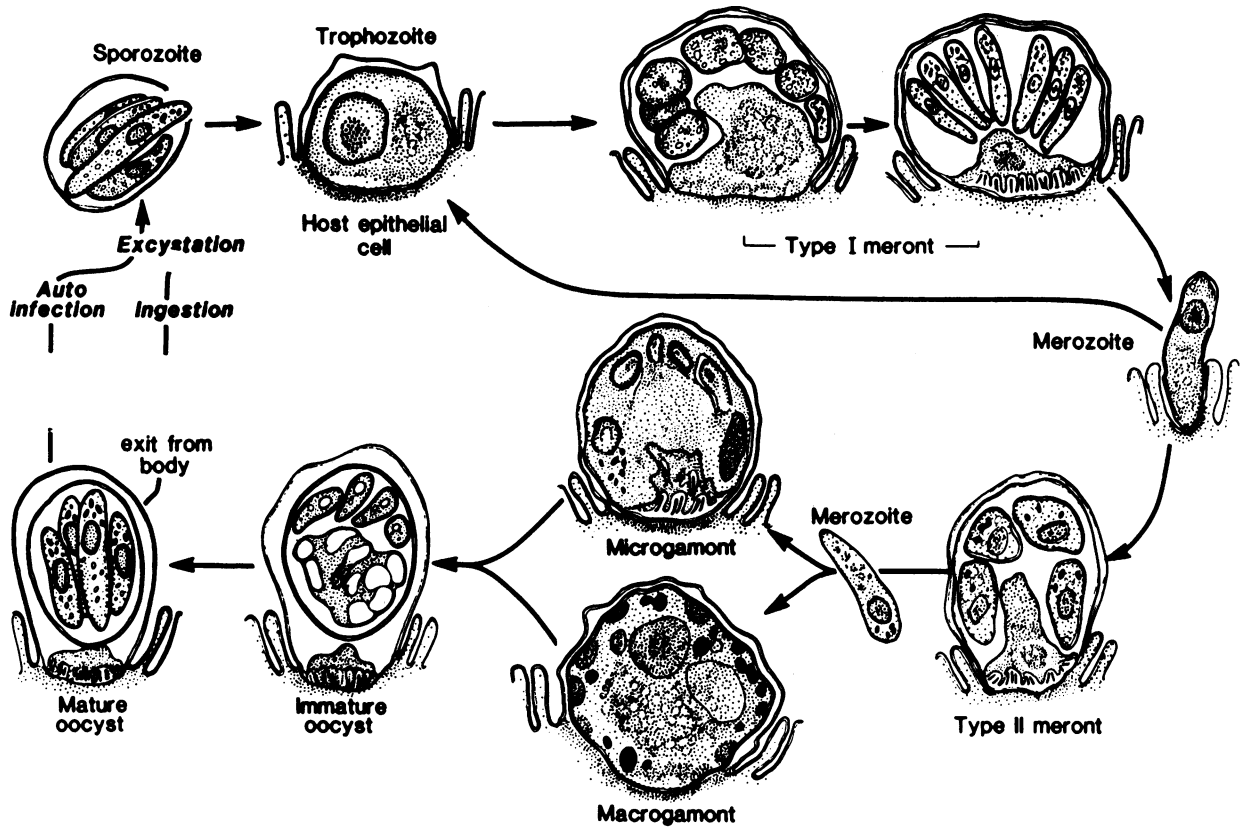


FIG. 1. Diagrammatic representation of life cycle of *Cryptosporidium*. Sporozoites excyst from an oocyst and enter the microvillus of an epithelial cell, where they differentiate into trophozoites. Trophozoites undergo nuclear proliferation to form type I meronts (schizont). A type I merozoite leaves the meront to form either a type I or II meront. A type II merozoite leaves the meront to form microgametes or a macrogamont. The microgamete fertilizes the macrogamont, which then develops into an oocyst. Oocysts sporulate in situ and either release sporozoites for autoinfection or passes from the body in the feces. (Drawing by R. B. Ewing, Animal Parasitology Institute.)

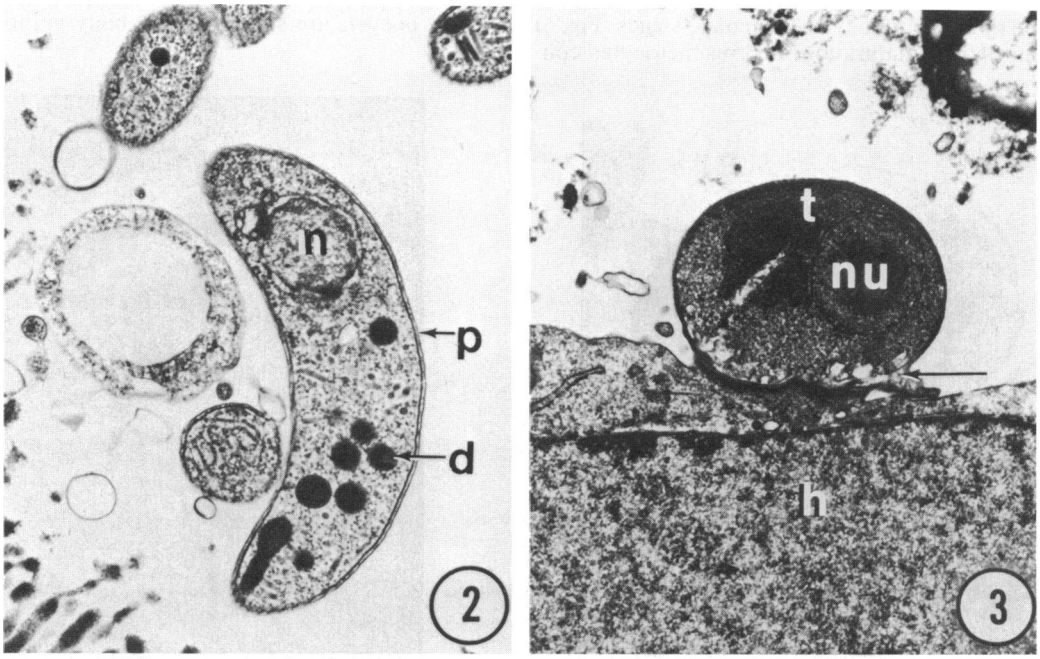
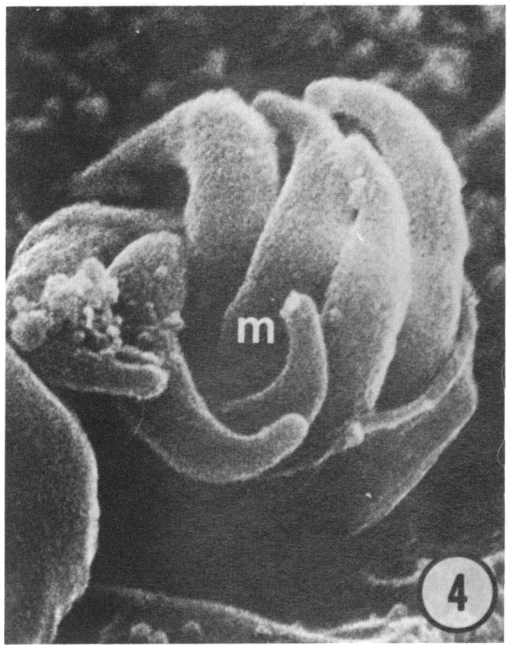


FIG. 2. Transmission electron micrograph of a merozoite on the luminal surface adjacent to microvilli in the jejunum of a germfree calf. The merozoite is covered by a typical double-unit membrane pellicle (p). The nucleus (n) is anucleolar and is surrounded by a dilated envelope. Dense granules (d) are prominent. Magnification, ×24,800. (Courtesy of J. Pohlenz, Iowa State University.)

FIG. 3. Transmission electron micrograph of a trophozoite (t) in a human cell grown in vitro. The nucleus has a large nucleolus (nu). A feeder organelle (arrow) consisting of parellel cytoplasmic bands is developing above the dense attachment zone with the host cell (h). Magnification, ×15,700. (Courtesy of D. Woodmansee and J. Pohlenz, Iowa State University.)



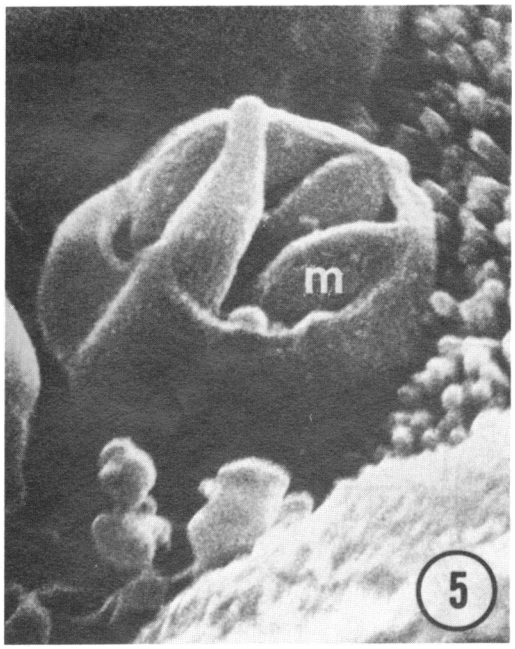


FIG. 4. Scanning electron micrograph of a type 1 meront with seven merozoites (m) visible. Magnification, ×12,000. (Courtesy of C. A. Speer, Montana State University.)

FIG. 5. Scanning electron micrograph of a type 2 meront with all four merozoites (m) visible. Magnification, ×12,000. (Courtesy of C. A. Speer, Montana State University.)

develops into another type I meront or a type II meront (Fig. 5), which contains four merozoites when mature. Merozoites from type II meronts invade new host cells where they initiate sexual multiplication (gamogony) by differentiating into either male (microgametocytes) or female stages (Fig. 6) (macrogamonts). Upon maturation, microgametocytes contain spermlike microgametes which will fertilize the macrogamonts. The fertilized macrogamont develops into an oocyst, which sporulates in situ (Fig. 7). Upon completion of sporogony, it contains four potentially infective sporozoites. Some oocysts are shed from the body via feces or perhaps

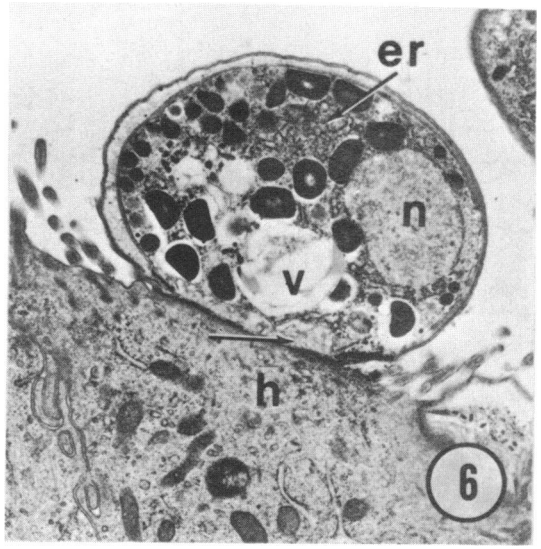


FIG. 6. Transmission electron micrograph of a macrogamont. A large nucleus (n), endoplasmic reticulum (er), a vacuole (v), and other granules are prominent. A feeder organelle (arrow) is present above the dense attachment zone with the host cell (h). Magnification, ×12,000. (Courtesy of H. Moon, Agricultural Research Service, Ames, Iowa.)

