

DTIC FILE COPY

Intestinal capillariasis

(2)

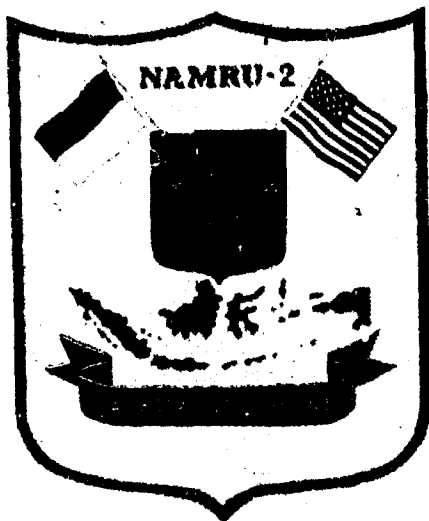
John H. Cross, Virginia Basaca-Sevilla

REPORT NO.

TR - 1045

AD-A201 888

DTIC
ELECTE
NOV 03 1988
S D^{CS} D



**UNITED STATES NAVAL
MEDICAL RESEARCH UNIT NO. TWO**

APO SAN FRANCISCO, CALIFORNIA 96328

NAVAL MEDICAL RESEARCH AND DEVELOPMENT COMMAND
BETHESDA, MARYLAND

**BEST
AVAILABLE COPY**

88 1031 115

UNCLASSIFIED

SECURITY CLASSIFICATION OF THIS PAGE

REPORT DOCUMENTATION PAGE				Form Approved OMB No. 0704-0188	
1a. REPORT SECURITY CLASSIFICATION Unclassified			1b. RESTRICTIVE MARKINGS		
2a. SECURITY CLASSIFICATION AUTHORITY			3. DISTRIBUTION/AVAILABILITY OF REPORT Distribution of this document is unlimited.		
2b. DECLASSIFICATION/DOWNGRADING SCHEDULE			5. MONITORING ORGANIZATION REPORT NUMBER(S)		
4. PERFORMING ORGANIZATION REPORT NUMBER(S) NAMRU-2-TR-1045			7a. NAME OF MONITORING ORGANIZATION		
6a. NAME OF PERFORMING ORGANIZATION U.S. Naval Medical Research Unit No. 2		6b. OFFICE SYMBOL (if applicable) NAMRU-2	7b. ADDRESS (City, State, and ZIP Code)		
6c. ADDRESS (City, State, and ZIP Code) APC San Francisco, California 96528-5000			9. PROCUREMENT INSTRUMENT IDENTIFICATION NUMBER		
8a. NAME OF FUNDING/SPONSORING ORGANIZATION Naval Medical Research & Development Command		8b. OFFICE SYMBOL (if applicable) NMRDC	10. SOURCE OF FUNDING NUMBERS		
8c. ADDRESS (City, State, and ZIP Code) Bethesda, Maryland 20814			PROGRAM ELEMENT NO. 61102A	PROJECT NO. M161102BS10	TASK NO. AF
					WORK UNIT ACCESSION NO. 429
11. TITLE (Include Security Classification) (U) Intestinal capillariasis					
12. PERSONAL AUTHOR(S) John H. Cross, Virginia Basaca- Sevilla, Department of Health, Manila, Philippines					
13a. TYPE OF REPORT Technical Report		13b. TIME COVERED FROM 1987 TO		14. DATE OF REPORT (Year, Month, Day) 1987 December	
				15. PAGE COUNT 12	
16. SUPPLEMENTARY NOTATION Published in the Bailliere's Clinical Tropical Medicine and Communicable Diseases, 2(3):735-746. This paper was done in cooperation with the Philippine Department of Health.					
17. COSATI CODES			18. SUBJECT TERMS (Continue on reverse if necessary and identify by block number)		
FIELD	GROUP	SUB-GROUP	Intestinal capillariasis		
			Capillaria philippinensis		
19. ABSTRACT (Continue on reverse if necessary and identify by block number) Capillaria philippinensis, the tiny nematode causing intestinal capillariasis in humans, is a unique parasite. It is one of the newest parasites that has been shown to infect humans; it can occur in epidemic proportions and chronic untreated infections can lead to death. Furthermore, its life cycle is unusual in that the female worms are capable of producing living larvae as well as eggs, leading to autoinfection and hyperinfections.					
20. DISTRIBUTION/AVAILABILITY OF ABSTRACT ☒ UNCLASSIFIED/UNLIMITED ☐ SAME AS RPT. ☐ DTIC USERS			21. ABSTRACT SECURITY CLASSIFICATION Unclassified		
22a. NAME OF RESPONSIBLE INDIVIDUAL RAM: I: Groves, M.			22b. TELEPHONE (Include Area Code) 301/663-7567		22c. OFFICE SYMBOL NMRDC

