WORLD HEALTH ORGANIZATION

ORGANISATION MONDIALE DE LA SANTE

PDP/EC/WP/86.5

ENGLISH ONLY

EXPERT COMMITTEE ON PREVENTION AND
CONTROL OF INTESTINAL PARASITIC INFECTIONS

Geneva, 3-7 March 1986

Draft agenda item 4

CRYPTOSPORIDIOSIS

by

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Biology

The subkingdom Protozoa has recently been reorganized and now accommodates the family Cryptosporidiidae[1]. This family has only one genus, Cryptosporidium, and 11 species[2]. No morphologic differences have been detected between these species; rather, differentiation is based on the species of the host from which the parasite was recovered (TABLE 1). Organisms found in rhesus monkeys are named C. rhesi, those found in mice are named C. muris, and so on. Such differentiation assumes that species of Cryptosporidium are host-specific, an assumption that is true for many organisms in the suborder Eimerina. Recent studies, however, demonstrate that there is probably a low order of host specificity for members of genus Cryptosporidium, and changes in the nomenclature within the genus can be expected[3,4,5,35,36,41,48,72,73]. Figure 1 illustrates the current taxonomic structure of the class Sporozoea[74].

The life cycle of Cryptosporidium is monoxenous. Unlike Toxoplasma oocysts which require a period of incubation outside the host before they sporulate to the infective stage, sporulated Cryptosporidium oocysts have been observed in faeces taken from the intestinal lumen of infected mice, and Cryptosporidium oocysts obtained from freshly passed faeces of infected animals have been shown to be immediately infective for other animals[3,5,8].

Following ingestion (or possibly inhalation) of the oocyst which measures 3-5 microns in diameter, sporozoites are released. The stimulus that triggers sporozoite release is presently unknown. In those animals who primarily develop intestinal infection, excystation presumably occurs when the wall of the oocyst is digested in the gastrointestinal tract of a new host. In many species of birds, however, cryptosporidiosis is a respiratory infection[33,55]. It is not clear if an inhaled oocyst can excyst in the trachea of birds or if oocysts excyst elsewhere (e.g. the digestive tract) with subsequent migration of sporozoites to the lungs by undetermined pathways.

Trophozoites and all other developmental stages are found only at the surface of infected epithelial membranes, never within the cytoplasm of the epithelial cells or beneath the epithelial layer. Development usually occurs on the gastrointestinal epithelium, but in birds development also occurs on the tracheal epithelium. An electron-dense attachment zone forms at the trophozoite's interface with the host cell.

Subsequently, four distinct membranes surround the trophozoite. The origin of these membranes is controversial; some authorities believe them to be part of the parasite, but recent evidence suggests the outer two membranes are of host origin[9,46,75]. If the membrane is of host origin, the location of the trophozoite is intracellular, but extracytoplasmic.

The trophozoite undergoes three nuclear divisions within the host cell to form eight daughter merozoites, resulting in a first-generation schizont . The eight first-generation merozoites are released from the schizont and re-infect other epithelial cells. After attachment, the elongated merozoite becomes round and undergoes two nuclear divisions to become the second-generation schizont, containing four second-generation merozoites[46].

As with other sporozoans, some merozoites differentiate into macrogametocytes and microgametocytes. The macrogametocyte undergoes little change as it becomes a macrogamete, but the microgametocyte undergoes nuclear division and forms several microgametes. The exact number of microgametes thus formed is not known but is believed to be between 12 and 16. A microgamete joins with a macrogamete to form a zygote which develops into an oocyst, completing the life cycle. Based on data from experimentally infected animals, the prepatent period is thought to be about 5 days.

Many parasites in the suborder Eimeriina are limited to one cycle of schizogony in the host. Thus, only sporozoites from an ingested oocyst can re-initiate the life cycle. Based on observations of Cryptosporidium infections lasting for months or years in immunocompromised humans, it is assumed that Cryptosporidium can undergo multiple cycles of schizogony in the same host. The actual path by which a first or second generation merozoite might re-initiate schizogony is unknown; three possible paths are shown as dotted lines in figure 2[74].

Oocysts are resistant to most disinfectants (Table 2). Available data suggest that 5% ammonia or 10% formalin solutions may inactivate Cryptosporidium oocysts. Further investigations, however, are needed to determine the sensitivity of the mouse model as an indicator of oocyst viability. There is little doubt about the inefficacy of disinfectants against oocysts when treated oocysts continue to produce infection in mice, but the reliability of failure of oocysts to infect mice as an indicator of oocyst death has yet to be determined.