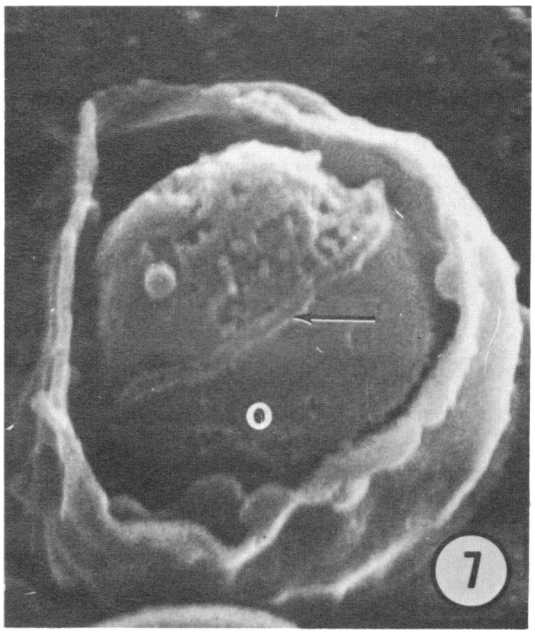


FIG. 7. Scanning electron micrograph of an oocyst (o) which has a suture (arrow) on its surface. Magnification, ×13,000. (Courtesy of C. A. Speer, Montana State University.)

respiratory secretions, whereas others release sporozoites within the body which may repeat the cycle of merogony, gamogony, and sporogony. Some investigators have reported observing morphologic differences among oocysts that correspond with these routes of infection: thick-walled oocysts which transmit infection to other susceptible hosts and thin-walled oocysts which release the sporozoites that initiate autoinfection (66).

Most genera of coccidia, including *Besnoitia*, *Eimeria*, *Hammondia*, *Isospora*, and *Toxoplasma*, undergo sporogony outside the body. Others such as *Frenkelia* and *Sarcocystis* sporulate endogenously but do not autoinfect the host. *Caryospora* is the only genus other than *Cryptosporidium* known to sporulate endogenously and to initiate autoinfection.

The timing of development varies. Prepatent periods (the interval between infection and oocyst shedding) range from 2 to 7 days in cattle (277), 5 to 10 days in cats (128), 2 to 14 days in dogs (27), 3 to 6 days in pigs (182, 274), and 2 to 5 days in lambs (262). In humans, based on known accidental infection of an oral inoculum, prepatency ranges from 5 to 21 days (10, 44, 234). The patent period (duration of shedding) lasted from 1 to 12 days in cattle (2, 277), 3 to 33 days in dogs (27), and 5 to 14 days in pigs (27, 90). In immunocompetent humans, patency may last for >30 days (182, 274). With in vitro development as a guide, type I meronts matured by 12 h, type II meronts matured by 24 h, gamonts were present by 48 h, and sporulated oocysts were found by 72 h after inoculation of sporozoites (67).

Morphology

Among the coccidia, the genus *Cryptosporidium* has the smallest oocysts. They are spherical to ovoid, and 50 fully sporulated oocysts averaged 7.4 by 5.6 μm for *C. muris* and 5.0 by 4.5 μm for *C. parvum*, the species infectious for most mammals (280). Sporulated oocysts each contain four sporozoites and a residuum composed of numerous small granules and a spherical or ovoid membrane-bound globule. Most, but not all, authors report no sporocyst wall within the oocyst (152). Other morphological features often observed in coccidian oocysts, such as a micropyle and polar granules, have not been found in oocysts of *Cryptosporidium* spp. The oocyst wall is smooth and colorless and averages about 50 nm in thickness. It is composed of two electron-dense layers separated by a thin electron-lucent space (234). A faint line sometimes seen with the light microscope extends from one pole of the oocyst partially over the circumference of the wall (281); it has been identified with transmission electron microscopy as a suture that dissolves during excystation (Fig. 7) (234).

Sporozoites are generally crescent shaped, with the anterior end slightly pointed and the posterior end rounded. Within the oocyst they lie parallel to one another against the oocyst wall, with the anterior end adjacent to the oocyst pole with the suture. Sporozoites of *C. muris* average 11.1 by 1.0 μm and those of *C. parvum* average 4.9 by 1.2 μm (281). Each sporozoite contains a prominent nucleus in the posterior third of the body. A detailed description of the ultrastructure of sporozoites is lacking.

Trophozoites are round or oval intracellular forms, 2.0 to 2.5 μm in diameter (128). They are transitional stages from sporozoites and merozoites to meronts (Fig. 3). They and all subsequent developmental stages are found within a parasitophorous vacuole surrounded by a host cell membrane, with an electron-dense attachment zone at the host cell interface. Trophozoites are further characterized by a large nucleus, 1.0 to 1.3 μm in diameter (128, 286), which contains a large nucleolus, and by an absence of the apical complex structures which characterize sporozoites and merozoites (Fig. 2).

As the nucleus replicates within the *Cryptosporidium* sp., it passes from the uninuclear trophozoite stage to the multinucleate meront (schizont) stage. Two physically different types of meronts about 4 to 5 μm in diameter (128) appear to develop sequentially (Fig. 4 and 5). Type I meronts develop as the first asexual generation from trophozoites or merozoites that leave a type I meront and invade new host cells. Type I meronts produce six to eight merozoites that bud from a distinctive region referred to as the "attachment zone" or "feeder organelle," where the meront interfaces with the host cell. Type II meronts (Fig. 5) develop from type I merozoites; they produce four merozoites and otherwise appear similar to the type I meront.

Type I and II merozoites appear to be morphologically identical. They are crescent shaped with rounded anterior and posterior ends and measure about 5 by 1 μm (128). They contain a single vesicular nucleus, endoplasmic reticulum, and a variety of unidentified granules. Like most other coccidian merozoites, at the anterior end are organelles such as the conoid, a polar ring, rhoptries, and micronemes (128, 285), but not refractile bodies, mitochondria, micropores, or polysaccharide granules (285).

Microgamonts are an infrequently found, apparently short-lived, male stage. As observed ultrastructurally, at an early stage the microgamont contains many condensed parts of nuclei, ribosomes, endoplasmic reticulum, and membrane-bound vacuoles (98). The condensed or compact spherical nuclei are found only at the periphery of a granular cytoplasmic mass, not in the region of the attachment zone (98, 285). Later in development the nuclei of microgametes move out of the cytoplasm of the microgametocyte into the parasitophorous vacuole (98). As many as 14 to 16 microgametes develop from a microgametocyte, which may reach 4 to 5 μm in diameter (98, 128). Mature microgametes of *Cryptosporidium* spp. (0.95 by 0.4 μm) are wedge shaped with a swollen apical pole and covered by a double-layered outer membrane that covers an inner membrane of the apical pole (98). Also at the apical pole is a polar ring from which microtubules extend posteriad in parallel arrangment beneath the inner and outer membranes (98). A compact nucleus fills most of the elongate body, and at midbody a large mitochondrion is adjacent to the nucleus (98).

Very young forms of the macrogamont (female stage) are indistinguishable from trophozoites. Macrogamonts are nearly spherical, contain a large single nucleus and endoplasmic reticulum, and are surrounded by a double membrane called a pellicle. Beneath the macrogamont cytoplasm is a feeder organelle (Fig. 6). Older macrogamonts, 3.2 to 5 μm in diameter (128, 285), are distinguished by a variety of granules (Fig. 6). Polysaccharide granules resemble those of some *Eimeria* spp.; dense granules appear similar to Scholtyseck's "wall-forming body type 1"; both types of granules accumulate as the macrogamont matures (285).

THE HOSTS

Infection in Fish and Snakes

Six species of *Cryptosporidium* which infect cold-blooded vertebrates have been named (Table 1). *C. ameivae*, *C. lampropeltis*, *C. ctenosauris*, and *C. crotali* are now recog-

nized as sporocysts of *Sarcocystis* spp. (280). Of the remaining two species, *C. nasorum* is the only named species for fish and *C. serpentis* is probably the only valid species for snakes.

Cryptosporidium sp. has been reported in a pet tropical marine fish, a naso tang (*Naso lituratus*), purchased in Illinois and kept in a home aquarium with mixed species (123). The naso tang was killed after a 2-month progressive illness characterized by intermittent anorexia, regurgitation of food, and passage of feces containing undigested food (123). The fish maintained its color but became emaciated. *Cryptosporidium* sp. was identified histologically in the intestinal epithelium. *Cryptosporidium* sp. has also been identified in 5 of 35 carp (*Cyprinus carpio*) from South Bohemia (203).

About 15 snakes (three genera; five species) have been reported to be infected with *Cryptosporidium* spp. (51, 253). They include the black rat snake (*Elaphe obsoleta*), trans-Pecos rat snake (*Elaphe subocularis*), corn snake (*Elaphe gutata*), Madagascar boa (*Sansinia madagascarensis*), and timber rattlesnake (*Crotalus horridus*). All acquired natural infections from unknown sources.

All snakes had clinical signs of infection. They displayed marked midbody swelling and had chronic gastric disease manifested by regurgitation of undigested food and weight loss. In addition, three had bronchopneumonia. Twelve eventually died after a protracted clinical course (51, 253).

At necropsy, 14 snakes had pale, tan, fatty livers (51). The gastric mucosa was generally edematous and thickened with exaggerated rugae and adherent copious mucus.

Histologically, organisms were found on the microvillous border of the gastric epithelium. The mucosa was hyperplastic, sometimes with areas of necrosis (see Fig. 11). Fibroplasia and collagenization of the submucosa and the lamina propria were associated with edema and an intense inflammatory response characterized by plasma cells, lymphocytes, and heterophils (51).

Snakes with clinical cryptosporidiosis were mature, unlike birds and mammals in which the young were most often affected. The clinical course in snakes has been protracted, whereas most immunocompetent mammals have usually recovered quickly.

The one attempt to treat cryptosporidiosis in a snake with gentamicin and then sulfamethazine was unsuccessful (253).

Infection in Birds

Cryptosporidium sp. has been found in avian species in Asia, Australia, Europe, and North America. It has been associated with morbidity and mortality in naturally infected chickens (77, 130), turkeys (118, 240, 254), peacocks (167), a pheasant (295), and a black-throated finch (93). Asymptomatic natural infections have been diagnosed histologically in red-lored parrots (79), chickens (88, 229), and a domestic goose (227). In Scotland, 22 of 25 chicken sera contained antibody against *Cryptosporidium* spp. (270). Experimentally, infections have been induced in chickens with oocysts from chickens (131) and in turkey poults placed in an environment contaminated by infected tom turkeys (97) and in other turkey poults and muscovy ducklings (Lindsay et al., in press). With oocysts isolated from mammals, chickens became infected in one study (262), but did not become infected in another. Failure to experimentally infect seven mammalian species with oocysts isolated from chickens strongly suggests that *Cryptosporidium* sp. from avian species is not a zoonotic threat to humans (Lindsay et al., in press).

The sites of infection are most often the intestinal and respiratory tracts. Oocysts from the bursa of Fabricius of chickens were found to infect the cloaca, bursa, terminal colon, cecum, trachea, bronchi, air sacs, salivary gland ducts, and nasal turbinates of experimentally exposed chicks (156). Associated clinical signs are variable. In diarrhetic quail and turkeys, the small intestine was infected (117, 240). In chickens without clinical signs, gut-related organs (the bursa of Fabricius and the cecae) were infected (88, 131, 229). Similarly, other infected species of parrots (cloaca) (79), domestic goose (intestine) (227), and turkeys (bursa) (118) lacked clinical signs. The species thought to be associated with the foregoing gut-related infections is *C. meleagridis*. A much more virulent species, *C. baileyi*, has been associated with avian respiratory infections (71). Depression, gurgling respiration, respiratory distress, coughing, sneezing, oculonasal discharge, bilaterally distended infraorbital sinuses, and frothy colored eyelids have been associated with respiratory and eye infections in chickens (77, 130), turkeys (118, 254), quail (258), peacocks (167), and pheasants (230, 295). Mortality has resulted from such infections but has been less common than morbidity. Postmortem observations included excess mucus in the nares, infraorbital sinuses, and trachea; swollen sinuses; opacity of the air sacs; red and gray mottling of the lungs; and necrosis of the ventral oral mucosa. Histologic alterations included hypertrophy, hyperplasia, or deciliation of the epithelium or all three and infiltration of subepithelial connective tissue with lymphocytes, plasma cells, histiocytes, and heterophils (77, 118, 130, 167, 229, 254, 258, 295).