DD Form 1473, JUN 86

Previous editions are obsolete.

SECURITY CLASSIFICATION OF THIS PAGE

S/N 0102-LF-014-6603

Unclassified

13b

Intestinal capillariasis

JOHN H. CROSS
VIRGINIA BASACA-SEVILLA

Capillaria philippinensis, the tiny nematode causing intestinal capillariasis in humans, is a unique parasite. It is one of the newest parasites that has been shown to infect humans; it can occur in epidemic proportions and chronic untreated infections can lead to death. Furthermore, its life cycle is unusual in that the female worms are capable of producing living larvae as well as eggs, leading to autoinfection and hyperinfection.

DISCOVERY AND DISTRIBUTION

The worm was unknown until 1963, when Chitwood et al (1964) reported finding the parasite in a Filipino school teacher from Northern Luzon, who died in a Manila hospital of a debilitating illness. In 1965, an epidemic of an unknown diarrhoeal disease emerged in the area of Tagudin, Ilocos Sur, also in Northern Luzon of the Philippines and, by early 1967, several hundred people had acquired the disease and many died. The epidemic was brought under control within a few years, but the disease has remained endemic in the area of Northern Luzon. Another epidemic of the disease occurred in Southern Leyte in the Philippines in the early 1980s. In a limited survey, 14% of 362 stool specimens from adults living in the area were positive for *C. philippinensis* eggs (Cross and Basaca-Sevilla, 1986).

Intestinal capillariasis is also known to be endemic in Thailand, where many cases and deaths have been reported from the central and the north eastern parts of the country (Bhaibulaya, 1975). In addition, parasitologically confirmed single human infections are reported from Japan (Mukai et al, 1983) and from Iran (Hoghooghi-Rad et al, 1986).

PARASITE

Capillaria philippinensis, described by Chitwood et al (1968), is found primarily in the lumen, the mucosa, or in the crypts of Lieberkühn in the human jejunum. Hyperinfection is the rule, with thousands of worms found.

Morphology

The parasite is closely related to *Trichuris* species and, characteristic of the group, has a narrow anterior end containing a stichostome with rows of stichocytes surrounding the oesophagus. The posterior half of the nematode is wider than the anterior half and contains the digestive tract and the reproductive organs. The males are 1.5–3.9 mm in length (Figure 1) with



Figure 1. Adult male *Capillaria philippinensis* in bowel fluid at autopsy. Arrow indicates spicule.

widths of 3–5 μm at the head, 23–38 μm at the mid-level of the stichostome, and approximately 18 μm at the cloaca. The male spicule is 230–300 μm in length and the unspined spicular sheath is about 440 μm . The anus is subterminal and the tail has ventrolateral expansions bearing two pairs of papillae. The female worms vary in length from 2.3–5.3 mm (Figure 2). Widths at the head, widest portion of the stichostome, vulva, and post-vulva, are 5–8 μm , 24 μm , 26–36 μm , and 29–42 μm , respectively. The vulva opening is immediately behind the stichostome, and there is no vulva flap (Figure 3). The uterus may contain thick-shelled bioperculated eggs or thin-shelled eggs, with or without embryos or first-stage larvae. The anus of the female is also subterminal. All stages of the parasite, eggs, larvae and adults are found in the small intestine, as well as in the faeces, of the host.

