Human anisakiasis transmitted by marine food products

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Seafood-transmitted parasitic diseases represent an emerging area of interest to the U.S. Food and Drug Administration. Human infections with marine parasites are generally the result of ingesting uncooked seafood products. Over 50 species of helminthic parasites are known to infect humans worldwide. Recently, the number of infections with one of these helminths, the juvenile stage of the marine nematode, Anisakis simplex, *has increased in the United States. Raw fish dishes such as lomi lomi salmon and sashimi are known to transmit the parasite to unsuspecting citizens and the most frequently implicated fish in the transmission of this zoonotic disease is the Pacific salmon (*Oncorhynchus *spp.). The risk of infection from fishes caught in Hawaiian waters is slight; however, a juvenile* Anisakis simplex *infected one patient from either locally caught aku or ahi. We report 4 new cases, which brings the total number of known cases in Hawaii to 7. Five of the 7 cases were diagnosed and treated by means of an endoscope and biopsy forceps. Serological profiles are presented in several of these cases. One case represents the first known instance of reinfection; the initial infection occurred 2 years prior. The second infection gave an opportunity to compare the human response to a challenge infection and to investigate the validity of the "double hit" theory. Increased awareness by physicians to the clinical features of this disease is warranted. The zoonotic disease, anisakiasis, should be considered in patients presenting with intense abdominal pain, if these patients admit they have recently eaten raw or undercooked seafoods.*

There may be a catch-22 associated with the catch-of-the-day; especially if that catch is to be consumed raw or partially cooked. Most U.S. citizens are aware of the alleged benefits of eating seafoods (eg, high in omega 3-fatty acids, low in saturated fats and an excellent source of protein), but remain oblivious to the potential health risks. The health hazards represent the catch-22. Repeated exposure to parasitic infections is one type of hazard for consumers of raw or partially-cooked seafood.

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Nearly every animal in the marine environment is infected with parasites[1]. The vast majority of the known marine parasites, whether they are mature or juvenile forms, do not seriously harm their marine host and will not infect humans. Some seafood parasites, however, may infect humans. These parasites — most often juvenile stages — are often found in the edible portions of the finfishes or shellfishes and survive the food preparation process.

The potential for transmission of parasites from seafood products to humans obviously is greater in areas where marine products comprise a large portion of the protein intake of a population; especially if those foods are ingested raw or not thoroughly cooked. For example, Japan reports about 1,000 episodes of just one parasitic disease, anisakiasis, per year[2]. Conversely, in areas like the U.S. where most seafood is thoroughly cooked, approximately 50 cases of anisakiasis have been reported.

The number of new cases reported in the U.S. is increasing and because of the inherent difficulty in diagnosing the disease, the known U.S. cases may be only the "tip of the iceberg"[1,3-6]. Changes in our dietary habits incorporating ethnic and "natural" foods, tendencies to reduce cooking times for marine food products, and our increasing usage of the marine environment play a role in this escalation. The consumption of raw fish dishes, such as sashimi, lomi lomi salmon, and ceviche, or other inadequately cooked seafood, can cause this disease.

In view of the numerous ethnic and "natural" seafood dishes served in Hawaii, it is puzzling why relatively few seafood-transmitted zoonoses have been reported[1]. Perhaps infections did occur but went undiagnosed. Accurate diagnoses of anisakiasis may be difficult on account of the broad spectrum of clinical manifestations associated with this disease. Further, there may exist a lack of awareness on the part of the local medical practitioners concerning this disease.

This article, therefore, reviews the salient features of the parasitic disease anisakiasis, reports 4 new human cases in Hawaii, and presents specific serologic data associated with these cases. We hope to increase the awareness of local clinicians and physicians concerning this rare but potentially infec-

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tive parasite transmitted by seafoods. Readers who are interested are referred to recent reviews concerning anisakiasis for a more global perspective and for additional details[1,4,5,7].

Human anisakiasis

In recent years, juvenile nematodes belonging to the genera *Anisakis* and *Pseudoterranova* have received considerable attention because of the increase in the number of cases of human infection in the United States[6,8-11] and elsewhere[7,12]. The consumption of contaminated raw or inadequately prepared seafoods transmits the infective juveniles to humans. The juvenile *Anisakis simplex* is about 2-cm-long, 1-mm-wide, white, and tightly coiled in the fish tissue. It is extremely difficult to see within the musculature even by the most experienced sushi chefs and parasitologists. When a viable juvenile anisakid nematode is ingested, the parasite may penetrate into or through the wall of gastrointestinal tract of a host. The resultant disease is called invasive anisakiasis.