Cryptosporidium sp. has been observed in the kidneys in a 4-month-old black-throated finch found dead at the San Diego Zoo (93). The kidneys were extremely large, pale, and firm, and in histologic sections numerous cryptosporidia were attached to intact and sloughed tubular epithelial cells.

The extent to which *Cryptosporidium* sp. acts as a primary pathogen is not clear. In some cases no significant viruses, mycoplasma, bacteria, or fungi were isolated from affected tissues (118, 167, 258, 295). Concurrent infection with adenovirus, Newcastle disease virus (serum antibody found), *Escherichia coli*, streptoccocci, *Pasteurella* spp., fungus, or ascarids was reported in other cases (77, 118, 167, 254, 295). In one case, some birds had been vaccinated with fowl cholera vaccine 8 days before an outbreak of cryptosporidiosis (118). Their response to the vaccine perhaps changed their immunocompetency.

The age range for infection by natural or experimental means is 1 to 11 weeks in chickens, turkeys, ducks, peacocks, pheasants, quail, and geese (118, 130, 167, 227, 229, 258, 295; Lindsay et al., in press). Clinical illness and ultimately death were observed throughout this age range.

Transmission by a fecal-oral route through contamination of the environment is likely. However, experimental transmission by intrasinus injection of 1-week-old turkey poults with sinus exudate from clinically affected turkeys indicates that contact with respiratory fluids may spread the disease within a flock (97).

Treatment was tried with oxytetracycline HCl at 200 ppm (200 μg/ml) in the drinking water in about 30 peacock chicks. All died despite treatment (167).

Infection in Small Mammals

Mice. Two species of murine *Cryptosporidium* have been named: *C. muris*, found only in the stomach (259, 260), and *C. parvum*, found only in the small intestine (261). Subse-

quently, *C. parvum* has been found in the cecum and colon of mice (98, 234). One unique report indicates that organisms were found also in liver, lungs, and heart of mice experimentally infected with *C. parvum* isolated from calves (204). *C. parvum* seems to lack strict host specificity and is thought to be the species transmitted to mice from cattle, deer, humans, guinea pigs, and sheep (Table 3). Of 115 wild mice trapped at calf-rearing facilities, 30% were infected with *Cryptosporidium* sp. and oocysts from these mice were infectious for seven calves, suggesting that a calf-mouse-calf cycle may exist in nature (P. H. Klesius, T. B. Haynes, and L. K. Malo, J. Am. Vet. Med. Assoc., in press).

There is wide variation in clinical illness and pathology associated with cryptosporidiosis in mice. In *C. muris* infections clinical illness was not observed; only in heavy infections were the gastric glands dilated, but without inflammatory response (261). With *C. parvum* none of 35 infected wild mice had clinical disease (Klesius et al., in press). In one study in laboratory mice, infection caused insignificant injury, with only minimal displacement of microvilli to accommodate for the individual parasites; there was no inflammatory response (261). Others (110), however, reported that white mice infected at 6 days of age and necropsied 11 days later had diffuse atrophy of villi and hyperplasia of crypts in the lower small intestine, with cuboidal to squamous epithelial metaplasia and infiltration of the lamina propria and epithelium with inflammatory cells. Similar aged nude mice littermates were equally or more affected (110). In other nude mice, beginning after 30 days of persistent infection diarrhea developed. The mice became dehydrated and lost weight, and some died. Neither white nor nude mice experimentally infected at 42 days of age developed diarrhea, and although some were infected, the infections were relatively light (110), which suggests an age-related resistance to infection. In support of this, hydrocortisone treatment augmented infection of 3- to 4-day-old mice, an effect which was lost by 7 to 8 days of age. In contrast, wild adult mice appear readily susceptible to infection and may have recurrent infections (Klesius et al., in press). Also, treatment of older mice with cyclosporin A (a drug primarily toxic for T helper cells, which may mimic the immunologic lesions seen in AIDS) increased the severity of infection.

Rats. Neonatal rats are as susceptible to infection with *Cryptosporidium* sp. as neonatal mice. They have been infected with oocysts from cattle, humans, mice, and sheep but not with oocysts from chickens (Table 3).

Rabbits. Presumed healthy adult rabbits (*Oryctolagus cuniculus*) have had natural infections with *Cryptosporidium* sp. in the jejunum and ileum (20, 235). In some, the ileum had short blunt villi with a decrease in the villus/crypt ratio, slight edema in the lamina propria, and dilation of lacteals (20). Rabbits became infected when inoculated with oocysts from cattle but not when inoculated with oocysts from guinea pigs (Table 3). Oocysts from rabbits have been implicated as the source of a human infection (Table 3).

Guinea pigs. Guinea pigs (*Cavia porcellus*) have been found naturally infected with *Cryptosporidium* sp. (284). Infection has not been associated with clinical signs, but descriptions of microscopic changes have indicated that a chronic enteritis may occur (133). Ultrastructural observations of cryptosporidia in the intestine of guinea pigs show organisms associated with follicular dome absorptive cells and M cells, both from Peyer's patches (M. A. Marcial and J. L. Madara, Gastroenterology, in press). *Cryptosporidium* sp. was identified within the cytoplasm of M cells (Marcial and Madara, in press). This is important because these cells may transport microorganisms from the lumen to the underlying intestinal immune system, where antigenic recognition takes place.

Cats. In 10 naturally infected domestic cats (*Felis catus*) in Asia (128), Europe (27, 155, 206), and North America (144; R. Fayer and J. P. Dubey, unpublished data), *Cryptosporidium* sp. was found in feces collected for parasite surveys or from pet cats of patients with cryptosporidiosis or incidentally in tissue at necropsy. Clinical illness was not noted, although feces were sometimes foul smelling and soft (144). The age range was 2 weeks to adult. Twenty of 23 cat sera tested in Scotland contained antibodies to *Cryptosporidium* sp. (270).

Cats experimentally infected with oocysts from calves (27) or cats (128) had prepatent periods of 2 to 11 days and patent periods of 2 to 25 days (27).

Dogs. Surveys of 200 domestic dogs (*Canis familiaris*) in Germany and of 57 in Finland failed to detect any *Cryptosporidium* oocysts in feces (27, 220). However, four puppies with natural infections were found in North America (90, 239, 298). They ranged in age from 1 week to 3 months. All had been clinically ill and died, and then *Cryptosporidium* was detected incidentally in the small intestine at necropsy. One puppy had distemper (27), another had toxaphene poisoning (239), and still another was from a litter of 8 that all died after a siege of dyspnea and diarrhea (298). A serologic survey from Scotland reported that 16 of 20 serum samples from dogs contained antibody against *Cryptosporidium* sp. (270).

Squirrels and raccoons. Natural infections of a young squirrel (*Sciuris carolinensis*) and a young raccoon (*Procyon lotor*) with *Cryptosporidium* sp. also have been reported (54, 252). The raccoon appeared healthy, but the squirrel was emaciated and had white nodules containing a poxlike virus on the skin.

Infection in Large Mammals

Nondomesticated ruminants. Eighty-two red deer calves up to 1 week old were caught and reared at a research station in Scotland (267). Within 4 weeks, 56 of them had diarrhea that lasted 2 to 14 days and 20 died. Oocysts were found in feces from 27 of 34 deer calves with diarrhea and from 11 of 22 healthy calves. Astroviruslike particles but no other viral or bacterial pathogens were found in feces from two diarrhetic and three healthy calves. An outbreak of cryptosporidiosis in beef calves 6 months earlier may have contaminated the premises and served as the source of infection.

At the San Diego Wild Animal Park in California, 44 ruminants less than 21 days old had diarrhea, dehydration, and emaciation (282). When their tissues were examined, *Cryptosporidium* sp. was found in the small intestine, cecum, or colon of 17; *Salmonella* sp. was found in 10 of these. Of the 17 *Cryptosporidium* sp.-infected ruminants, 10 were black buck (*Antilope cervicapra*), 2 were scimitar-horned oryx (*Oryx gazella dammah*), 2 were fringe-eared oryx (*Oryx gazella callotis*), 2 were addax (*Addax nasomaculatus*), and 1 was a sable antelope (*Hippotragus niger*).

Horses. Based on fecal or histologic examination, 13 of 82 horses without clinical signs in France (247), 0 of 23 foals without clinical signs in Colorado (243), 0 of 14 diarrhetic mares and foals in Ohio (236), and 2 of 2 diarrhetic foals in Canada (91) were infected with *Cryptosporidium* spp. Twenty of 22 horse sera obtained in Scotland had antibody to *Cryptosporidium* spp. (270).

Two Arabian foals in Australia (96) and five of six in Colorado (243) with severe combined immunodeficiency syndrome suffered severe diarrhea associated with *Cryptosporidium* sp. and died. The common bile duct, pancreatic ducts, gall bladder, stomach, small intestine, cecum, and colon all contained stages of the parasite (243). The lack of immunity is thought to influence the severity and distribution of infection.

Pigs. In Australia, four piglets dead from other causes with concurrent bacterial enteropathogens also had *Cryptosporidium* in histologic sections of small intestine (157). In South Dakota, a survey of piglets with necrotic enteritis in 81 herds showed one piglet with *Cryptosporidium* sp. (37). In Kansas, *Cryptosporidium* sp. was found in the large intestine of three pigs orally inoculated with crude colon contents from pigs with dysentery (139). In Scotland, 41 of 43 serum samples from five sources were positive for antibodies to *Cryptosporidium* sp. (270).

Age had a marked effect on the severity of infection (278). In an experiment with pure *Cryptosporidium* oocysts disinfected of other pathogens, piglets infected at 1 or 3 days of age were severely affected, whereas those infected at 7 days of age were moderately affected. Others infected at 15 days of age had no clinical signs. Four-week-old specific-pathogen-free piglets infected during weaning had no post-weaning diarrhea (263).

Pigs have been infected with oocysts from cattle, sheep, and mice as well as from other pigs (Table 3).

Although it has been stated that clinical illness attributed to cryptosporidiosis does not appear to be common in pigs (278), experimental infections show a range of clinical responses from subclinical to severe (182, 274, 278). Piglets, 1 to 3 days old, orally dosed with an unknown number of oocysts, exhibited vomiting, diarrhea, and anorexia (182, 274). Stages were found in the ileum, cecum, and colon; they were most numerous in epithelial cells lining the crypts of Lieberkuhn (139). Histopathologic changes were most notable in the posterior small intestine, where extensive mucosal damage was characterized by shortened, fused, and cross-bridged villi. There was sloughing of some tips with edema in adjacent inflamed lamina propria (182, 274). Mononuclear cells and neutrophils were the most numerous inflammatory cells in the lamina propria (139). Leukocytes in colonic crypts phagocytized cryptosporidia and caused physical disruption of the mucosa in the process (139). The tracheal and conjunctival epithelia of pigs have been infected with oocysts from human and bovine isolates, respectively (111, 263).These infections substantiate the hypothesis that *Cryptosporidium* sp. has the ability to infect extraintestinal sites because oocysts can excyst without pancreatic enzymes or bile salts as required by other coccidia (84).

Sheep. Cryptosporidiosis has been associated with morbidity and mortality in naturally infected lambs in Australia, Scotland, Germany, Idaho, and North Dakota and in an adult sheep in Belgium (4, 14, 29, 36, 80, 116, 265, 275). In Scotland, *Cryptosporidium* sp. was the major factor causing diarrhea which affected about 40% of 1,064 lambs born in 1981 (14).

Neonates are most susceptible to natural infections (4, 14, 29, 36, 80, 116, 265, 275). Experimental studies have shown that older lambs also were susceptible to infection, 30-day-old lambs were infected but had only a mild clinical response, and lambs as old as 7 months were infected but no clinical information was provided (265).