Life cycle

The life cycle of *C. philippinensis* has been established experimentally in some laboratory animals (monkeys and Mongolian gerbils), and it is believed that the natural life cycle is similar (Cross et al. 1972, 1978). Small freshwater and brackish water fish are intermediate hosts. Eggs in faeces



Figure 2. Adult female *Capillaria philippinensis* in bowel fluid at autopsy. Stichocytes can be seen in the anterior half of the body, and eggs in the uterus in the posterior part of the body.

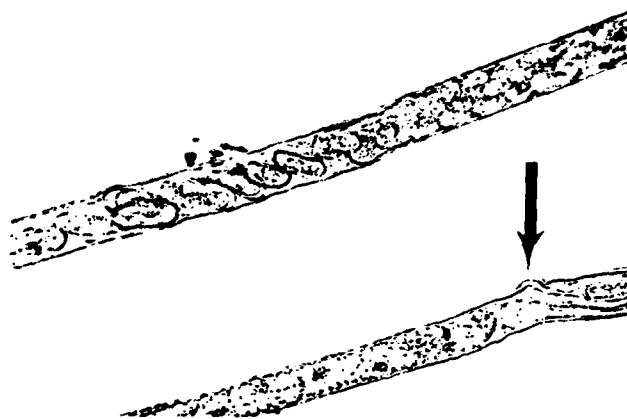


Figure 3. Adult female *Capillaria philippinensis* with eggs in the uterus and stichocytes in the lower anterior end. Note salient vulva, arrow.

reach water where the eggs embryonate in 5–10 days at ambient temperatures. The embryonated eggs are ingested by fish, and larvae emerge from the egg in the fish intestine. After 3 weeks, the larvae double in size, from 150 to 300 μm , and become infective. When infected fish are eaten uncooked, the larvae are released in the intestine of the definitive host and become sexually mature within 2 weeks. The first generation adult females become larviparous, releasing larvae into the intestines of the host. These larvae reach sexual maturity within another 2 weeks and the second generation female worms produce eggs which pass in the faeces. The pre-patent period is approximately 26 days. A few larviparous females are always present to produce larvae to maintain the population. Autoinfection leads to hyperinfection and, in one experiment, 2520 and 5353 worms were found in two Mongolian gerbils given only two infective-stage larvae from fish (Cross et al, 1978).

EPIDEMIOLOGY

Hosts of *C. philippinensis*

Intestinal capillariasis has occurred in areas where people eat small freshwater or brackish water fish uncooked. In endemic areas of the Philippines and Thailand, the populations relish eating raw fish, and the cases reported from Japan and Iran occurred following the ingestion of raw fish. A number of fish have been experimentally infected with the parasite (Cross et al, 1972, 1978; Bhaibulaya et al, 1979), and on three occasions, the ingestion of live fish from the lagoons of Northern Luzon in the Philippines resulted in *C. philippinensis* infections in Mongolian gerbils. It is believed that many species of fish may serve as intermediate hosts, and when man eats these infected fish, capillariasis philippinensis results.

Only one fish-eating bird, a yellow bittern (*Ixobrychus* sp.), has been found naturally infected with the parasite, but several species of fish-eating birds have been experimentally infected in Thailand and Taiwan (Bhaibulaya and Indra-Ngarm, 1979; Cross and Basaca-Sevilla, 1983). Most of these birds have migratory habits; therefore, it is quite possible that infection persists in fish and birds along the migratory flyways and that a fish–bird life cycle may exist throughout Asia as well as elsewhere.

