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Gnathostoma spinigerum and Human Gnathostomiasis

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ABSTRAK

Marsetyawan Soesatyo — Gnathostoma spinigerum *dan gnathostomiasis pada manusia*

G. spinigerum adalah sejenis Nematoda yang hidup sebagai parasit pada Carnivora seperti kucing, anjing, harimau dsb. Infeksi pada manusia banyak terjadi di kalangan masyarakat penggemar makan ikan air tawar mentah atau setengah matang, yang mengandung larva infektif *G. spinigerum* tingkat tiga.

Manusia merupakan *incidental host*, sehingga tidak memungkinkan perkembangan larva cacing menjadi bentuk dewasa; tetapi larva ini di dalam tubuh manusia dapat bermigrasi ke seluruh organ dan menimbulkan gejala-gejala penyakit yang berbeda-beda, tergantung pada organ apa yang terserang. Infeksi *G. spinigerum* pada sistem saraf pusat umumnya bersifat fatal, dengan gejala khas myeloensefalitis eosinofilik.

Saat ini belum ada obat yang bersifat efektif terhadap cacing ini. Usaha menanggulangi penyakit ini hanyalah mencegah penyebaran dari *second intermediate host* ke manusia.

Key Words: Gnathostoma spinigerum — fresh-water fish — CNS-gnathostomiasis — myeloencephalitis — Nematoda

INTRODUCTION

Gnathostoma spp. is a spirurid nematode (Spiruroidea) found in the stomach of cats, dogs and other carnivores. This worm has been found to have a wide distribution in some geograhical areas in Asia, *e. g.* Thailand, Japan, Malaysia, India, China, Burma, the Philippines, and Indonesia (Bunnag *et al.*, 1981; Daengsvang, 1949, 1980, 1981; Daengswang *et al.*, 1966; Lim, 1976; Miyazaki, 1960).

The genus *Gnathostoma* was first discovered by Richard Owen in 1836 and described as *Gnathostoma spinigerum* Owen. This parasite was found in the stomach wall of a young tiger (*Felis tigris* Linn.) which died in a London zoological garden (Chitanondh, 1967; Daengsvang, 1949; Myazaki, 1960).

Reports on human infection were not found in the literature until 1889, when Levinson published the identification of such worm obtained by Deuntzer

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from a swelling in the breast of a young Thai woman in Bangkok (Daengsvang, 1949, 1976, 1980), and after that has become a medically important infection in human being.

Regarding the human gnathostomiasis, the most important species is *G. spinigerum*, being considered as the causative agent of the disease in Southeast Asia, particularly in Thailand (Bunnag *et al.*, 1981; Chitanondh, 1967; Daengsvang, 1981; Miyazaki, 1960; Nitidandhaprabhas, 1975; Punyagupta, 1978; Ratanarapee, 1982). This would be important as a local public health problem in this country, since some people in Thailand are fond of consuming raw or inadequately heated fresh-water fish harbouring infective third stage larve of *Gnathostoma*, leading to the transmission of the disease in humans. Similarly it occurs among the Japanese people who love swallowing live leaches "to get energy" (Kawamura *et al.*, 1983), and get infection from it.

Although man apparently is an unnatural host, and during a course of infection there is no further development of larva, they can however migrate throughout almost all parts of the body, survive and live happily, even though they can cause severe disorder which is sometimes fatal. About three fatal cases of eosinophilic myeloencephalitis have been reported in Thailand in 1967 caused by *G. spinigerum* (Chitanondh, 1967; Punyagupta *et al.*, 1968), and 34 cases of human gnathostomiasis involving CNS have been described. All of them were from Thailand. From the clinical surveys, a yearly average of about 900 highly suspected human gnathostomiasis during 1961 – 1963 were diagnosed by doctors of 92 provincial and Bangkok hospitals and rural health centers. Moreover, at least 63 confirmed cases, including some deaths, due to the involvement of CNS were reported from 1889 to 1979 (Daengsvang, 1980, 1981).

Based on those facts, we realized that human gnathostomiasis is still an important disease, needs much more attention as well as other parasitic diseases in the tropics, though it is not one of the five mayor parasitic diseases recommended by WHO.