Epidemiology

The first human case of cryptosporidiosis was reported in 1976 in a 3 year old child[79]. During the next 5 years 6 additional cases were reported [72,80,81, 82,83,84]. The epidemic of Aquired Immune Deficiency Syndrome served to focus greater attention on the parasite. As of June 3, 1985, the Centers for Disease Control (CDC) had received over 400 reports of AIDS patients with severe cryptosporidiosis (CDC, unpublished data). This represents about 4% of all AIDS patients in the USA , and is probably an underestimate of Cryptosporidium infection in patients with AIDS since patients who are initially reported to CDC with one opportunistic infection (e.g. pneumocystosis) are not reported again if they develop another infection (e.g. cryptosporidiosis) at a later date.

Table 3 summarizes the results of 14 prevalence studies of Cryptosporidium infections. All except seven of the persons with Cryptosporidium infections in these studies were thought to be immunocompetent. The prevalence of Cryptosporidium in patients with gastroenteritis ranged from 1.1% in a study from Canada[85] to 11.1% in a study from Rwanda[86]. In general, slightly higher prevalences were reported in studies in developing countries than in developed countries; of 1135 persons examined in Costa Rica, Liberia, Peru, and Rwanda, 82 (7.2%) had Cryptosporidium. In contrast, 191 (2.5%) of the 7779 persons from Australia, Canada, Denmark, Finland, the United Kingdom, and the United States were positive.

Neither laboratory diagnostic nor patient enrolment criteria were standardized in these studies and, therefore, comparisons of results from one country with those from another must be made with caution. For example, one study included only hospitalized patients, while other studies included both hospitalized and clinic patients. Another potential difference, not always specified in sufficient detail, was the definition of what constituted a person with symptoms of gastroenteritis. For example, the Canadian study[85] included persons submitting stool specimens "for routine bacterial and parasitological examinations." Presumably these persons had some symptoms to suggest infection with bacteria or parasites, but their symptoms might have been different from those of the persons included in the Rwandan study[86], who had "more than three liquid stools per day." The studies also employed different diagnostic tests and involved different age groups. Nevertheless, even when the differences between the studies are taken into account, there appears to be a higher prevalence of cryptosporidiosis in persons studied in developing countries.

Seven prevalence studies examined asymptomatic as well as symptomatic persons[86,87,88,89,92,93,94]; each found the prevalence in symptomatic persons to be much higher than that in asymptomatic persons. Taken together, only 3 (0.4%) of 854 asymptomatic persons had Cryptosporidium. The true prevalence of Cryptosporidium in asymptomatic persons may be even lower than 0.4%, since some infected persons may have had typical symptoms of cryptosporidiosis a short time before they were tested but were considered asymptomatic at the time of the examination. In fact, in one of the three cases, such an occurrence was thought to be likely[94].

Although most persons with Cryptosporidium infections stopped excreting oocysts at about the time that symptoms resolved[39,93,94], some continued to excrete oocysts for several days to weeks afterwards[93,94].

In several of the studies that included asymptomatic persons, it was not clear that the persons tested were chosen randomly, making the true prevalence of Cryptosporidium infections in asymptomatic persons even more difficult to estimate. Nevertheless, the finding that infections appear to be much rarer in asymptomatic compared with symptomatic persons, and the finding that the resolution of symptoms tends to coincide with the disappearance of oocysts suggest that Cryptosporidium should not be thought of as an opportunistic parasite.

Children appear to be more commonly infected than adults. In four of the five studies that evaluated both adults and children, children were more commonly infected, usually by a substantial margin[85,87,93,94,95]. If the results of these five studies are taken together, 151 (4.9%) of the 3051 children examined were positive for Cryptosporidium, whereas only 20 (1.8%) of the 1101 adults were positive.

Since cryptosporidiosis has been reported from several countries, it is not surprising that travellers to foreign countries can become infected. Jokipii et al. noted that 12 of 14 persons diagnosed in their clinic as having Cryptosporidium had recently returned from Leningrad[90]. As the authors point out, because Finnish doctors and citizens are aware that travel to Leningrad is often associated with acquiring giardiasis, such travellers may have been more closely scrutinized for possible parasitic infections than those who had not travelled there. In the United States, Soave and colleagues found Cryptosporidium infections in several members of a family who had recently returned from Egypt[98]. No information was available about how the family might have acquired the infection, but none had direct contact with animals during their trip. In another report from the United States, four tourists who had returned from the Caribbean island of Saint Lucia developed cryptosporidiosis[99]. During their trip to Saint Lucia, they had no contact with young animals or children. All four denied eating raw or undercooked meat or consuming fresh dairy products. They ate fresh salad greens several times and drank substantially more tap water than did tourists who did not have diarrhoea. Filter samples of water from the stream that supplied the hotel and of treated tap water were obtained