Diarrhea, the most prominent clinical sign of ovine cryptosporidiosis, lasted 2 to 12 days and was sometimes accompanied by anorexia, poor growth, stiffness, hyperpnea, slow gait, limb muscle fasciculations, and depression (14, 29, 275). Most cases were diagnosed by identification of oocysts in feces. At necropsy, blood or mucoid fluid and bright yellow watery feces have been found in the colon, and both the small and large intestine have appeared mildly hyperemic (36, 265). Histologic lesions included shortened, fused, and cross-bridged villi with low columnar or cuboidal epithithelium and congested vessels in the lamina propria with mononuclear cell and neutrophil infiltrates (14, 29, 36, 80, 265, 275).

Infrequently, concurrent *Salmonella* sp. *Clostridium perfringens*, enterotoxigenic *E. coli*, rotavirus, coronalike virus, and bovine diarrhealike virus were isolated (4, 14, 36, 80, 265, 275).

In experimental studies no differences were found in clinical manifestations, disaccharidase activity in the small intestine, or histologic lesions in lambs inoculated with *Cryptosporidium* sp. alone or together with either enterotoxigenic *E. coli* or rotavirus (275). These findings suggest that *Cryptosporidium* sp. was the primary pathogen and that coinfection did not have synergistic effects (275).

Artificial rearing conditions have been blamed for infection of 48 lambs removed from their dams immediately after birth: 40 had diarrhea attributed to cryptosporidiosis and 16 eventually died; 2 months later, 100 suckled lambs were born and housed in the same building but none had diarrhea (263). From this latter group, four orphan lambs were reared artificially, three became diarrhetic, and two of these had cryptosporidiosis. It is unclear what factors associated with artificial rearing might affect the severity of cryptosporidiosis, whether lack of colostrum or stress from handling.

Treatment with oral trimethoprim and sulfadiazine supplemented with oxytetracycline was ineffective (14), as was sulffonamide therapy (29).

Goats. Cryptosporidiosis in naturally infected goats has been reported from Australia (168, 273), Belgium (80), and Tanzania (168). It was identified histologically in the small intestine of a 2-week-old Angora goat that died with diarrhea (168) and in a 6-month-old crossbred goat from a heard of 10 suffering intermittent episodes of diarrhea (80). In a herd of 29 kids less than 3 weeks old, 21 had severe diarrhea and 3 eventually died; 11 had cryptosporidia detected in either feces or histologic sections of small intestine (269). Of those with diarrhea and *Cryptosporidium* sp. that recovered, seven relapsed shortly thereafter. Poor sanitation may have had a role in the outbreak since the premises were thought to be contaminated with large numbers of oocysts from an artifically reared kid.

Cattle. Numerous reports of individual infections, herd outbreaks, and regional surveys of cattle indicate that bovine cryptosporidiosis is distributed worldwide. It is found in a variety of dairy and beef breeds and is very prevalent in young calves often associated with diarrhea. Reports of natural infections come from Australia (29, 132), Bangladesh (228), South Africa (74, 126), Ireland (100, 210–212), Scotland (242, 270, 272), Belgium (214), Switzerland (191), Denmark (112), Germany (85, 109, 137, 248), Czechoslovakia (201, 202, 207, 208, 246, 286, 287, 305), Hungary (190), Romania (72), Israel (196), Cuba (99), Mexico (188), Canada (186), and throughout the United States including Alabama, Connecticut, Idaho, Iowa, Nebraska, North Dakota, Maryland, Minnesota, Ohio, Oklahoma, Oregon, South Dakota, and Tennessee (2, 5, 9, 11, 38, 148, 176, 182, 183, 187, 200, 222, 223, 226, 234, 237).

Prevalence of cryptosporidia in bovines varies widely.

Whereas none of 136 healthy calves in Montana were infected based on fecal examination (189), all of 25 bovine sera in Scotland had antibodies to *Cryptosporidium* sp. (270). Among groups of strictly diarrhetic calves examined in Denmark, Hungary, Canada, Germany, Ireland, and Australia, *Cryptosporidium* oocysts were detected in 16, 27, 33, 40, 44, and 68%, respectively (100, 109, 112, 132, 187). Among groups in five general farm populations in the United States, Germany (two groups), Belgium, and Czechoslovakia, oocysts were detected in 27, 51, 96, 53, and 100%, respectively (137, 148, 202, 214).

Bovine cryptosporidiosis appears to be age related. It is predominately found in calves less than 3 weeks old and mostly in those exposed between 4 and 15 days old (202, 187).

Oocysts of *Cryptosporidium* sp. isolated from calves infected virtually all mammals studied (Table 3). Conversely, sources of infection for calves can be from many mammalian species. Under farm conditions, the most likely sources appear to be other calves (66, 263), wild rodents (Klesius et al., in press), and perhaps pet dogs and cats (66). *Cryptosporidium* spp., *Clostridium perfringens*, enterotoxigenic *E. coli*, rotavirus, and coronavirus have been identified in calves with neonatal diarrhea (calf scours). In some diarrhetic calves with cryptosporidiosis one or more of the other pathogens have been identified (38, 83, 132, 210, 213, 222, 223, 237, 242). In other diarrhetic calves with cryptosporidiosis no other pathogens were found, suggesting that *Cryptosporidium* sp. was the primary pathogen (9, 29, 38, 126, 186, 272). This suggestion has generally been supported by experimental studies with disinfected oocysts as inoculum in specific-pathogen-free hosts (19, 52, 269), in effect fulfilling Koch's postulates.

Estimates of the economic impact of a single disease agent is difficult, especially when other agents produce similar effects. Such is the problem in determining dollar losses for calves with *Cryptosporidium* sp.-induced diarrhea. Based on data available from one study, the annual average loss due to cryptosporidiosis in the United States was estimated at $6.2 million (125). Recently updated and expanded data suggest that this estimate is very low.

Clinical signs, gross lesions, and histopathologic changes associated with bovine cryptosporidiosis have been reported by many investigators (5, 9, 19, 29, 38, 83, 132, 176, 182, 183, 186, 190, 200, 223, 226, 237, 242, 264, 272). They vary greatly. The most prominent sign is diarrhea, usually profuse, watery, and yellow and sometimes tinged with blood. Calves often are dehydrated and febrile. Some have rough coats and are debilitated or ataxic. A few die, but most recover spontaneously. On necropsy, the small or large intestine or both may be distended with gas and contain watery yellow fluid. Enteritis and colitis may be apparent. A variety of histopathologic changes have been reported. Most often the villi are atrophied, the ends are blunted, and adjacent villi are fused. Epithelial cells are often low columnar, cuboidal, or even squamous, and in some areas there may be focal necrosis. The lamina propria is often hypercellular and edematous, and vessels are congested. Mononuclear cell infiltration of the lamina is not uncommon. Crypts may be enlarged and contain neutrophils. In some cases the mesenteric lymph nodes have been edematous, and reticuloendothelial cell hyperplasia has been noted.

Isolates of *Cryptosporidium* sp. vary in virulence. Experimentally induced clinical cryptosporidiosis in neonatal calves with doses of 5×10^6 oocysts isolated from calves in Maryland was not always successful (83). Subsequently, utilizing a dose of 10^4 oocysts (0.2% of previous level) isolated from calves in Alabama to inoculate similar calves under similar conditions resulted in clinical illness (R. Fayer and P. H. Klesius, unpublished data).

Colostrum does not appear to provide protection against cryptosporidiosis (83, 182, 185, 277). Of 12 experimentally infected calves that received colostrum from their dams or were fed colostrum pooled from several cows, all shed oocysts and had diarrhea (182). Of 40 experimentally infected colostrum-fed calves, 31 became infected and shed oocysts (185). Of 22 calves maintained as pathogen-free, colostrum fed, or sucklings and then infected orally or by contact with cryptosporidia, no significant differences were found in the clinical course of disease or in the pathologic findings among any of the calves (277). Among 17 experimentally infected calves, no discernible differences were found between 9 colostrum-fed or colostrum-deprived calves (83).

Attempts to prophylactically or therapeutically treat bovine cryptosporidiosis have been unsuccessful (29, 176, 185, 226). The only drug that prevented infection was the ionophore lasalocid (185). However, it appeared to cause toxicity at effective levels and was ineffective at lower levels (see "Treatment and Control").

Infection in Nonhuman Primates

Cryptosporidiosis in nonhuman primates has rarely been reported (61, 146, 297) and, then, always in macaques: *Macaca mulatta* (61, 146, 297), *M. radiata* (297), and *M. fascicularis* (297). Levine named the species found in rhesus monkeys *C. rhesi* (151) but that species is probably *C. parvum*, which is found in virtually all mammals. Most were infants (297) or juveniles (146, 297) housed in primate centers, and all had diarrhea. During the course of a 9-month outbreak at a primate research center 67 infants with diarrhea all shed oocysts for periods of 3 to 66 days, but no deaths resulted.

Infection in Humans

History. In humans, *Cryptosporidium* infection has been described only within the past decade. In the early 1980s the onset of AIDS in the United States brought attention to the association of *Cryptosporidium* sp. with diarrheal illness when 21 patients with AIDS and cryptosporidiosis were reported to the Centers for Disease Control (22). Prior to this late 1982 report, only 11 cases, including four in immunologically healthy persons, had been noted in the world literature (10, 21, 28, 87, 147, 175, 195, 249, 268, 291, 292), and a 1980 World Health Organization report on parasite-related diarrheas (302) did not include *Cryptosporidium* spp. Now, more than 110 patients with AIDS and cryptosporidiosis have been reported to the Centers for Disease Control (24), and at least 119 case reports (see Table 5 for references), 36 large-scale surveys (see Table 4 for references), and 22 reviews (3, 7, 13, 40, 42, 56, 58, 59, 66, 75, 81, 115, 141, 142, 160, 161, 192, 193, 198, 263, 264; J. A. Moore, B. L. Blagburn, and D. S. Lindsay, Compend. Contin. Educ. Pract. Vet., in press) have been published. These present a much clearer picture of the epidemiology, clinical features, and pathology of human *Cryptosporidium* infection.

Geographic distribution and prevalence. Human infection with *Cryptosporidium* sp. has been described on six continents, in developed and less developed countries, and in

TABLE 4. Human cryptosporidiosis: geographic surveys based on fecal examination or IFA serology[a]

Geographic location	Population examined (dates)	Principals (no. positive for Crypto/ no. examined)	Controls (no. positive for Crypto/ no. examined)	Other pathogens (no. positive/no. examined with Crypto)[b]	Reference
Africa					
Liberia	Children with diarrhea (no dates given)	22/278[c] (7.9%)	ND	ND	119
	Children with diarrhea (1/83–4/83)	20/237 (8.4%)	6/102 children without diarrhea (5.9%)	ND	120
Rwanda	Patients with diarrhea (10/83–1/84)	23/293[d] (7.8%)	0/94 with formed stools	5/293	47
	Children with diarrhea +/− measles (3/84–4/84)	2/48 without measles; 6/24 with measles[e] (11.1%)	1/55 without diarrhea +/− measles (1.8%)	ND	76
Asia					
Bangladesh	Patients with diarrhea (1/84–5/84)	25/578 (4.3%)	ND	5/25	238
	Dairy farm attendants and family members with diarrhea (12/82–11/83)[f]	7/88 attendants (7.9%) 7/77 family members (9.1%)	0/155 family members without diarrhea	ND	228
India	Children <3 yr of age with diarrhea <3 days (8/83–2/85)	89/682 (13.1%)	41/418 children without gastrointestinal or infectious disease (9.8%)	39/76*	170
Thailand	Children with diarrhea (1/85–6/85)	13/410 (3.2%)	1/410 without diarrhea (age matched) (0.2%)	6/13	255
Australia					
Adelaide	Specimens submitted to laboratory (mostly from adults) (1981–1984)	11/9,056[g] (0.12%)	ND	ND	159
Alice Springs	Children with diarrhea (7/84-unspecified)	9/94 (9.6%)	ND	ND	159
Melbourne	Patients hospitalized with gastroenteritis (2/81–6/82)	36/884[h] (4.1%)	0/320 without gastroenteritis	5/26*	276
New Zealand					
Auckland	Children with diarrhea (12/84–3/85)	8/36 (22%)	ND	ND	257
Europe					
Denmark	Patients with gastrointestinal symptoms (Spring, 1983)	16/800 (2%)	0/120 without gastrointestinal symptoms	1/16	122
Finland	Specimens from different patients submitted to parasitology laboratory (12/82–3/83)	14/154[i] (9.1%)	ND	3/14	135
	Continuation (3/83–4/84)	119/4,545 (2.6%)	ND	ND	136
	Travellers to Leningrad (unspecified)	0/34 before trip; 9/34 after trip (26.5%)	0/17 nontravellers	2/9*	134
France					
Tours	Children hospitalized with diarrhea (4/84–3/85)	4/190 (2.1%)	0/37	2/4*	26
Spain					
Barcelona	Patients with gastroenteritis	25/107[j] (23%)	2/103 without gastrointestinal symptoms	ND	225
Madrid	Specimens submitted to laboratory (unspecified)	3/339[k] (0.9%)	ND	ND	158