In rare instances, a juvenile *Pseudoterranova decipiens* may migrate from the stomach up the esophagus, tickle the throat, and be coughed-up by the patient. This type of infection has been termed luminal or non-invasive anisakiasis[5]. The worms causing this "tickling throat" syndrome are commonly called codworms because of their occurrence in fillets of Atlantic cod (although they may be found in the flesh of other bottom-feeding fishes). Public health authorities probably receive more consumer complaints about codworms than any other nematode. The codworm is approximately 5-cm-long and generally reddish; hence, it is easily observed in the white flesh of cod fillets. The cod fish industry has admitted that this parasite has had a considerable adverse effect on marketing the fish and it spends millions of dollars a year in removing the worms. Heavy infections represent an adulterated product and may lead to its rejection. We have seen live juveniles of *Pseudoterranova decipiens* in imported fishes in Hawaii. However, no cases of human infection with the larvae of this genus have been reported in Hawaii.

Clinical presentation

Sudden, severe, episodic, epigastric distress, sometimes accompanied by nausea and vomiting, usually occurs within 1 to 12 hours after eating the seafood. The literature suggests that the acute epigastric pain generally occurs within 6 hours after consumption of the raw fish; however, episodes have been reported where acute gastric pain was not experienced by the patient until 14 days after eating raw seafood[8,13-15]. Diarrhea and urticaria have been associated with some infections. As in the case of most helminth infections, an increase in peripheral blood eosinophils (from 4 to 41%) may occur in the chronic stages of the disease. Occult blood in the gastric juice or in the stools, slight elevation of temperature and moderate leukocytosis (10,000 to 15,000 leukocytes per mm^3) may result.

Patients with intestinal anisakiasis often present with symptoms suggestive of acute appendicitis although the pain, often associated with the lower right quadrant, may not be as well defined as in acute appendicitis. Edema of the bowel wall may be visible in radiographs or during surgery.

Diagnosis and treatment

The importance of determining whether raw seafood has been eaten recently cannot be over emphasized in terms of making a diagnosis. Clinical features of this can be specific or ambiguous and, therefore, often confuse the diagnostician. Clinicopathologic-confirmed cases of anisakiasis occur in Japan in cases of such divergent preoperative diagnoses as appendicitis, ileitis, diverticulitis, cholecystitis, tuberculosis peritonitis, gastric or pancreatic tumors, and Crohn's disease[16]. The association of juvenile *Anisakis* with cancer has been noted but the worm is not suspected to have induced the cancer[17,18].

An endoscope is very effective in making the diagnosis (Fig. 1) and it is useful in subsequent treatment of gastric anisakiasis. The use of a biopsy forceps to grasp and remove the juvenile worm is demonstrated in Figure 2. Physicians should note that, although the worm's anterior end may be attached to the wall of the lower stomach, the helminth is quite capable of rapid movement within the lumen of the stomach and thus may evade the instrument. The degree of difficulty in removing these lively juvenile worms increases if the worm is not attached to the gastric lining. They move with great speed; their mobility is further enhanced because of the narrow field of vision of the endoscope. Recapturing a worm inadvertently released from the forceps, a scenario one of us (TF) experienced with our first patient, can be time-consuming and frustrating. Figure 3 shows the live worm removed from the gastric lining in Case 5.

Radiography may be helpful as a diagnostic method in some instances but is not totally reliable[9,13,15]. The characteristics of intestinal anisakiasis are not unlike those in cases of intestinal submucosal hemorrhage, ischemic ileitis and regional enteritis[14].

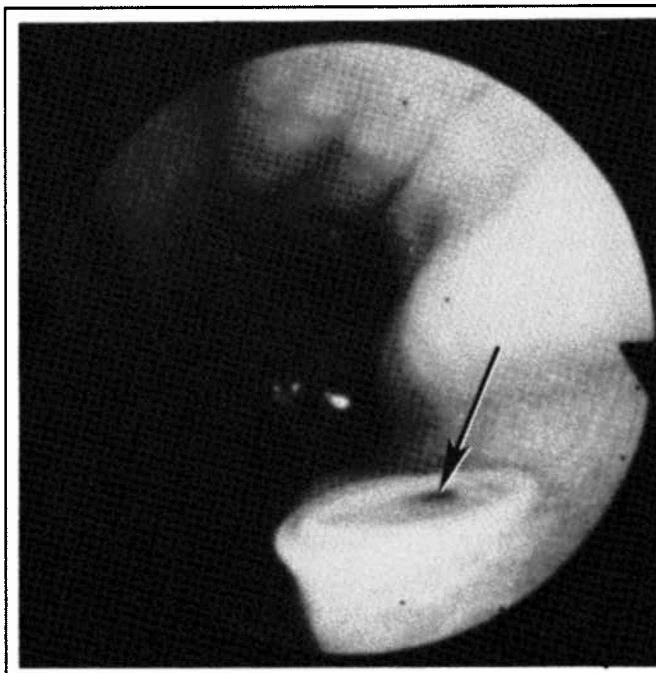

Fig. 1. Endoscopic photograph of a juvenile *Anisakis simplex* tightly coiled at the anterior lesser curvature of the stomach of our patient in Case 2. Note reddened area in center of coil indicating site of penetration (arrow).