MORPHOLOGY OF *G. SPINIGERUM*

The morphological study of adult worms revealed differences from species to species. As previously mentioned, *G. spinigerum* was the first species discovered by Owen (1836), and subsequently many species of the genus *Gnathostoma* have been reported from different kinds of animals in various localities. From 19 species found, there are only 7 species which have been described as distinct ones (Miyazaki, 1960), while only 5 species of *Gnathostoma* were at present reported from Southeast Asia with specific diagnostic characteristics (Daengsvang, 1981), namely *G. spinigerum, G. hispidum, G. doloresi, G. vietnamicum,* and *G. malaysiae*. The first three have already been known as regard to their experimental life cycles. In this paper we are dealing only with *G. spinigerum* (FIGURE 1).

The general appearance of the adult worms and measurements obtained from the stomach of many dogs and after being fixed in warm 70% ethanol show the anterior body of the adult worm is less tapering than the posterior portion, with a graceful curve of the whole body. The maximum width is normally found

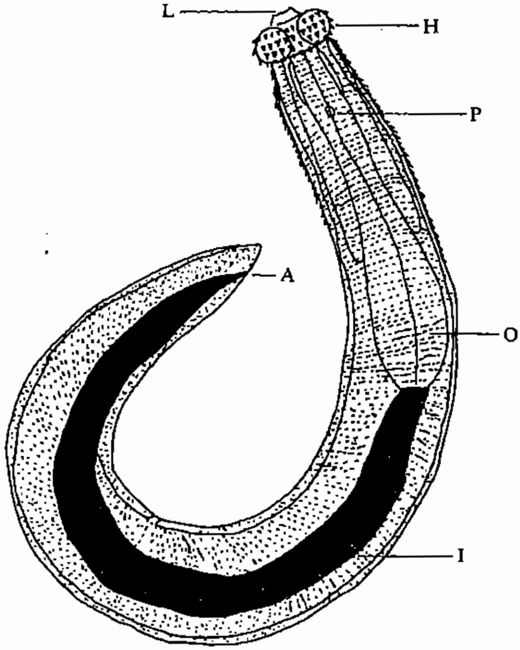

FIGURE 1. — Third stage larva of *G. spinigerum* (Redrawn from Miyazaki, 1960).
L : lip; H: head bulb; A: anus; O: esophagus; I: intestinum; P: cervical papilla

at about the middle part of the worm (Daengsvang, 1980). The average size for males was 26.2 mm long (ranging 16—40 mm) and 1.8 mm wide (ranging 1—3 mm), while the average size for females was 34.7 mm long (ranging 13—55 mm) and 2.3 mm wide (ranging 1—3 mm). This worm has a characteristic head-bulb, provided with 7—9 cephalic hooklet rows. The numbers of hooklets generally increase from row 1 next to the lips to row 8 near to the neck. Most of the heads examined were provided with a range of 40—80 hooklets in rows 2, 3, 4 and 8, but a range of 60—100 hooklets were found in rows 5, 6, and 7.

The body is also armed with cuticular spines about the anterior half or two thirds, leaving the hinder part of the body naked, except on the greater part of the posterior ventral surface of the male caudal extremity, where the cuticular striae were closely set with very small spines (Daengsvang, 1980). It was found that the shape and size of cuticular spines vary with their positions. The first few rows behind the head-bulb, each showing 3 to 5 unequal teeth closely arranged in irregular manner with straight margins and oblong-shaped spines. There are altogether about 30 rows of such spines after which are followed by many rows of more densely arranged longer 3-tooth spines. The cuticular spines become slightly shorter but larger, each carries 2 to 3 rather small equal teeth. The number of cuticular spines gradually decrease in density and zize posteriorly. On the body cuticle of the posterior third the cuticular striations were clearly seen (Daengsvang, 1981).

At the posterior end of male worms there were four large caudal papillae on each side which lie close together in the caudal alae. Near the caudal papillae, there were pairs of ventral papillae. The cloacal opening lies in front of these. There were also provided with two unequal spicules. Female worms was provided with a slight transverse vulva behind the middle of the body, opening into a long muscular vagina which runs anteriorly then posteriorly and dorsally before splitting into two uterine branches. The tail of the female was, in lateral view, rounded dorsally and flattened ventrally. The eggs are released from the vagina with thin colourless shell, a marked thinning at one pole before a cap-like knobbed end.

Those cuticular spines which were already mentioned are good criteria for distinction (Miyazaki, 1960), while some other specific diagnostic points relating to the worms should be born in mind as size and general body shape, number of rows and the arrangement of cephalic spines. For the male worm, the size of caudal pedunculate papillae and Y-shapped spineless area at the posterior end show specificity (FIGURE 2b) (Daengsvang, 1981).