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urban and rural areas (Table 4). Large-scale surveys have generally examined stool specimens from selective populations such as adults or children with diarrhea or other gastrointestinal complaints who seek medical attention or are hospitalized or from stool specimens simply submitted to a particular diagnostic laboratory. In Europe, prevalence was most often between 1 and 2% of those screened. In North America, non-outbreak-associated prevalence rates

TABLE 4—*Continued*

Geographic location	Population examined (dates)	Principals (no. positive for Crypto/ no. examined)	Controls (no. positive for Crypto/ no. examined)	Other pathogens (no. positive/no. examined with Crypto)[b]	Reference
United Kingdom					
England					
Blackburn	Specimens submitted to laboratory (4/84–9/84)	24/2,174[l] (1.1%)	ND	ND	303
Bristol	Patients with diarrhea (10/83–1/84)	43/867 (5%)	ND	ND	127
Liverpool	Children with gastroenteritis (6/83–4/84)	27/1,967 (1.4%)	ND	1/27*	107
	Continuation (unspecified)	72/5,242 (1.4%)	ND	6/72*	105
London	Children hospitalized with diarrhea (9/83–2/84)	7/213 (3.2%)	1/112 without diarrhea (0.9%)	2/7*	129
Sussex	Specimens submitted to laboratory (unspecified)	14/800[m] (1.8%)	ND	ND	194
Yorkshire	Specimens (diarrheal) submitted to laboratory (8/84–9/84)	12/166 (7.2%)	ND	ND	304
Wales	Patients with diarrhea (5/83–8/83)	7/500 (1.4%)	ND	0/7*	57
	Continuation (unspecified)	25/1,500 (1.6%)	ND	ND	55
Central and South America					
Brazil	Patients with diarrhea (5/78–10/80)	9/117 (8%)	0/22 without diarrhea	6/9*	290
Chile	Children hospitalized with diarrhea (unspecified)	4/100 (4%)	ND	ND	293
Costa Rica	Children with diarrhea (1/82–12/82)	12/278[n] (4.3%)	0/90 without diarrhea	3/12*	169
Venezuela	Children <3 yr with diarrhea (3–4/83 and 5–9/84)	13/120 (10.8%)	ND	ND	215
North America					
Canada					
British Columbia	Patients with diarrhea (10/83–10/84)	46/7,300 (0.63%)	ND	ND	181
Newfoundland	Specimens from different patients submitted to laboratory (5/84–11/84)	19/1,621 (1.2%)	ND	4/19*	231
United States					
California	Day-care center attendees[o] (9/84)	7/11 (63.6%)	ND	0/6*	23
Georgia	Day-care center attendees[o] and staff (2/84; 8/84)	12/90 (13.3%)	ND	ND	23
Massachusetts	Specimens from different patients submitted to parasitology laboratory (2/83–1/84)	47/1,703 patients (2.8%)	ND	15/43[p]	301
Michigan	Specimens submitted to laboratory (3/84–2/85)	63/1,752[q] (3.6%)	ND	ND	48
Michigan	Day-care center attendees[o] (9/84)	22/39 (56.4%)	ND	2/21*	23
New Mexico	Day-care center attendees[o] (9/84)	12/31 (38.7%)	ND	3/31	23
Pennsylvania[1]	Medical personnel caring for patient with cryptosporidiosis (6/82–8/82)	8/26 (30.7%)	3/18 not exposed to patient (16.7%)	ND	143
Pennsylvania	Day-care center attendees[o] (6/84)	14/45 (31.1%)	ND	0/45*[r]	1

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ranged from 0.6 to 4.3%. In contrast, prevalence rates in Asia, Australia, Africa, and Central and South America generally began at 3 to 4% (238, 255, 276) and reached 10 to 20% (76, 159, 170, 215, 257). Prevalence in control groups for these areas was 2.8% (43 of 1,564), with 41 positive from a single study (170). These surveys suggest that *Cryptosporidium* sp. is associated with diarrhea in all areas of the world but is most prevalent in the less developed regions. In many

TABLE 4—*Continued*

Geographic location	Population examined (dates)	Principals (no. positive for Crypto/ no. examined)	Controls (no. positive for Crypto/ no. examined)	Other pathogens (no. positive/no. examined with Crypto)[b]	Reference
S. Carolina	Specimens from different patients submitted to parasitology laboratory (1/84–12/84)	25/582 (4.3%)	ND	1/25	121
Texas	Persons with common water supply[o] (7/84)	47/79 (59.5%)	12/194 outpatients with gastroenteritis not sharing water supply (6.2%)	6/23	73
Texas	Day-care center attendees (8/84)	18/50 (36.0%)	ND	6/18*	256
Texas	Specimens from children submitted to laboratory (7/83–10/83)	5/553 (0.9%)	ND	0/5	296

[a] All surveys were based on fecal examination except for one in Pennsylvania, which was based on IFA serology and is marked with superscript 1. ND, Not done.
[b] Examinations were performed in all cases for bacterial enteropathogens and intestinal parasites. Those which also included examination for at least one viral enteropathogen are marked with an asterisk.
[c] 15/154 (9.7%) from urban slum areas and 7/124 (5.6%) from rural villages.
[d] 20/193 (10.4%) children and 3/100 (3.0%) adults.
[e] The association with measles is statistically significant ($P < 0.05$).
[f] 14% of 208 calves with diarrhea and 1% of 202 age-matched other calves had *Cryptosporidium* sp. on fecal examination.
[g] Eleven positives represent 10 patients.
[h] 33/697 (4.7%) children and 3/187 (1.6%) adults ($P < 0.05$).
[i] Of specimens from 1,422 patients submitted and concentrated, 154 were stained and examined for *Cryptosporidium* spp.; 14/1,422 positive gives only 0.98% prevalence (82).
[j] 18/22 children in a day-care center and 7/85 hospitalized others had *Cryptosporidium* sp.
[k] Three positives represent 2 patients (brothers); 90 specimens (2 positive) were diarrheal while 249 (1 positive) were not.
[l] No difference in urban or rural locations; 14/153 (0.9%) individuals were from hospital populations and 10/651 (1.5%) individuals were from general practices.
[m] Fourteen positives represent 10 patients.
[n] 4/95 (4.2%) from rural areas and 8/183 (4.4%) from urban environments.
[o] Outbreak associated.
[p] Only 23 cultured for bacteria.
[q] Sixty-three positives represent 53 patients.
[r] Number examined for viruses not specified.

areas, *Cryptosporidium* sp. is among the top three or four enteric pathogens identified (47, 107, 122, 127, 181, 231, 256, 290, 303, 304). In addition to geographic variability, there appear to be seasonal differences in *Cryptosporidium* infection, with more infections ocurring in warmer or more humid months (48, 170, 181, 228, 238, 276, 301).

Age and sex distribution. Age range for *Cryptosporidium* infection is from 3 days old (a vaginal delivery of a mother with cryptosporidiosis) (48) to 95 years of age (122). Children may be most susceptible (1, 23, 57, 105, 127, 181, 231, 276, 301, 304), and those <2 years old may have the greatest prevalence (119, 170, 238, 256). Infections were not found in breast-fed children in two studies (169, 290), whereas a third study found that breast feeding was not a statistically significant variable (170). Based on large-scale surveys reporting sex distribution, males and females appear to be equally susceptible (M = 149; F = 160) (47, 57, 107, 122, 127, 129, 135, 136, 169, 290, 301).

Clinical features. Clinical features are summarized from large-scale surveys and from case reports of immunocompetent patients, those with AIDS or the AIDS-related complex, and those with other causes of immunosuppression such as immunoglobulin deficiencies and exogenous immunosuppression (Table 5). Diarrhea is the sine qua non of symptomatic infection, although this was the symptom leading to diagnosis of *Cryptosporidium* sp. in most individual cases. Characteristically, the diarrhea is profuse and watery, with as many as 71 stools per day and up to 17 liters/day reported (12, 22). While comparative quantitative studies are lacking, diarrhea appears to be more copious in immunocompromised persons than in immunocompetent individuals. It sometimes contains mucus but rarely blood or leukocytes. Significant weight loss may result. Crampy abdominal pain, nausea, vomiting, and low-grade (<39°C) fever are less frequent symptoms. Occasionally there are nonspecific symptoms such as anorexia, malaise, myalgia, weakness, and headache (10, 43, 73, 76, 281, 301). Symptoms may wax and wane in any patient and severity of symptoms may correlate with intensity of oocyst shedding (45, 57, 76, 107, 121, 231).

Duration of symptoms and outcome typically vary according to the immunologic health of the host. In the AIDS/AIDS-related complex group, infections of long duration followed by death are most frequent, although spontaneous clinical recovery has been reported (41, 150, 171) and treatment may modify symptoms (see "Treatment and Control").

Patients with reversible immune deficiencies usually recover when the cause of immunosuppression is removed. One child with leukemia on immunosuppressive therapy had two episodes of diarrhea and cryptosporidiosis associated with active infection in a pet cat (155); both episodes resolved when immunosuppressive therapy was withdrawn. Another child, with leukemia, however, had disappearance of clinical symptoms and fecal oocysts despite continuation of anticancer chemotherapy (199). Patients at either end of the age spectrum or with nutritional deficiencies may respond like patients with immune deficiencies (47, 231, 238); diarrhea and respiratory infection attributed to *Cryptosporidium* sp. have been associated with the acute phase

TABLE 5. Clinical features of human cryptosporidiosis compiled from case reports and geographic surveys

Clinical features	No. of infected persons			
	Case reports			Surveys (no. with symptom/no. of reports of symptom) (n = 586)[d]
	Immunodeficient patients		Immunocompetent patients (n = 35)[c]	
	AIDS/ARC (n = 67)[a]	Others (n = 17)[b]		
Symptom				
Diarrhea	63	16	31	501/547 (92%)
Abdominal pain	24	6	14	104/231 (45%)
Nausea/vomiting	18	4	11	204/403 (51%)
Fever (<39°C)	26	3	11	110/309 (36%)
No symptoms	4	1	4	31
Duration of symptoms (days)				
<3	0	0	5	NR[e]
4–10	2	1	13	NR
11–20	0	1	9	NR
21–30	1	0	4	NR
>30	52	12	0	NR
Unknown	12	3	4	NR
Outcome				
Recovery	12	8	34	NR
Nonrecovery[f]	3	1	0	NR
Death	31	5	0	NR
Unknown	21	3	1	NR

[a] These 67 patients were described in 31 references: 12, 35, 41, 46, 49, 60, 62, 64, 70, 89, 102, 104, 144, 149, 164, 171, 179, 180, 197, 216, 217, 218, 224, 244, 283, 289, 291, 294, 299, 306, 307. ARC, AIDS-related complex.