with a 1 micron high-volume filter[100]. Neither the raw nor the treated water samples contained Cryptosporidium, but both samples contained nematode eggs and larvae measuring 20-30 microns in diameter. Since Cryptosporidium oocysts measure 3-5 microns in diameter, finding such large organisms suggests that, if Cryptosporidium had been present, the water treatment process would not have removed the parasite.

The potential for animal-to-human transmission of cryptosporidiosis is now well documented. Cryptosporidium from humans has been shown to infect a number of animal species[35,41,73]. Outbreaks of cryptosporidiosis in animal handlers have been linked to handling infected calves[39] and infected antelope fawns at a zoo(CDC, unpublished data). Two cases of cryptosporidiosis have been reported in which the infected person had contact with a cat infected with Cryptosporidium[96,101].

It is clear that contact with animals does not account for all cases of cryptosporidiosis. Three of the prevalence studies listed in Table 3 included questions to determine whether the infected persons had contact with animals[96,89,94]. The percentages of persons with such contact ranged from 33% to 72%; when taken together, only 44 (54%) of 82 infected persons had contact with domestic or farm animals. Moreover, it is difficult quantitate animal contact or assess the degree of exposure to animal faeces by administering a questionaire. Therefore, one can not assume that every patient who has had an animal exposure acquired their infection from animals.

Several pieces of epidemiologic data suggest that person-to-person transmission of cryptosporidiosis is common. Based on studies of other protozoan infections[102], oral-anal contact among homosexual men is thought to place this group at high risk of acquiring Cryptosporidium infection. Hunt et al.[94] examined stool specimens from 24 household contacts of 10 heterosexual index cases with cryptosporidiosis. Four (17%) contacts from three households were excreting Cryptosporidium. Two of the four were asymptomatic, and the other two had mild to moderate gastroenteritis. Hart et al.[96] questioned family members of persons with cryptosporidiosis concerning the occurrence of diarrhoea. Although they apparently did not routinely obtain stool specimens for microscopic examination, they found that 12 (44%) of 27 family members reported diarrhoea.

Several investigations of cryptosporidiosis in day-care centres have provided important insights into the potential for person-to-person transmission among children. Of the seven investigations reported from the United States[103,104], five included stool examinations of all students in the classrooms affected. Prevalences of cryptosporidiosis in children for these five studies ranged from 6% to 54%, and, taken together, results showed 48 (26%) of 183 children were infected. The parents of 22 of the 48 infected children were interviewed with a standardized list of questions regarding possible other sources of infection (CDC, unpublished data). Thirteen (59%) of the infected children had had contact with domestic, farm, or zoo animals, had travelled abroad, or had drunk untreated surface water, although in the case of the farm and zoo animals the contact was restricted to petting the animals. The parents of 54 children with negative stool examinations and without symptoms were also interviewed with the same questionnaire; 27 (50%) of these children had participated in similar activities. Although it was not possible to know the source of infection for each child, the findings that only about half the infected children were exposed to alternative sources of infection and that a similar percentage of presumably uninfected children had the same exposures suggest that many, if not most, of the Cryptosporidium infections observed were the result of person-to-person transmission. In a more recent outbreak, investigators identified 23 stool confirmed cases (87% of whom were symptomatic) among children receiving day-care. Four staff members, 5 parents, and 3 older siblings exposed to the infected children also became infected; 66% of these persons also developed symptoms.

These data indicate that Cryptosporidia infection and disease occur world wide, that infection is usually accompanied by symptoms, that children may be at greatest risk of infection, that infection is probably more common in developing than developed countries, and that transmission involves all of the pathways recognized for other enteric protozoa (e.g. person-to-person, waterborne, and possibly foodborne) plus a greater potential for zoonotic spread than for other enteric protozoa.