A further morphological observation using scanning electron microscope of the advanced third-stage larva of *G. spinigerum* has been done recently (Anantaphruti *et al.*, 1982). These advanced third-stage larvae were obtained from the experimentally infected mice, and measured 3.31 mm in length and 0.305 mm in width at the location of the excretory pore. The head-bulb appeared globular-like. The mouth bears a pair of lateral lips of equal size and quadrate in shape. On the lips, the lateral papillae are clearly seen on the surface, two papillae on each lip. Between the two labial papillae of each lip, a small amphid was seen. The head-bulb shows four transverse rows of well developed single pointed spines. The number of hooklets in each row numbering 43 (39—47) for the first row next to the mouth, 44 (41—48) for the second row, 45 (38—49) for the third row and 49 (45—53) for the fourth row. The cuticle of the body was transversely striated and the whole body was covered with transverse rows of single-pointed spines. On the anterior half of the body, there was a pair of lateral cervical papillae, one on each side of the body. The excretory pore was clearly seen on the ventral surface below the cervical papillae. A pair of small body papillae was seen on the lateral side at about the middle part of the posterior half of the body.

Studies on the internal structure of the larva showed:

1. the cervical sacs, four muscular tubes, each opened into respective ballonets in the head-bulb, being filled with somewhat muddy liquid. These systems seem to play an important role in swelling and contracting the head-bulb.
2. the esophagus was divided into the muscular and glandular portions. The latter was further divided into dorsal and subventral glands.
3. the larva contains the red-blood celomic fluid, and this color was much deeper in the larva parasitic in warm-blooded animals than those in cold-blooded ones (Myazaki, 1960).

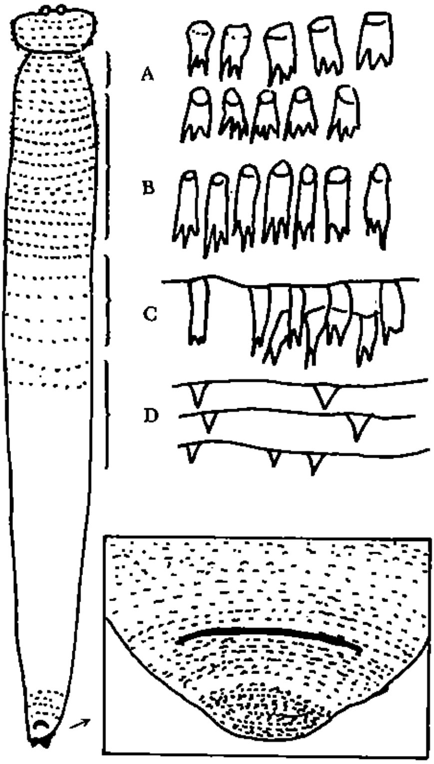

FIGURE 2a. — Diagram of female *G. spinigerum*, ventral view. Notice the shape of its cuticular spines (Redrawn from Miyazaki, 1960).

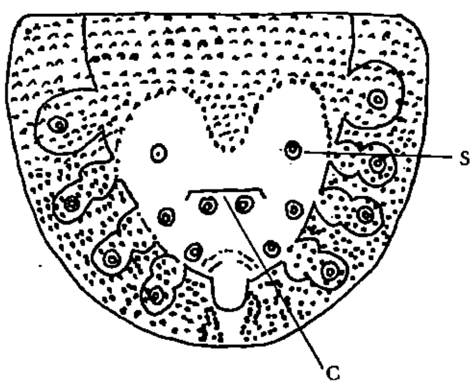

FIGURE 2b. — Ventral side of the terminal end of a male *G. spinigerum*.

S : small ventral papilla
L : large pedunculate papilla
C : cloacal aperture

BIOLOGY OF *G. SPINIGERUM*

Life cycle

After the discovery of *G. spinigerum* about 100 years had passed without clarifying its life cycle, until the real study of the life cycle was begun by Prommas & Daengsvang (1933, 1936, 1937) in Thailand (Daengsvang, 1980; Miyazaki, 1960). They first completed the study of experimental life cycle (FIGURE 3), and found that the first intermediate host was cyclops and the second one was two kinds of fresh-water fish, namely *Clarias batrachus* Linn. (catfish) and *Ophicophalus striatus* Bloch (snake-headed fish). These are responsible for the larval development before becoming adult *G. spinigerum* in the stomach wall of the definitive host (Daengsvang, 1976, 1980, 1981).