[b] These 17 patients were described in 16 references: 21, 25, 63, 70, 87, 145, 147, 155, 166, 171, 175, 178, 224, 241, 249, 292.

[c] These 35 patients were described in 15 references: 10, 28, 31, 44, 63, 70, 162, 171, 173, 195, 234, 245, 251, 268, 281.

[d] These 586 patients were the total about whom any symptom was reported in the large-scale surveys; all references listed in Table 4 were included here except 48, 136, 159.

[e] NR, Not reported.

[f] Nonrecovery means persistent clinical symptoms or oocyst excretion or both.

of measles, a time of transient immune suppression (76, 103).

Immunologically healthy persons normally have shorter duration of symptoms (<20 days) and spontaneous complete recovery. Increasing numbers of asymptomatic individuals are now being identified in surveys (23, 73, 121, 122, 129, 158, 194, 256, 301). Oocysts have been found more than a week after cessation of diarrhea in some immunocompetent patients (47, 107, 119, 231). In one study, patients excreted oocysts twice as long, on an average, as they had diarrhea (30). This may be important in transmission (see below). There has been no documented recurrent infection in an immunologically healthy host.

There are no characteristic laboratory findings other than organisms in intestinal biopsy sections or oocysts in feces. Identification of oocysts in stool samples has replaced intestinal biopsy as the preferred diagnostic technique (see "Diagnosis" section). Eosinophilia has been reported by some (25, 107, 147, 195, 217, 241), and abnormal tests of malabsorption have been reported by others (12, 26, 62, 95, 171, 180, 216, 241, 244, 249, 291, 292, 294). Radiographic findings have been nonspecific, including prominent mucosal folds, air-fluid levels, distended loops of intestine, and disordered motility (28, 39, 43, 195).

Pathological features. Early experience with intestinal biopsy and continuing autopsy experience have helped to identify the site of *Cryptosporidium* infection in the human body. It is usually found in the intestinal tract, particularly attached to the surface epithelial cells of villi and crypts of the small intestine (12, 21, 87, 175, 244); however, organisms have also been found in the stomach, appendix, colon, and rectum (35, 101, 102, 147, 161, 175, 195, 217, 249, 291, 292). The gall bladder and pancreatic duct have also been parasitized (46, 102, 145, 218). Recently several reports (49, 89, 145, 164, 166, 179) have described *Cryptosporidium* sp. associated with the pulmonary tree, although not as clearly attached to cells as in the intestinal tract. Histologic changes in the intestinal tract include blunting and loss of villi, lengthening of crypts, infiltration of the lamina propria with lymphocytes, polymorphonuclear leukocytes, and plasma cells (12, 62, 175, 292).

By strict definition, Koch's postulates have not been fulfilled for cryptosporidiosis in humans, and some doubt remains as to whether *Cryptosporidium* sp. is an agent of clinical disease or simply a commensal which occasionally causes clinical illness perhaps in conjunction with superimposed pathology or other organisms. Empiric evidence, however, suggests that *Cryptosporidium* sp. is an agent of diarrhea: clustering of cases in families (63, 121, 129, 145, 155, 158, 171, 178, 228, 245, 268, 290, 301), in day-care centers (1, 23, 127, 256, 301), and in close personal contacts of infected individuals such as medical personnel (31, 47, 57, 107, 122, 143, 181, 276) all point to person-to-person transmission of a single agent. Infection of persons exposed to infected animals suggests animal-to-person transmission of a single agent (10, 44, 69, 70, 144, 155, 228, 234). Finally, presumed common source outbreaks in groups (73, 134, 135, 162, 245) also suggest exposure to a single agent.

Although it is difficult to exclude simultaneous presence of other enteropathogens, case reports show that the number of stool specimens which contained other bacterial or parasitic pathogens was less than one-third of those examined (Table

TABLE 6. Concurrent human infections with *Cryptosporidium* sp. and other enteric pathogens (from case reports)

Pathogen	Infected persons			References
	No. positive	Total examined	% Positive	
Viruses[a]	12	26	46	10, 12, 46, 89, 95, 144, 155, 171, 178, 199, 216, 218, 244, 268, 281, 291, 292
Bacteria[b]	10	54	19	10, 12, 31, 35, 41, 43, 46, 49, 60, 62, 63, 144, 145, 147, 149, 155, 164, 166, 173, 175, 178, 195, 199, 216, 217, 224, 244, 245, 249, 251, 268, 281, 283, 291, 292, 299
Fungi[c]	32	33	97	12, 31, 35, 41, 46, 49, 60, 62, 64, 89, 164, 175, 180, 216, 218, 224, 244, 292, 294, 299
Protozoa[d]	12	43	28	35, 41, 43, 46, 62, 63, 145, 147, 164, 166, 175, 178, 179, 195, 218, 224, 244, 249, 283, 291, 292, 306, 307
Clostridium difficile toxin	0	8	0	43, 46, 63, 144, 178, 199, 216, 244

[a] Does not include elevated serologic titers only; the 12 positives were all cytomegalovirus plus 1 with adenovirus as well.
[b] Not all case reports specified what bacteriologic tests were done. The positive cases include one potentially pathogenic *E. coli*, seven *Salmonella* or *Shigella* sp., one *Campylobacter* sp., and one *Staphylococcus aureus*. None of 11 other specimens specifically mentioned as examined for *Campylobacter* or *Yersinia* sp. was positive.
[c] All positive cases were *Candida albicans* primarily from AIDS patients.
[d] The positive cases include eight *G. lamblia*, four *Entamoeba histolytica*, and one *Isospora belli*.

6). *Candida albicans* was found (mostly in AIDS patients) in all cases examined for yeasts. Fewer specimens were examined for viruses or *Clostridium difficile* toxin (Table 6). Survey reports show that, of 846 specimens examined, another potential pathogen was found in only 123 (15%), and these included virtually the entire spectrum of enteropathogens (from references in Table 4). In one study in Bangkok, polymicrobial infections were not found more frequently with *Cryptosporidium* than with other gastrointestinal pathogens (255). Although some have suggested that a significant association exists between *Giardia lamblia* and *Cryptosporidium* (136, 300), others have disagreed (121, 174), and such a synergistic association is not supported by the composite survey studies (from references in Table 4).

The mechanism by which *Cryptosporidium* causes disease in humans is unknown. The voluminous watery diarrhea is reminiscent of cholera and a toxin-mediated process is possible, although cytophathic changes in cell lines sensitive to toxins have not been demonstrated (58). It is unclear whether cryptosporidiosis is a primary infection or whether in some instances it is a reactivation of an earlier infection or an asymptomatic carrier state (164).

Transmission. Potential sources of infection are summarized in Table 7. Pets and farm animals may be important sources, although such zoonotic infections have been rarely reported (144, 155, 228). Laboratory and research animals have been implicated in several instances (10, 44, 69, 70, 234).

Many infected persons had recently travelled extensively, and outbreaks have been reported among several groups of travellers (134, 135, 162, 245). In one group of infected travellers to the Caribbean, a statistically significant association with consumption of tap water was noted (162). Infected households in a neighborhood in San Antonio, Tex., were served by a common, presumed contaminated, water supply (73). Such common-source waterborne outbreaks may result when *Cryptosporidium* oocysts escape filtration and are not susceptible to routinely used disinfectants (18, 52, 106, 205). Though undocumented, the use of contaminated water in food preparation could contribute to transmission of *Cryptosporidium* spp., as could consumption of improperly pasteurized milk.

Contact with other infected persons, particularly members of the same household, health care providers, or attendees at

TABLE 7. Putative sources of human cryptosporidiosis compiled from case reports and geographic surveys[a]

Putative source(s)[a]	No. of infected persons			References
	Case reports		Surveys	
	Immunodeficient (n = 25)[b]	Immunocompetent (n = 33)[b]		
Pet cats or dogs[c]	7	8	38	43, 60, 107, 127, 135, 143, 145, 155, 178, 195, 217, 244, 245
Farm animals (cattle or horses)[c]	3	7	66	28, 43, 60, 122, 127, 136, 162, 171, 173, 175, 181, 195, 228, 281, 303, 304
Laboratory animals (infected)	0	13	0	10, 44, 70, 234
Water supply	0	3	47	43, 73, 162, 173, 195
Association with presumed infected persons	5	9	102	31, 47, 57, 63, 107, 121, 122, 127, 143, 145, 155, 171, 173, 178, 194, 245, 268, 276, 289, 290, 296, 301–304
Attendance at day-care centers	0	0	89	1, 23, 26, 127, 256, 296, 301
Following international travel	11	12	64	121, 122, 129, 135, 136, 162, 171, 244, 245, 251, 276, 291, 303, 304

[a] An individual was included in each category which was a reported potential source.
[b] Total number of patients for which a potential source was suggested.
[c] Actual infection was demonstrated in only a few instances (144, 155, 228).

the same day-care center seem to be other common sources (1, 23, 31, 63, 105, 121, 127, 129, 143, 145, 155, 158, 171, 178, 228, 245, 256, 268, 290, 301). Important reservoirs of infection may be persons with persistent oocyst excretion after resolution of clinical symptoms or asymptomatic carriers (47, 107, 119, 121, 170, 231, 256). The relatively small number of infected individuals, other than the immunocompromised, who seek medical attention or require hospitalization suggests that more asymptomatic or barely symptomatic individuals may exist than realized (23, 63, 162, 245, 268). But overall, relatively few persons in survey control groups (Table 4) have been identified as oocyst excretors.

The interval from exposure to clinical illness or infection ranged from 5 to 21 days based on known contact with an infected laboratory animal or human patient or on arrival at a foreign destination (10, 31, 44, 63, 134, 162, 234, 251). The infective dose may be small and has been calculated at <1,000 oocysts by one investigator (107).

Immune response. Immunoglobulin M (IgM) and IgG responses have been found in immunocompetent and immunocompromised patients by immunofluorescent assay (IFA) or enzyme-linked immunosorbent assay (44, 143, 245, 251, 270, 279). It is not known if these confer protection. Immunologically healthy patients showed early rise and fall of IgM and later elevation (within 6 weeks) of IgG; IgG response may disappear within a few months postinfection or may persist, perhaps signifying continuous exposure or an undetected infection (53, 279). Some AIDS patients produced IgM and all produced IgG, which remained elevated throughout the course of illness (279). In one study with the Western blot technique, serum from 93% of patients with cryptosporidiosis reacted with a single 23,000-dalton *Cryptosporidium* oocyst antigen separated by polyacrylamide gel electrophoresis (278a).

DIAGNOSIS

Diagnosis of human infection was initially based on identification of developmental stages in biopsy sections, usually from the small intestine and occasionally from the rectum (21, 147, 175, 195, 249, 291, 292). Stages are recognized by size and location: they vary from 2 to 5 μm in diameter, are located individually or in clusters on epithelial surfaces of the gastrointestinal and respiratory tracts, and appear as spherical projections into the lumen (Fig. 8 to 10). Special tissue strains have not facilitated identification more than the standard hematoxylin and eosin strain in which *Cryptosporidium* sp. appears basophilic. Drawbacks to diagnosis by biopsy include invasiveness, restricted sampling which may miss an affected area, necessity for immediate careful specimen processing to avoid autolysis, or removal of the organisms from the surface membrane (161); touch preparations may help to minimize the latter problem. Electron microscopy allows resolution of cellular detail and was initially often necessary for confirmation (78, 147, 149, 175, 195, 249, 292).

Noninvasive diagnosis was first reported in 1978 for calves (223) and in 1980 for humans (268) when oocysts were detected in fecal smears stained with Giemsa stain. Subsequently, numerous techniques to concentrate stool specimens and to stain oocysts have been applied to the detection of *Cryptosporidium* spp., but there is little consensus on which methods are most satisfactory.