Mortality and morbidity

Since the Philippine epidemic, there have been nearly 1900 confirmed cases of intestinal capillariasis in Northern Luzon and over 100 deaths associated with the infection. In 1967–1968, over 1300 cases were recorded, and 5–74 new cases were documented yearly from 1969 up to 1986. An unknown number of undiagnosed cases have undoubtedly occurred, as well as deaths, and additional cases and deaths have occurred in Southern Leyte, as well as in Thailand. In the northern Philippines, 70% of the infections have occurred in adult males, mostly between the ages of 20 and 50 years. The few cases

seen in recent years have been predominantly in males. This is probably because males, more often than females, eat uncooked, freshly caught fish from traps in lagoons. While bathing in the lagoons in the afternoon, after a day's work in rice fields, the men are hungry and will usually collect fish and a variety of other aquatic life from the traps and eat them raw.

Transmission

Certain groups of Filipinos, such as Ilocanos in the north, are accustomed to eating a variety of uncooked foods. Raw animal organs, crabs, snails, clams, shrimp, squid, goat and water buffalo meat, and intestinal juices and bile from animals are used to season rice and other foods. Some Thai populations also enjoy eating raw fish.

Most of the Asian rural populations have intestinal parasites and, in the endemic areas, people are usually infected with a variety of nematodes, trematodes, and protozoan parasites. It is common to find over 95% of the villagers in Northern Luzon with multiple parasitic infections (Cross and Basaca-Sevilla, 1984).

Sanitary facilities in these rural areas are poor, as most people prefer to defaecate in the fields rather than in privies or water seal toilets. Water may be from the lagoons or from wells, and it is usually not boiled or treated before drinking.

More cases of intestinal capillariasis in the Philippines have been recorded during the rainy season than during the dry season. This may be associated with the breeding habits of some fish. One species in particular, *Hypseleotris bipartita* (Figure 4), is preferred uncooked when the females are gravid, which happens during the rainy season. This species was found to naturally transmit the parasite to Mongolian gerbils (Cross and Bhaibulaya, 1983).



Figure 4. *Hypseleotris bipartita*, intermediate host for *Capillaria philippinensis*. These are small brackish water-freshwater fish, ranging 2-6 cm in length and often eaten raw in the Northern Philippines.

PATHOLOGY

Localization

The parasite has been found primarily in the jejunum in biopsy specimens (Whalen et al, 1969) and at autopsy, but in some autopsies, worms have been found in the lumen of other portions of the intestine, possibly due to migration of the worm after death. All stages of the parasite, eggs, larvae, and adults have been found in the jejunal mucosa (Figure 5), the crypts of Lieberkühn (Figure 6) and the lumen (Figure 7). Extremely large numbers of worms may be present and, at one autopsy, 200 000 worms were estimated to be in one litre of bowel fluid; many more were in the mucosa. The parasite has not been found in any other organ but the small intestine, except on one occasion when sections of worms similar to *Capillaria* species were found in the liver at autopsy (Fresh et al, 1972).

Pathological changes

Most of the pathological processes of the disease have been found in the jejunum. The small bowel wall is usually thickened and indurated with a prominence of the surface vessels. Pathological changes were noted in other organs at autopsy, probably resulting from hypokalaemia and malnutrition. Vacuolization of some myocardial cells was noted, as was congestion and some oedema in the lungs. The spleen of some patients was congested, with prominent Malpighian corpuscles present. Fatty metamorphosis was seen in the liver, and the kidneys showed vacuolization of the renal proximal



Figure 5. Histological section of human intestine showing sections of *Capillaria philippinensis*. Arrow indicates rows of stichocytes.

tubular lining cells. Vacuolization of striated muscle was also noted. Histological examination of the small bowel showed parasites throughout the tissue. The crypts were atrophic and contained parasites or cellular debris. The villi were flattened, the mucosal glands were dilated, and the lamina