Table 1.
Animals reported to be infected with *Cryptosporidium*.*

Animal	Reference	Animal	Reference
Calves	(3-31)	Turkeys	(32,33)
Lambs	(4,5,26,34-38)	Cats	(39,40)
Pigs	(8,41-44)	Dogs	(39)
Guinea Pigs	(45-47)	Deer	(48)
Goats	(39,49,50)	Foals	(51)
Mice	(52-54)	Peacocks	(55)
Rabbits	(56,57)	Geese	(58)
Snakes	(59,60)	Parrots	(61)
Monkeys	(62,63)	Pheasants	(64)
Chickens	(65,66)		

*Other reports of *Cryptosporidium* in snakes [67], wild cats [68], wild dogs [69], lizards [70], and foxes [71], have not been included in this table because the validity of the identification has been questioned [45].

TABLE 2

Survival of Cryptosporidium oocysts in Disinfectants

	STUDY CONDITIONS		EVALUATION OF TREATMENT			REFERENCE
	Cyst Source	Contact Time	Test Animal	Shedding of oocysts	Histological evidence	
Distilled water	Calf	18 Hrs.	Mouse	+	-	(76)
Phosphate buffered saline	Calf	18 Hrs.	Mouse	+	+	(76)
0.33 per cent iodophore	Calf	18 Hrs.	Mouse	+	+	(76)
1 per cent iodophore	Calf	18 Hrs.	Mouse	+	+	(76)
4 per cent iodophore	Calf	18 Hrs.	Mouse	+	-	(76)
10 per cent formol saline	Calf	18 Hrs.	Mouse	-	-	(76)
2.5 per cent cresylic acid	Calf	18 Hrs.	Mouse	-	+	(76)
5 per cent cresylic acid	Calf	18 Hrs.	Mouse	+	+	(76)
3 per cent sodium hypochlorite	Calf	18 Hrs.	Mouse	+	+	(76)
5 per cent benzylkonium chloride	Calf	18 Hrs.	Mouse	+	+	(76)
10 per cent benzylkonium chloride	Calf	18 Hrs.	Mouse	+	-	(76)
5 per cent ammonia	Calf	18 Hrs.	Mouse	-	-	(76)
0.02M sodium hydroxide	Calf	18 Hrs.	Mouse	+	+	(76)
2.5 per cent sodium dichlorocyanuran	Calf	4 Hrs.	Mouse	+	+	(77)
8.5% Tegodor (Th. Goldschmidt)*	Bovine	1 Hrs.	Mouse	+	ND	(78)
8.5% Tegodor (Th. Goldschmidt)*	Bovine	6 Hrs.	Mouse	+	ND	(78)
40.0% Formula-H (Hoechst)**	Bovine	1 Hrs.	Mouse	+	ND	(78)

* Each 100 gram of concentrate contains: 3 g. cetykonium chloride
3 g. benzalkonium chloride
10 g. glutaraldehyde (50%)
20 g. formaldehyde (37%)

** Each 100 ml. of concentrate contains: 129 mg. tri-n-butylbenzoate
4.6 ml formaldehyde sol. (37%)
1.33 ml isopropyl alcohol

Table 3.
Studies of the occurrence of Cryptosporidium infections in persons with gastroenteritis.

Location of study	Persons Positive	Persons Examined	%+	Definition of Gastroenteritis	Population Studied	Reference
Australia	36	884	4.1%	"diarrhea"	Hospital[a]	(87)
Canada	15	1317	1.1%	not specified	Laboratory[b]	(85)
Costa Rica	12	278	4.3%	"acute diarrhea"	Survey[c]	(88)
Denmark	16	800	2.0%	not specified	Laboratory	(89)
Finland	14	154	9.1%	not specified	Laboratory	(90)
Liberia	22	278	7.9%	"liquid stool"	Survey	(91)
Peru	8	103	7.7%	"diarrhea"	Survey	(92)
Peru	9	111	8.1%	"diarrhea"	Survey	(92)
Rwanda	23	293	7.8%	"liquid stool"	Laboratory	(93)
Rwanda	8	72	11.1%	"liquid stool"	Laboratory	(86)
U.K.	43	867	5.0%	"diarrhea"	Laboratory	(94)
U.K.	7	500	1.4%	"diarrhea"	Laboratory	(95)
U.K.	27	1967	1.4%	"diarrhea"	Laboratory	(96)
U.S.A.	33	1290	2.6%	not specified	Laboratory	(97)
TOTAL	273	8914	3.1%			

a. Hospital = hospitalized patients
b. Laboratory = persons submitting stool specimens to laboratory for routine diagnosis
c. Survey = prospective survey of diarrhea in predefined population