Concentration of stool specimens is important in nonacute illness with small numbers of oocysts (122), in evaluation of household or other contacts of infected individuals, and in epidemiologic surveys. Diarrheal stool specimens usually contain enough oocysts to be readily identified despite fluctuations in the number of organisms (92, 289) and intermittent shedding (2, 45). Stool concentration techniques include flotation in Sheather sucrose solution, in zinc sulfate (33% to saturated), or in sodium chloride (36% to saturated) or sedimentation with Formalin ether (modified Ritchie) or Formalin ethyl acetate. One comparison of four techniques found no appreciable difference among methods (6), while another found Formalin ether to be the most sensitive for sedimentation and sodium chloride the most sensitive for flotation (56); others have found Sheather sucrose as or more effective than Formalin ether or Formalin ethyl acetate (161, 174, 308). Sheather solution allows immediate recognition of pink-tinged oocysts by using high-power magnification, but oocysts begin to disrupt and lose their characteristic spherical shape after as little as 15 min (161, 174, 308); furthermore, they may not adhere to glass slides for permanent record and staining may be altered. Other concentration techniques require subsequent staining for identification. A modification of Formalin ethyl acetate concentration, using a disposable parasite concentrator, offers the advantages of shorter processing time and less chance of direct contact with fecal specimens (308). Phase-contrast or interference-contrast microscopy of concentrated specimens may facilitate identification compared with bright-field microscopy (92, 108) but are not always available (Fig. 13).

A large number of staining techniques have been used to detect *Cryptosporidium* oocysts. The most widely used have been the modified acid-fast procedures, which differentiate red-stained oocysts from similarly sized and shaped green-stained yeast forms (113) (Fig. 12). Further modifications have utilized dimethyl sulfoxide-carbol fuchsin (50, 55, 92, 163, 221). Oocyst internal structures, particularly sporozoites, have been clearly delineated in some preparations (56, 161). One investigator has reported finding two types of oocysts with smooth or granular walls, which stain pink and red, respectively (161); other investigators suggest that there is variability in uptake and retention of the red carbol fuchsin stain by oocysts (33, 56, 194) and that acid-fast properties may be lost with time (33).

Other staining procedures for detecting *Cryptosporidium* include the following: (i) Giemsa, which does not differentiate oocysts from yeasts but which is almost as good as the acid-fast strains in showing morphologic detail and small numbers of organisms (92); (ii) safranin-methylene blue (malachite green), which compares well with modified acid-fast techniques (30, 31, 138); (iii) methanamine silver, which stains yeasts black while oocysts remain unstained (15); (iv) nigrosin, which is also a negative stain (32, 219); (v) periodic acid-Schiff (92, 124); (vi) trichrome (92, 94); (vii) methylene blue-eosin, which stains yeasts darker than oocysts (65); (viii) Gram stain, which stains yeasts purple and oocysts pale red, if at all (65, 94); and (ix) analine-carbol-methyl violet followed by tartrazine, which stains oocysts but not yeasts (177). These stains are best visualized by using the high dry or oil immersion objective of a bright-field light microscope.

Flourescent stains also have been used to detect *Cryptosporidium* spp. These include acridine orange, which causes fluorescence in both oocysts and yeast forms (163); auramine-rhodamine, which stains only oocysts but not always uniformly (92, 163, 209); and auramine-carbol fuchsin, which also distinguishes between yeasts and *Cryptosporidium* spp. (55) and which was significantly better than modified acid-fast staining in one report (56). Fluorescent staining does not allow visualization of detail of the

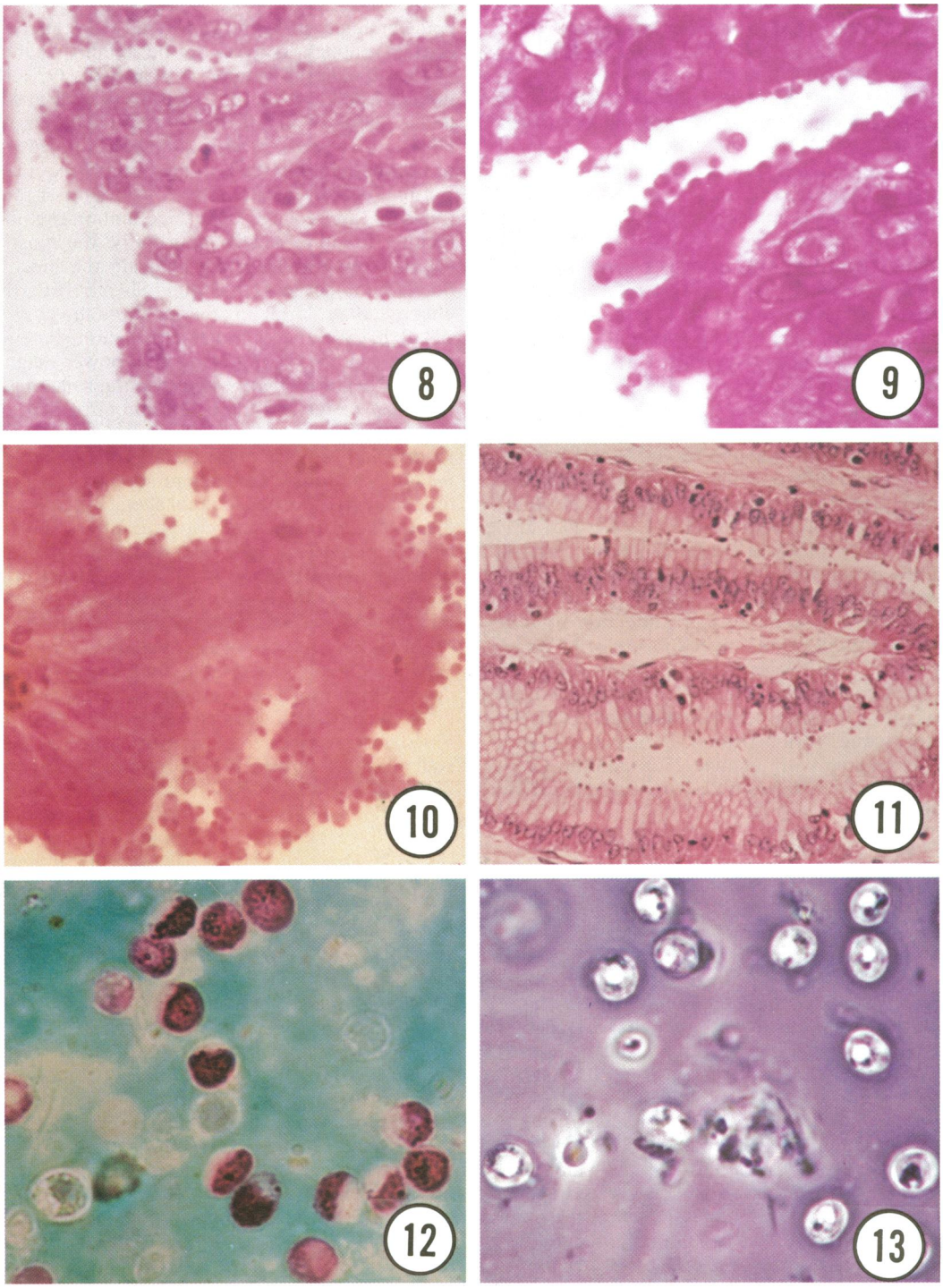

FIG. 8. Bright-field photomicrograph of mouse intestines infected with *Cryptosporidium* sp. Round organisms are on the epithelial surface. Epithelial cells are cuboidal to squamous; bridging of villi is apparent. Hematoxylin and eosin stain. Magnification, ×400. (Courtesy of D. S. Lindsay, Auburn University.)

FIG. 9. Bright-field micrograph of human gallbladder infected with *Cryptosporidium* sp. Round organisms are on the epithelial surface. Epithelial cells are squamous; mucosa is hypercellular. Hematoxylin and eosin stain. Magnification, ×500.

FIG. 10. Bright-field photomicrograph of chicken trachea infected with *Cryptosporidium* sp. Round organisms are on the epithelial surface. Hematoxylin and eosin stain. Magnification, ×400. (Courtesy of D. S. Lindsay, Auburn University.)

FIG. 11. Bright-field photomicrograph of snake stomach infected with *Cryptosporidium* sp. Dark round organisms are on the epithelial surface. The mucosa is hyperplastic. Hematoxylin and eosin stain. Magnification, ×125. (Courtesy of R. Montali, National Zoological park, Washington, D.C.)

FIG. 12. Bright-field photomicrograph of oocysts (red). Yeast cells and some oocysts appear green. Acid-fast strain. Magnification, ×1,400.

FIG. 13. Phase-contrast photomicrograph of oocysts (white) suspended in Sheather sugar solution. A budding yeast cell in the upper right side of the micrograph appears light brown and is surrounded by a halo. Magnification, ×1,400.

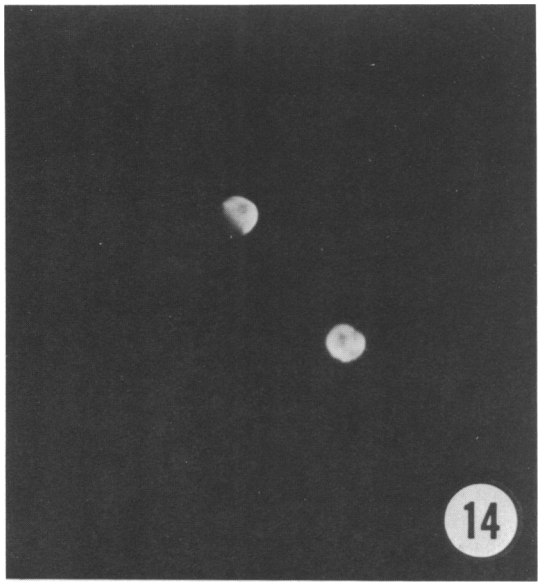

FIG. 14. Fluorescence microscopy of auramine-stained oocysts. Magnification, ×1,000. (Courtesy of C. S. Weikel, University of Virginia.)

oocyst, and confirmatory staining may be necessary (Fig. 14) (55).

Stool specimens may be preserved in 2.5% potassium dichromate, in 10% Formalin, or in polyvinyl alcohol. Laboratory procedures may require modification depending on preservative used: for example, specialized treatment of polyvinyl alcohol-preserved specimens before acid-fast staining (92).

At least three studies have compared techniques for diagnosing *Cryptosporidium* sp. by stool examination. One study, which compared six staining procedures, recommended a three-step examination: iodine wet-amount preliminary examination, Sheather sucrose flotation to concentrate oocysts, and modified acid-fast staining for confirmation (163). Another study compared 15 different methods and recommended modified acid-fast staining on concentrated stool specimens preserved in 10% Formalin and treated with 10% potassium hydroxide as most effective (92). A final study compared five staining procedures and also found modified acid-fast staining to be most effective (94).

Direct immunoflourescent assays on stool preparations have been used in the laboratory setting (161, 250) but not for large-scale clinical diagnosis. A fluorescein-labeled IgG1 monoclonal antibody to oocyst wall material has also been used for detection of oocysts in water (C. E. Musiel, M. J. Arrowood, C. E. Sterling, and C. P. Gerba, submitted for publication).

Modified acid-fast staining procedures have been applied to other body fluids such as duodenal aspirates, bile, sputum, or bronchial washings (49, 89, 145, 164, 166). Auramine staining of sputum has caused fluorescence of *Cryptosporidium* spp. (179).

Humoral antibodies to *Cryptosporidium* sp. have been detected by IFA and enzyme-linked immunosorbent assay techniques (44, 52, 56, 251, 270, 279). Specific anti-*Cryptosporidium* IgM or IgG or both were detected by enzyme-linked immunosorbent assay in 95% of patients with cryptosporidiosis at time of medical presentation and in 100% within 2 weeks (279). An IFA-IgG technique for presumptive diagnosis of *Cryptosporidium* sp. has been used in two large clusterings of cases (73, 143). In serologic surveys more than 50% of persons not known to be infected may demonstrate specific anti-*Cryptosporidium* IgG, suggesting that infection sometime in life is common (143, 270, 279). Findings are similar in many other animal species (270). Use of these techniques has so far been limited to a few centers.