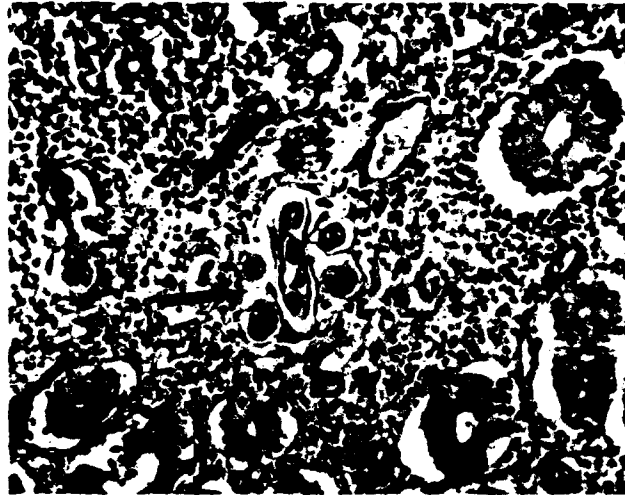


Figure 6. Section of human intestine showing denuded crypt containing *Capillaria philippinensis* (arrow).



Figure 7. Section of human intestine showing lumen filled with sections of *Capillaria philippinensis*.

propria was infiltrated with plasma cells, lymphocytes, macrophages, eosinophils, and neutrophils (Canlas et al, 1967; Fresh et al, 1972).

Jejunal biopsy tissue was examined by electronmicroscopy and the tissue showed a loss of adhesion specialization and widespread separation of epithelial cells. Gerbil jejunal tissue was also studied by electronmicroscopy and micro-ulcers were seen in the epithelium. There also was compressive generation of the cells, mechanical compression and homogeneous material was evident at the anterior end of a parasite. It is believed that the damage seen by electronmicroscopy to the mucosa may contribute to the protein, fluid and electrolyte loss in patients with chronic disease (Sun et al, 1974).

CLINICAL ASPECTS

Symptoms and signs

Chronic manifestations of intestinal capillariasis are seen in persons with infections of several months' duration. Symptoms of diarrhoea with 4-5, and up to 8-10, watery stools per day, borborygmi, and vague abdominal pain, are experienced by most patients, as is weight loss, malaise, and vomiting. Physical findings consist of muscle wasting and weakness, diminished reflexes, distant heart sounds, hypotension, gallop rhythm, and pulsus alternans, indicating a cardiomyopathy, as well as borborygmi, abdominal distension, epigastric tenderness, oedema, hyporeflexia, and cachexia. Laboratory findings show a severe protein-losing enteropathy, malabsorption of fats and sugars, decreased excretion of xylose, and low serum levels of K^+ , Na^+ , Ca^{2+} , carotene, and total protein (Whalen et al, 1969). Immunoglobulin studies show elevated IgE and diminished IgG, IgM, and IgA (Rosenberg et al, 1970). The immunoglobulin levels return to normal several months after treatment.

Clinical course

Patients with infections of one to three months duration do not suffer severe manifestations of the disease. They present with borborygmi, abdominal pain and diarrhoea. However, if the infection remains untreated, chronic symptoms and signs gradually develop over a period of months. Long-term untreated infections usually result in death due to the irreversible effects of the disease. Death has been attributed to heart failure and intercurrent bacterial infections (Dauz et al, 1967; Whalen et al, 1969; Fresh et al, 1972; Watten et al, 1972).

LABORATORY DIAGNOSIS

The diagnosis may easily be missed if the eggs and larvae of *C. philippinensis* are not recognized in the stools. Eggs are easily recovered by direct microscopic examination or after concentration of the faecal specimen. Patients are

seen by physicians complaining of a gurgling stomach, belly ache, and diarrhoea, and eggs are usually found in the faeces. In some instances, eggs may not be present, but can easily be found on subsequent faecal examinations, especially following initiation of anthelmintic therapy. Physicians and laboratory technicians in endemic areas should be familiar with egg characteristics. The peanut-shaped eggs have flattened bipolar plugs and measure 36–45 μm by 20 μm (Figure 8). Serological tests have been evaluated but are not reliable and not necessary, since parasites and eggs are usually found in the faeces.



Figure 8. Egg of *Capillaria philippinensis* showing flattened bipolar plugs; measures 20 $\times$ 40 μm .