When the second intermediate host or paratenic host was eaten by the definitive host or final host, *i.e.* cats, dogs etc., then the advanced third-stage larvae penetrate the gastric wall of the host and enter into the liver and then wander through the muscle and connective tissue, and grow gradually in size there. During the migration period in the tissue and before reaching the adult stage, they undergo moulting. Subsequently these immature worms enter into the gastric wall of the host from outside and become mature. During this period, there were host reaction as a characteristic tumour, which has a small cavity and communicates with the stomach lumen through a small opening. The adult female worms lay eggs which come out through the opening of the tumour into the stomach lumen and passed out in the feces of the host.

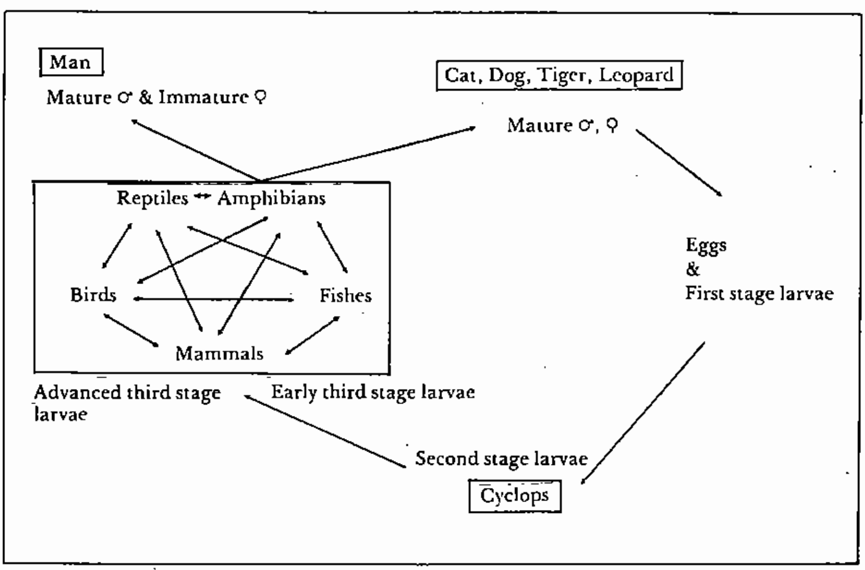

FIGURE 3. — Diagram showing life cycle of *G. spinigerum* in Thailand (From Daengsvang, 1981).

The development of adult worms in the definitive host stomach were also successfully achieved by skin penetration of the host by advanced third-stage larvae (Daengsvang *et al.*, 1970). Similar results also show when those larvae penetrate the skin of mice and rats. The total time required for the complete life cycle, that is the development of the adult worms in the stomach wall of the cats, was about 7 months (Daengsvang, 1981). There were 44 species of vertebrates being naturally infected by *G. spinigerum* advanced third-stage larvae including amphibians, reptiles, birds and mammals, of which fresh-water fish was considered to be the most significant intermediate host transmitting the infection to humans (Daengsvang, 1980).

Mode of transmission

There were 3 modes of experimental transmission of *Gnathostoma* infection (Daengsvang, 1968, 1976, 1981; Daengsvang *et al.*, 1970), namely:

1. ingestion (oral transmission),
2. skin penetration,
3. parental infection.

Ad 1. Ingestion (oral transmission):

It has been demonstrated that *G. spinigerum* larvae obtained from species of experimentally infected fresh-water fish would develop into adults in the stomach of cats, after these latter being fed with such larvae.

Ad 2. Skin penetration:

G. spinigerum advanced third-stage larvae through skin penetration was experimentally proved in cats and dogs; also the life cycle of the parasite could be completely shown by this method of transmission. Eventually the period required for the development into adult worms after this penetration of the larvae in some cases was shorter than after oral route (Daengsvang *et al.*, 1970).

Ad 3. Prenatal infection:

Experimental pregnant mice indicate that of 152 offsprings, two had one unencysted third-stage larvae each; one larva was found in the liver and the other in the costal muscles. Two human gnathostomiasis cases discovered in babies have been reported in Thailand (1965), from whom a small round worm was removed from a small area of creeping eruption on the skin of the chest, while another immature worm was removed from the skin of the umbilical area of a breast-fed baby (Daengsvang, 1968).