EXPERIMENTAL

Animal Models

Experimentally induced infections and disease have been studied in chickens (131, 266; Lindsay et al., in press), ducklings (Lindsay et al., in press), turkeys (Lindsay et al, in press), guinea pigs (17, 266, 284), mice (17, 70, 98, 109, 110, 204, 234, 260, 261, 265–268, 271; Klesius et al, in press), rats (70, 109, 234, 259, 265, 266, 268, 269), rabbits (109), cats (27, 70, 128), dogs (27, 70), pigs (111, 139, 182, 184, 274, 278), sheep (4, 19, 109, 265, 266, 269, 275), goats (70, 109), and cattle (70, 83, 182, 185, 266, 277; Klesius et al, in press). The intent and outcome of most of these studies have been discussed under animal host headings. Although many animal species have been infected experimentally, no small animal species meets the criteria of an easily maintained, highly susceptible model that develops symptoms typical of large animal or human infection.

Cross-Transmission

Experiments involving cross-transmission to determine host specificity are summarized in Table 3 and discussed briefly under "Host Specificity."

Virulence

Comparison of the virulence of different isolates has not been conducted within the scope of a single study. Results of experimental infections of calves with two isolates at different dosage levels indicate a significant difference in virulence between the two (see "Cattle").

Oocyst and Sporozoite Isolation

Methods have been developed to isolate viable oocysts by filtration from a variety of water sources (Musiel et al., submitted) and to separate viable oocysts from various types of debris, including feces (67, 84, 110, 114, 234, 288; M. J. Arrowood and C. R. Sterling, J. Parasitol, in press). All separation techniques use density centrifugation alone or involving glass bead columns (114) or ether phosphate-buffered saline (288). The least contaminated isolations of oocysts and sporozoites were obtained from sucrose and Percoll gradients (Arrowood and Sterling, in press).

Excystation

Whereas excystation of sporozoites from oocysts requires exposure to reducing conditions, pancreatic enzymes, and bile salts for most coccidia, excystation of sporozoites of *Cryptosporidium* sp. can occur in aqueous solutions without any of the foregoing stimuli (84, 232, 263). Exposure to air (259), stimulation of enzymes within the oocyst by heat (232), and hypotonic stress (84) all have been suggested as possible mechanisms. Whatever the reason, the ability to

excyst without the prerequisites provides insight into why *Cryptosporidium* sp. can infect extraintestinal sites and why autoinfection occurs. Nevertheless, in vitro studies show that the greatest number of *Cryptosporidium* sporozoites excyst from oocysts incubated in a mixture of trypsin (0.25%, wt/vol) and sodium taurocholate (0.75%, wt/vol) at 37°C (84, 232). An ultrastructural study showed that a suture that extended partway around the inner layer of the oocyst wall underwent dissolution during excystation (Fig. 7) (233).

Cultivation

Cryptosporidium sp. has developed in tissue culture (Fig. 3), using a variety of cell lines, and in chicken embryos (67, 68). Neither system is yet in widespread use. Sporozoites released from oocysts of a human isolate of *Cryptosporidium* sp. were added to monolayers of human fetal lung, primary chick kidney, or porcine kidney (67) cells. Within each cell type development proceeded through type I and II meronts (schizonts), sexual stages, and oocysts. Furthermore, oocysts sporulated in vitro. The number of developing parasites was greatest in human fetal lung cells, where the cycle was completed within 72 h. Such oocysts were found to be infective for neonatal mice. Sporozoites excysted from oocysts of human, goat, and calf isolates of *Cryptosporidium* sp. were inoculated into the allantoic cavity, onto the chorion, or intravascularly into 8- to 10-day-old chicken embryos (68). The only site of development was within the microvillous region of endoderm cells of the chorioallantoic membrane, where all three isolates completed the life cycle to sporulated oocysts. These oocysts also were infectious for suckling mice.

TREATMENT AND CONTROL

Treatment

Supportive care with oral or intravenous hydration is the primary therapeutic intervention available for humans with cryptosporidiosis. The disease is self-limiting in immunocompetent individuals, but dehydration and failure to thrive may necessitate hospitalization (106). In immunocompromised individuals removal of exogenous causes of immunosuppression is usually required for cure (155, 166, 175, 178, 199, 292). For the majority of immunocompromised patients, such as those with AIDS whose illness is fulminant and life-threatening, no agent or antidiarrheal compound offers clear benefit.

Development of effective treatment has been limited by lack of simple in vitro cultivation systems to study biochemical and metabolic requirements of *Cryptosporidium* spp. and by the lack of a good small animal model of clinical disease for screening efficacy of drug compounds (see "Experimental"). To date, most evaluations have been performed by attempting to prevent infections in animals (Table 8). Efficacy of 15 anticoccidial prophylactic regimens was tested in suckling mice by dosing before and after infection (16). Even at high concentration, none prevented infection, although amprolium, arprinocin, dinitolmide, salinomycin, and sulfaquinoxaline reduced oocyst excretion. Upon retesting in another host species (lambs), the most efficacious of these drugs (arprinocin) did not control cryptosporidiosis (16). In calves, nine drugs were tested and only lasalocid was effective, but at a toxic dosage (86, 184). In mice, none of 16 antimicrobial agents prevented or altered the infection (271). In pigs, treatment with the ornithine decarboxylase inhibitor DL-α-difluoromethylornithine did not affect infection (185), although it has been active against other coccidia in animals.

TABLE 8. List of therapeutic and preventive modalities used for *Cryptosporidium* infections

Amphotericin B[a]	Kaolin-pectin[a,b]
Ampicillin[a,b]	Ketoconazole[a]
Amprolium[a,b]	Lasalocid[b]
Arpinocin[b]	Levamisol[a]
Bismuth salicylate[a]	Lincomycin[b]
Bleomycin[b]	Loperamide[a]
Bovine transfer factor[a]	Mepacrine[a]
Carbenicillin[a]	Methylbenzoquate[b]
Cefamandole[a]	Metronidazole[a,b]
Chloramphenicol[b]	Monensin[b]
Chloroquine[a]	Naproxyn[a]
Cholestyramine[a]	Neomycin[b]
Cimetadine[a]	Nicarbazin[b]
Clindamycin[a]	Nystatin[b]
Clonidine[a]	Paramomycin[a]
Clopidol[b]	Penicillin[a]
Cloxacillin[a]	Pentamidine[a]
Colistin[a]	Phenamidine[b]
Cotrimoxazole[a]	Piperazine[a]
Decoquinate[b]	Primaquine[a]
Difluoromethyl-ornithine[a,b]	Pyrimethamine[a]
Diloxanide furoate[a]	Quinacrine[a,b]
Dimetridazole[b]	Quinine[a]
Dinitolmide[b]	Robenidine[b]
Diphenoxylate HCl[a]	Salinomycin[a,b]
Doxycycline[a]	Septrin[a]
Emtryl[b]	Spectinomycin[b]
Enterolyte N[b]	Spiramycin[a]
Erythromycin[a]	Streptomycin[b]
Ethopabate[b]	Sulfonamides[a,b]
Furaltadone[b]	Tetracycline[a]
Furazolidone[a,b]	Thiabendazole[a]
Gamma globulin[a]	Trimethoprim[a,b]
Gentamicin[a,b]	Trimethoprim-sulfamethoxazole[a,b]
Gluten-free diet[a]	Tincture of opium[a]
Halofuginone[b]	Trinamide[b]
Indomethacin[a]	Vancomycin[a]
Interleukin-2[a]	Zoaquin[b]
Iodoquinol[a]	
Ipronidazole[b]	
Ivermectin[b]	

[a] Humans.
[b] Other mammals.

Many drugs have been used unsuccessfully in uncontrolled tests in AIDS patients (Table 8). Anecdotal successful treatment has been reported for the following: diloxamide furoate in one case coincident with discontinuation of prednisone (22); furazolidone for 2 months in one case with definite clinical and possible parasitologic improvement (22); quinine plus clindamycin in one case with clinical but not parasitologic cure (24); amprolium in one case with symptomatic improvement (283); and interleukin-2 in two cases with remission of diarrhea (140). The macrolide antibiotic spiramycin, which is similar to erythromycin and clindamycin and has long been used to treat *Toxoplasma gondii* and bacterial infections in Europe and Canada, appears most promising (24). With this agent, nine AIDS patients and two post-bone marrow transplant patients all had some resolution of diarrhea occasionally within 1 week; seven had complete clinical cure, but three of these continued to shed oocysts (63, 294). The Centers for Disease Control reported on 14 patients, some of whom overlap with the above and one of whom was a child: 5 had clinical and parasitologic cure (in one case after 3.5 months of therapy); 2 had initial clinical improvement with recurrence of diarrhea when the drug was discontinued; 7 did not improve, and 3 of these patients died within a week of beginning therapy (24). While

neither spiramycin nor any other agent offers a certain cure, additional experience, laboratory testing, and, in the case of spiramycin, controlled clinical trials may identify an agent with at least adequate clinical suppression to warrant its use. Testing of DL-α-difluoromethylornithine in humans is also in progress.

Control

Controlling the spread of *Cryptosporidium*, or other coccidia, requires reduction or elimination of oocysts from the environment. However, under favorable conditions oocysts remain infectious for a relatively long time. Oocysts of *Cryptosporidium* spp. stored in aqueous suspensions at about 4°C began to lose infectivity at 2 to 6 months (182) but were still viable at 6 to 9 months (263) and were infectious for cell cultures after storage for up to 12 months (67). Oocysts seem to withstand storage best when suspended in 2.5% aqueous potassium dichromate (67, 232). Temperature extremes affect oocyst viability. Freezing and heating to 65°C for 30 min rendered oocysts of *Cryptosporidium* sp. noninfectious (263). Moist heat treatment of *Cryptosporidium* sp. in calf feces and intestinal contents caused loss of infectivity after warming from 9° to 55°C over 15 to 20 min or holding at 45°C for 5 to 20 min (8). These may be used as a guide for treatment of food and drinks when contamination is known or suspected.

By reducing the potential of oocyst ingestion from soil, water, and foods cleaned with contaminated water, as well as from humans and animals, transmission may be reduced or prevented. For veterinary, medical, and laboratory personnel avoidance of contact with infected material is paramount. For patient care, and to minimize risk of nosocomial transmission, standard enteric precautions are indicated, including handwashing, use of gloves and gowns, and private rooms for patients with poor hygiene. Potentially contaminated equipment should be autoclaved. As for other coccidian oocysts, few commercial disinfectants have been found effective in killing oocysts of *Cryptosporidium* spp. (18, 52, 205). Neither of the two aldehyde-based disinfectants (18) Tegodor (containing cetylkonium chloride, benzalkonium chloride, glutaraldehyde, and formaldehyde) and Formula-H (containing tri-*n*-butylbenzoate, formaldehyde, and isopropyl alcohol) nor five other disinfectants (52) including 3% cresylic acid, 2.5% hypochlorite solution, 5% benzylkonium chloride, 0.02 M sodium hydroxide, and 1 to 4% iodophore destroyed oocyst infectivity for newborn specific-pathogen-free mice. Subsequent attempts with 3% Dikonit, 5% formaldehyde, 3% chloramine B, 3% Joctonal A, 0.2% Lastanox Q, and 0.2% Mycolastanox also failed to destroy oocyst infectivity for neonatal mice (205). Because only 10% formol saline and 5% ammonia, after 18 h of exposure, rendered oocysts noninfectious for mice, fumigation with formaldehyde or ammonia was recommended as the most appropriate form of decontamination (52).

There are no vaccines available for prevention of cryptosporidiosis in either animals or humans.

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