TREATMENT

Patients with severe disease are given electrolyte-replacement therapy, an anti-diarrhoeal, an anthelmintic, and a high protein diet. Thiabendazole, in a dosage of 25 mg/kg per day or 1 g per day for 30 days, was the drug of choice for several years. However, side-effects and relapses were common (Singson, 1974); one patient experienced 15 relapses over a 12-year period (Alcantara et al, 1985). The present drug of choice is mebendazole, 400 mg per day given in divided doses for 20 days for new cases, and for 30 days for relapse cases. Eggs and parasites disappear from the faeces within 4 days, and symptoms within a week. Relapses and side-effects are rare with mebendazole therapy, and electrolyte replacement is usually not necessary when patients are treated in the earlier stages of the disease.

Albendazole has also been found effective in treating intestinal capillariasis, using the same dosages as mebendazole. Preliminary studies,

however, indicate that the treatment time can be reduced to 10 days.

In the Philippines, it has been found necessary to hospitalize patients during the course of treatment since they do not follow the physician's instructions when treated as outpatients. Patients feel better a few days after treatment begins, and they often stop medication, sell the drugs, or give them to friends and relatives with belly-aches, rather than complete their own therapy regimen.

PREVENTION AND CONTROL

Populations in the Philippines and Thailand, where capillariasis philippinensis is highly endemic, consider raw freshwater and brackish water fish a delicacy. The fish are usually small in size and are eaten whole. Changing eating habits is difficult, but it is the most pragmatic means of preventing the disease. Thorough cooking of the fish before consumption would also prevent the disease. Health education and the sanitary disposal of human faeces, as well as widespread administration of an effective anthelmintic, would be beneficial for control. The widespread use of thiabendazole is thought to have been responsible for curtailing the Philippine epidemic in 1967-1968.

SUMMARY

Capillaria philippinensis is endemic in parts of the Philippines and Thailand, with single case reports from Japan and Iran. The nematode parasite is small and usually confined to the small intestines where female worms produce larvae leading to autoinfection and hyperinfection. Females also produce eggs which pass in the faeces, embryonate and become ingested by small freshwater or brackish water fish. The eggs hatch in the fish intestine and develop into infective-stage larvae in 3 weeks. The fish are eaten raw by a susceptible host and the larvae develop into adults in the small intestine and reproduce. The prepatent period is approximately 26 days. Monkeys, Mongolian gerbils, and some species of fish-eating birds have been experimentally infected with the parasite. Fish-eating birds are suspected natural hosts.

The parasitoses can be fatal in humans if treatment is delayed. Patients usually have borborygmi, abdominal pain, and diarrhoea early in the infection, leading to weight loss, malaise, body weakness, oedema, and cachexia. There is an electrolyte loss. A protein-losing enteropathy develops along with a malabsorption of fats and sugars, and low levels of plasma protein, K^+ , Ca^{2+} and carotene. Histological examinations of intestinal tissue at autopsy show the crypts of Lieberkühn to be atrophic, the villi flattened, the mucosal glands dilated, and the lamina propria infiltrated with inflammatory cells.

A clinical diagnosis in endemic areas can be made from symptoms of borborygmi, abdominal pain, and diarrhoea, but the confirmed diagnosis is made by detecting eggs, larvae or adult forms of *Capillaria philippinensis* in

the faeces. The current anthelmintic of choice for treatment is mebendazole, 400 mg per day, in two equal doses for 20 days. Electrolyte replacement, an anti-diarrhoeal drug, and a high protein diet are recommended for patients with chronic manifestations of the disease.

Avoidance of eating raw or poorly cooked freshwater fish would prevent infection.