Most of the definitive host of *Gnathostoma* worms recorded in Thailand and Southeast Asia were domestic and some wild animals, such as cats, dogs, tigers and leopards (Daengsvang, 1981) (TABLE 1).

The infectivity of *G. spinigerum* larvae have also been tested in monkeys (*Macaca* sp., and *Presbytis* sp.) (Daengsvang, 1971). The results showed that these monkeys served both as second intermediate host and paratenic host after being fed with third-stage larvae of *G. spinigerum* of 10 – 12 days old in cyclops and advanced third-stage larvae respectively.

TABLE 1. — Human and animal gnathosomiasis reported in Southeast Asia.

Country	Gnathostoma and Host										
	G. spinigerum			*G. hispidum*		*G. doloresi*		*G. vietnamicum*		*G. malaysiae*	
	Man	Animal		Animal		Animal		Animal		Animal	
		Def.	Int.	Def.	Int.	Def.	Int.	Def.	Int.	Def.	Int.
Thailand (1889 – 1979)	+ +	cat, dog, tiger, leopard	fish, amphibian, reptile, avian, rodent	pig	—	pig	—	otter	—	—	—
Vietnam (1914 – 1965)	+	cat, tiger	fish	pig	—	pig	—	otter	—	—	—
Philippines (1918 – 1967)	+	cat, dog	fish	pig	—	pig	—	—	—	—	—
Malaysia (1933 – 1976)	+	cat, civetcat, tiger, leopard	—	—	—	pig	—	—	—	*Rattus*	—
Burma (1957 – 1968)	+	cat	—	—	—	pig	—	—	—	—	—
Cambodia (1963 – 1976)	+	—	—	pig	—	—	—	—	—	—	—
Laos (1975)	+	—	—	—	—	—	—	—	—	—	—
Indonesia (1949)	+	—	—	—	—	—	—	—	—	—	—

Note: Def.: definitive host; Int.: intermediate host (Daengsvang, 1981).

PATHOLOGY AND PATHOGENICITY OF HUMAN GNATHOSTOMIASIS

Pathologic changes produced by *G. spinigerum* result mainly from damage to the host tissue by their mechanical action, *e. g.* movement of their spines (Chongchitnant, 1978). Some believe that symptoms and signs produced in the infected host are due mostly to *Gnathostoma* toxin, consisting of factors, namely acetylcholine-like substance, hyaluronidase, proteolytic and hemolytic substances (Miyazaki, 1960).

The basic changes consist of inflammation, inflammatory mass or hemorrhage. Histopathologic changes of the lesions involving the CNS show necrosis of neural tissue, inflammation with eosinophilic perivascular cuffing and demyelinization (Chitanondh & Rosen, 1967; Chongchitnant, 1978).

To make it easy and clear, many clinicians and parasitologists classify the human gnathostomiasis into two groups, *i. e.* gnathostomiasis externa or cutaneous gnathostomiasis, and gnathostomiasis interna or visceral gnathostomiasis (Daengsvang, 1981). The first one shows symptoms and signs on the skin or mucous membrane, whereas the latter occurs in many visceral organs including the respiratory system, alimentary tract, genitourinary tract, eyes, CNS etc.

Cutaneous gnathostomiasis

Symptoms and signs consist of:

1. intermittent migratory swelling of various circumscribed sizes, no pitting on pressure and lasting about one or two weeks. Very rarely cases have been reported without the migratory swelling (Chitanondh & Rosen, 1967);
2. signs of inflammatory reactions over the affected parts;
3. itching and painful, but some cases show neither itching or pain at all.

Visceral gnathostomiasis

Symptoms and signs were varied, depending on the affected organs, location and damage produced by the presence of the worm and host reactions (Daengsvang, 1980, 1981).