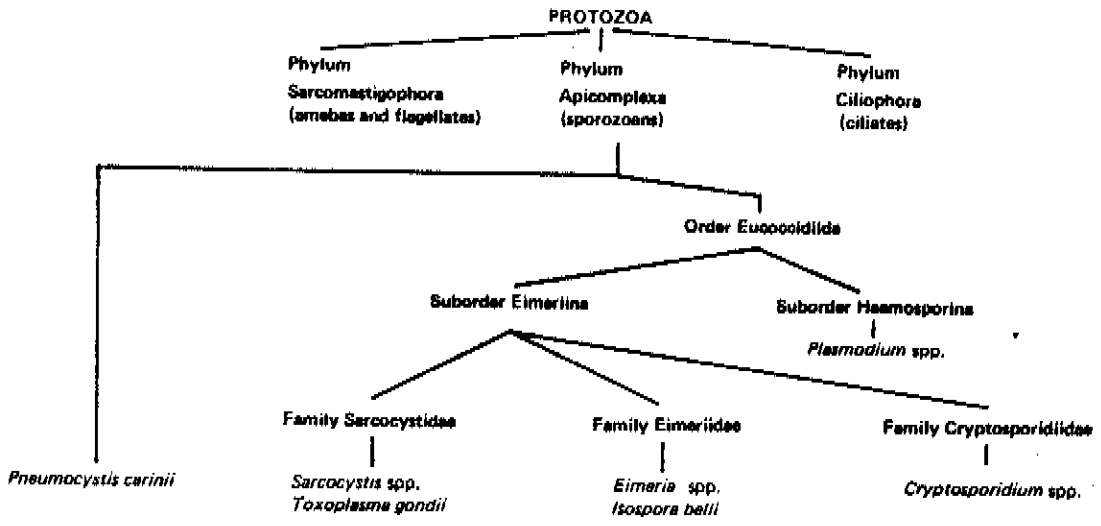

Figure 1. Taxonomic position of *Cryptosporidium*.

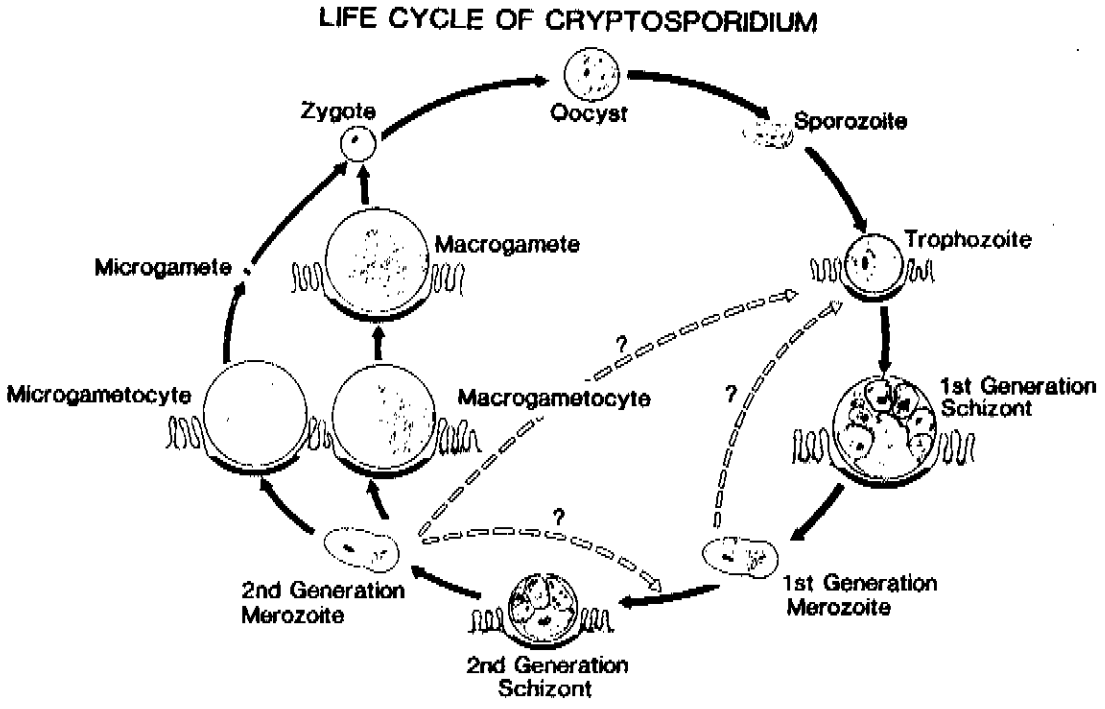

Figure 2. Life cycle of *Cryptosporidium*.

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