REFERENCES

- Alcantara AK, Uylangco CV & Cross JH (1985) An obstinate case of intestinal capillariasis. *Southeast Asian Journal of Tropical Medicine and Public Health* 16: 410-413.
- Bhaibulaya M (1975) Studies on capillariasis philippinensis in Thailand. I. Epidemiologic survey. *Report of the Thailand National Research Council*, p 11.
- Bhaibulaya M & Indra-Ngarm S (1979) *Amaurornis phoenicurus* and *Ardeola bacchus* as experimental definitive hosts for *Capillaria philippinensis* in Thailand. *International Journal for Parasitology* 9: 321-322.
- Bhaibulaya M, Indra-Ngarm S & Anathapruit M (1979) Freshwater fishes of Thailand as experimental intermediate host for *Capillaria philippinensis*. *International Journal for Parasitology* 9: 105-109.
- Canlas B, Cabrera BD & Daus U (1967) Human intestinal capillariasis. II. Pathological features. *Acta Medica Philippina* 4: 84-91.
- Chitwood MB, Velasquez C & Salazar NG (1964) Physiological changes in a species of *Capillaria* (Trichuroidea) causing a fatal case of human intestinal capillariasis. *Proceedings of the First International Congress of Parasitology, Rome, Italy, 1964*, 2: 797.
- Chitwood MB, Velasquez C & Salazar NG (1968) *Capillaria philippinensis* sp. n. (Nematoda: Trichuroidea) from intestine of man in the Philippines. *Journal of Parasitology* 54: 368-371.
- Cross JH, Banzon TC, Clarke MD et al (1972) Studies on the experimental transmission of *Capillaria philippinensis* in monkeys. *Transactions of the Royal Society of Tropical Medicine and Hygiene* 66: 819-827.
- Cross JH, Banzon TC & Singson CN (1978) Further studies on *Capillaria philippinensis*: Development of the parasite in the Mongolian gerbil. *Journal of Parasitology* 64: 208-213.
- Cross JH & Basaca-Sevilla V (1983) Experimental transmission of *Capillaria philippinensis* to birds. *Transactions of the Royal Society of Tropical Medicine and Hygiene* 77: 511-514.
- Cross JH & Basaca-Sevilla V (1984) Biomedical Surveys in the Philippines. *NAMRU-2* SP-47.
- Cross JH & Basaca-Sevilla V (1986) Intestinal capillariasis—Current concepts, laboratory diagnosis and treatment. In *Monograph 7. Parasites and Parasitic Infections, Asian Journal of Clinical Science*, pp 63-67.
- Cross JH & Bhaibulaya M (1983) Intestinal capillariasis in the Philippines and Thailand. In Croll N & Cross JH (eds) *Human Ecology and Infectious Diseases*, pp 103-136. New York: Academic Press.
- Daus U, Cabrera BD & Canlas B (1967) Human intestinal capillariasis. I. Clinical features. *Acta Medica Philippina* 4: 72-83.
- Fresh JW, Cross JH, Reyes V et al (1972) Necropsy findings in intestinal capillariasis. *American Journal of Tropical Medicine and Hygiene* 21: 169-173.
- Hoghoghi-Rad N, Maraghi S & Narenj-Zadeh A (1986) A case of intestinal capillariasis in the Khozestan Province, Iran. *Proceedings of the Sixth International Congress on Parasitology, Brisbane, Australia, 1986*, p 151. Australian Academy of Sciences.
- Mukai T, Shimizu S, Yamamoto M et al (1983) A case of intestinal capillariasis. *Japanese Archives of Internal Medicine* 30: 163-169.
- Rosenberg EB, Whalen GE, Bennich H & Johansson SGO (1970) Increased circulating IgE in a new parasitic disease—human intestinal capillariasis. *New England Journal of Medicine* 283: 1148-1149.
- Singson CN (1974) Recurrences in human intestinal capillariasis. *Philippine Journal of Micro-*

- biology and Infectious Diseases* 3: 7-13.
- Sun SC, Cross JH, Berg HS et al (1974) Ultrastructural studies of intestinal capillariasis—*Capillaria philippinensis* in human and gerbil hosts. *South east Asian Journal of Tropical Medicine and Public Health* 5: 524-533.
- Watten RH, Becker WM, Cross JH, Gunning J-J & Jarimillio J (1972) Clinical studies on capillariasis philippinensis. *Transactions of the Royal Society of Tropical Medicine and Hygiene* 66: 828-834.
- Whalen GE, Strickland GT, Cross JH et al (1969) Intestinal capillariasis—a new disease in man. *Lancet* i: 13-16.