As already known these worms can exist in almost every organ and tissue of the body, however, the presence of *G. spinigerum* in the CNS would be the most important thing, because of the possibility of death in the patient, even due to only one worm (Chitanondh & Rosen, 1967; Punyagupta *et al.*, 1968). Most of CNS gnathostomiases produced eosinophilic pleocytosis, referred to as eosinophilic myeloencephalitis (Chitanondh & Rosen, 1967; Punyagupta, 1978; Punyagupta *et al.*, 1968). This eosinophilic pleocytosis also occurs in human angiostrongyliasis caused by *Angiostrongylus cantonensis;* however, the symptoms seem to be different according to the clinical features (Punyagupta, 1978). In *A. cantonensis* infection, the disease varies from asymptomatic to acute neurological disorder which may lead to fatal outcome, while gnathostomiasis produced a unique symptom complex consisting of severe agonizing pain over the trunk and extremities for a few days, followed by paralysis of the extremities. This suggested spinal cord lesion and cerebral hemorrhage. The sequences of the neurological symptoms corresponded well with the neuropathological findings. Bloody and xanthochromic spinal fluid is characteristic. Eye lid swelling may be observed before or after the CNS symptoms appear. It was estimated that *G. spinigerum* was responsible for about 20% as a cause of intracranial hemorrhages among the Thais. The mortality rate of CNS gnathostomiasis is 13–25%, compared with eosinophilic meningoencephalitis caused by *A. cantonensis* which is only 1.2% (Punyagupta, 1978; Punyagupta *et al.*, 1968). The hemorrhage which usually occurs in gnathostomiasis may be due to its spinous body and marked activity of *G. spinigerum* which can inflict a great deal of damage upon tissue and blood vessels.

Another symptom of visceral gnathostomiasis appeared in the alimentary tract simulating acute appendicitis (Ratanarapee & Jesadapatarakul, 1982; Sirikulchayanonta & Chongchitnant, 1978), leading to the misdiagnosis of appendicitis and subsequently appendectomy was done. In fact, these two cases produced distinct signs such as eosinophilia, the absence of fever and history of previous cutaneous manifestations which were unlikely to occur in common acute appendicitis.

A case of urinary gnathostomiasis in a 32-year old Thai woman caused by adult *G. spinigerum* has been reported (Nitidandhaprabhas *et al.*, 1975). The patient had suffered from intermittent subcutaneous gnathostomiasis for about 10 years, developed pneumonia and followed by a swelling on the right hypochondrium. Paresis of both legs occured and accompanied by perianal numbness and retention of urine. It seems reasonable to assume that the parasite migrated to the lungs, hypochondria and the cauda equina respectively. She later passed the worm from the bladder.

From other countries such as Japan, only two cases of CNS gnathostomiasis have been reported; one of them had aphasia and the other generalized convulsion. Recently, one case of eosinophilic meningoradiculomyelitis caused by *G. spinigerum* has been investigated (Kawamura *et al.*, 1983).

A study on experimental mice suggested that the route of migration of the worm into the spinal cord was via the nerve trunk. The disruption of neural tissue and together with the depression by blood clot to the spinal cord produced symptoms of cord lesion, such as paralysis, retention of urine etc. (Bunnag *et al.*, 1981). It is worthy to note that severe morbidity did not occur in the primary passage of infection, in contrast with the repeatedly infected mice exhibiting signs of neural disturbances. This may be due to the immature, surviving larvae in subsequent passages would gain more strength and activity to injure any vital tissue before encystment.

It may be speculated that if man gets the infection through incidental hosts, such as chicken or frog, more changes of tissue damage by this nematode invasion is expected (Bunnag *et al.*, 1981).

HOST—PARASITE INTERACTION

By its nature, the parasites survive and establish in the host because of their ability to adapt themselves in such a new environment. The development into mature adult worms will be achieved when these parasites come across and reside in the appropriate definitive host; on the contrary, they will not develop into adult forms, and persist in a particular stage of development in an unnatural host or parasite host.

In *Gnathostoma* infection, as previously described, the human served as an unnatural, wrong host or accidental host who gets infection after ingested second intermediate hosts harbouring infective third-stage larvae. Surprisingly, despite of no further larvae development, they can, however, actively migrate throughout the body. These migratory *Gnathostoma* larvae, during aberrant migration, fail to develop, lacking the necessary signals from the host, and they wander through the peripheral or deeper tissue, often for long period and causing pathologic response in the host. In the carnivores, as a final natural host, *Gnathostoma* larvae would migrate straight away via a common route to the stomach of the host as a target site, where they become sexually mature adult worms. This type of migration followed the pattern of ontogenic migration. It is not unusual that the migration is closely related to events that lead to transmission.

Another parasite has a characteristic type of migration which was associated with the feeding patterns of the host. For instance, *Hymenolepis diminuta* tapeworms will migrate to the posterior region of the intestine of rats during the day, and anterior region by night. This takes place when the rats are feeding by night and fasting by day. The patterns of migration can be reversed experimentally (Chappell, 1979).

Human gnathostomiasis which has no pattern of migration specifically or even no site selection and recognition, was certainly difficult to study. Some people are interested in investigating the CNS type of migration because it is medically important.

The real mechanisms, why the parasites can not fully mature in a wrong host, while they become adult worms in suitable host, were still unclear and no satisfactory explanation available so far. It was speculated that probably some genes operate in such a way which play a role in recognizing the parasite by the host. Although in *Gnathostoma* infection, the complete development would not be achieved, yet the parasites may survive for some considerable time, because of their successful adaptation, either physiologically or biochemically.

Like in other nematodes, the infective third-stage larvae of *G. spinigerum* are typically aerobic organisms. They possess a functional glycolytic pathway, TCA cycle and β-oxydation..Their electron transfer system operated whereas in the adult form in the suitable host they possess anerobic mechanism for carbohydrate metabolism. The switching for aerobiosis to anerobiosis during normal development must be true for other parasites in general, since this is one of such adaption. The presence of izoenzymes that catalyze the same chemical conversion must be important during invasion, because of the marked alteration in pH and temperature confronting a parasite on its journey from a free living state to the internal tissue of the host. Temperature and high pCO_2 play an important role in metabolic switching during invasion.

Physiologically, the third-stage larvae of *G. spinigerum* have to adapt themselves in the sense of their nutrient uptake, overcome the digestion by, and more important they resist, the host defence mechanism. The third-stage larvae of *G. spinigerum* is already equipped with relatively complete alimentary tract, developed mouth on its head-bulb, necessary for ingestion and digestion. The cuticle covered with spines distributed on the whole body resist the digestive juices from the host.

Host immune response

There are several features of the immune response to parasitic helminths. Inversely, those parasites have evolved an extraordinary variety of mechanism for surviving in the face of the natural and acquired immune responses of their host (Bloom, 1979). These are the games parasites play to evade immune surveillance.

First of all, we realized that parasites, unlike bacteria and viruses, are poorly immunogenic, and are not effective in including the immune response in affected hosts, yet it has been shown that both humoral and cellular immune responses are stimulated during the course of infection (Sirisinha, 1978). The characteristics of both immune responses against parasitic helminths include the presence of IgE antibodies and the appearance of large numbers of eosinophils, mast cells and basophils at the site of infection (Ogilvie & Love, 1974). The mechanisms somehow cooperated with each other in eliminating the parasites from the host.

From the parasites point of view, they have mechanisms of immune-evasions such as antigenic mimicry, in which helminths may coat themselves with molecules resembling their host and so be unrecognized by the host immune response. They may modify the host immune responses by becoming less antigenic when invading a partly immune host or they may actively durate or inhibit the immune response mounted by their host. Another protozoan parasite, such as trypanosome formed antigenic variation, which is able to change the antigenic character of its glycoprotein surface coat and so evade the host immune response (Vickerman, 1978).

Discussing about *G. spinigerum* or in a wide sense, the nematodes as a model, they are usually associated with some properties of their surface coat. Some authors suggested the similarity of nematode cuticle and mammalian cell membrane, such as permeability to chemical compund and the presence of certain constituent chemical groups. This analogy between two coats are of considerable importance when investigating the interaction between the parasite's surface and the components of host immune system. Some reports show that larvae of nematodes can be killed, at least *in vitro,* by cellular attack against the cuticle mediated by antibodies and complement (Jungery *et al.*, 1983). The expulsion of *Nippostrongylus brasiliensis* from the intestine of rats shows this kind of host immune mechanism, as a result of collaboration between humoral and cellular components of immune response (Dineen *et al.*, 1973).

Other groups have been interested in using *Angiostrongylus cantonensis* as a model system to study acquired immunity to infection by tissue nematode (Sirisinha, 1978).

Unfortunately, a few reports on immunological aspects of *Gnathostoma* infection have so far been published in terms of protective immunity. Mostly, they have been conducted on immunodiagnosis of gnathostomiasis by using either a simple method such as intradermal test (Morisita *et al.*, 1969; Tada *et al.*, 1966), or sophisticated RIA methods (Kasemsuth *et al.*, 1981). They have prepared *Gnathostoma* antigen from *G. doloresi* and extract adult worms of *G. nipponicum* for intradermal test to detect *Gnathostoma* infection in human. The RIA technique has been conducted for the diagnosis of gnathostomiasis in cats by means of measuring antibody activity.

PREVENTION AND CONTROL

Up to now there is no anthelmintic drug known to have therapeutic effect on tissue-infected helminths especially in human gnathostomiasis; therefore, the prevention methods or controlling the transmission to humans were the best and most important ones.

Drug trials against mice infected with third-stage larvae of *G. spinigerum* using Bithionol, Thiabendazole, Niridazole, Banocide, Hetal, Flagyl, Dehydroemetine, Jonit etc. show no theurapeutic effect. However Ancylol (2,6-diiode-4-nitrophenol) given parentally, will eliminate adult worms from alimentary tract of infected cats, but not for migrating stage of larvae in the cat's tissue

(Daengsvang, 1981). This drug is still useful and has therapeutic effects to the migrating stage of larvae when it was given subcutaneously in multiple doses with specified intervals (Daengsvang, 1980). Unfortunately Ancylol is very toxic to man; that is why it is not recommended for human use, while in cats it can be used so that the source of infection may be controlled.

Attempts to remove surgically the worms from any precise location on the human body can be safely done, especially in some external gnathostomiasis. The things that should be kept in mind is the short duration of some gnathostome infection, therefore requiring prompt and effective treatment before the worms could greatly damage the affected organs and kill patients particularly those involving the CNS.

At present, the most important way to prevent human infection is in principle (Daengsvang, 1981), to avoid dishes that contain raw or partially cooked fresh-water fish, moreover, not to eat raw or poorly cooked meat suspected to be the source of infection of *Gnathostoma*. For those persons involved in long handling of meat for business or family use, it is suggested to clean their hands with water and soap frequently or wearing thick rubber gloves while preparing the meat, since bare hands might be vulnerable to skin penetration. Also drinking properly treated water in endemic areas of *Gnathostoma* infection is encouraged, because untreated water from shallow wells or surface ground water collections might be contaminated by living infective larvae after being separated from the decomposed flesh or dead infected intermediate or paratenic host (Daengsvang, 1981).

DISCUSSION

After human gnathostomiasis caused by *G. spinigerum* has been reported, many investigations are extensively being conducted, particularly on its pathology and pathogenicity, while others are interested in the diagnostic aspects. This is because of difficulties which usually arise when making a proper diagnosis, especially of visceral gnathostomiasis. Logically the diagnosis of human gnathostomiasis should be confirmed by identification of the worm; however, in general practice clinical symptoms and laboratory findings without the parasites may be useful as well. Recently immunologic approaches have been carried out to erect diagnosis more specifically and sensitively, such as RIA and other simple conventional methods.

CNS gnathostomiasis with eosinophilic syndrome has to be differentiated correctly from eosinophilic meningoencephalitis caused by another nematode, *A. cantonensis*, which causes much less severe disease in the sense of its mortality (Punyagupta *et al.*, 1968).

G. spinigerum has a quite complicated life cycle involving two kinds of intermediate hosts. The second intermediate host, namely fresh-water fish is very important in terms of controlling the transmission to human. This raw fish is consumed popularly amongst Thai and Japanese people, therefore it seems to be a great community problem in local health and probably needs much more intensive health education to the ignorant people. Eventhough it is simple to say, it is not so easy to change their eating habits.

A drug known as Ancylol (2,6-diiodo-4 nitrophenol) has been proposed for the treatment of cat gnathostomiasis (Daengsvang, 1980), but this drug still needs further investigation on its toxicity when used for a relatively long period, whereas none of anthelmintic drugs are so effective in human gnathostomiasis so far. Operative treatment will be successfully achieved only if the parasites can be precisely located in certain areas of the body (Daengsvang, 1981).

SUMMARY

The biology of *G. spinigerum* and its infectivity to humans have been discussed. Among five distinct species of *Gnathostoma* reported in Southeast Asia, *G. spinigerum* is the only causative agent of human gnathostomiasis.

Man serves as an unnatural host, however the migration of infective larvae of the worm throughout the whole body can cause damage and severe host reactions, particularly when they enter into the CNS, resulting in a characteristic eosinophilic myeloencephalitis.

Three fatal cases of eosinophilic myeloencephalitis have been reported in Thailand and many more have probably gone unrecognized or misdiagnosed.

There is no effective treatment for human gnathostomiasis in general; the only best way is preventing the disease and controlling its transmission properly.

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