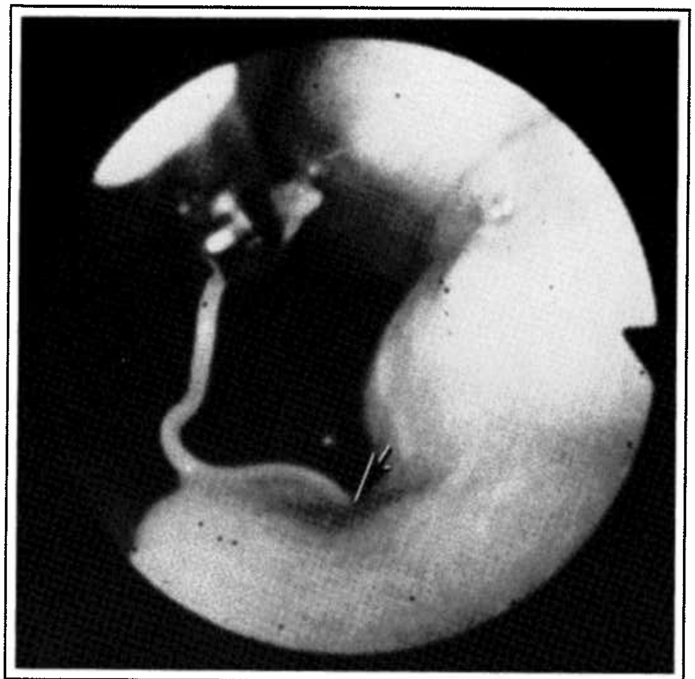

Fig. 2. Removal of worm with biopsy forceps. Note anterior extremity of worm still attached (arrow) to mucosal lining.

If the worm is lodged in an area inaccessible to the endoscope, surgery may be required to remove the worm. A recent report suggested that surgical intervention is not necessary in most patients with intestinal anisakiasis because conservative treatment may be successful[14]. Our Cases 6 and 7 (Table 1), for example, experienced acute pain but recovered without treatment. Death is unlikely, although 2 fatalities in the literature were attributed to peritonitis following perforation of the bowel at the site of intestinal resection[4]. The worm does not mature in humans and research has shown that the worms do not survive in vivo beyond 3 weeks post-infection in a mouse host[19]. Currently there is no effective drug as an anti-helmintic against this parasite.

Life cycle and history

The life cycle of anisakid worms, which begins and ends in marine mammals such as whales, sea lions, seals, and dolphins, may be complex (Fig. 4). Adult female worms (the sexes are separate) lay eggs in the stomach of the marine-mammal host and the eggs pass out with the feces into the water. A second-stage juvenile will emerge within a few days from the egg and may be eaten by a variety of crustaceans (eg copepods and shrimp). If that crustacean represents an acceptable intermediate host, the worm develops into a third-stage juvenile in the hemocoel of that animal. It may be infective to some marine mammals at this stage. Should that crustacean not be a suitable host, the life cycle may involve fishes. When the fish eats the infected crustacean, it becomes infected. Finally, marine mammals feed on the infected fishes and the life cycle of the anisakid nematode is completed. Humans may become infected by intervening in the natural life cycle by eating the infected fish.

Because the worms mature in marine mammals, it is generally assumed that the prevalence and intensity of potentially invasive parasites in fishes is greater in areas where mammals are plentiful. Thus, marine mammals may serve as a barometer to predict the infective potential of worms in fishes. The U.S. Food and Drug Administration (FDA) conducted studies to determine the incidence and pathogenic potential of anisakine nematodes in marine fin- and shell-fishes from the coastal waters of the continental U.S. These studies revealed that fishes caught off the Pacific coast have a greater worm burden than fishes caught in other survey areas. Concomitantly, the concentration of marine mammals along the Pacific coast is significantly greater compared with the other survey areas. Other studies have confirmed the correlation between the numbers of invasive worms and the presence of marine mammals.

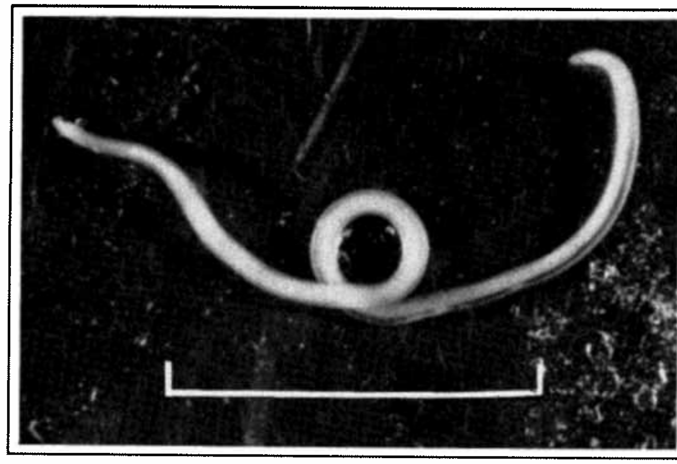

Fig. 3. Close-up of juvenile *Anisakis simplex* retrieved from stomach of patient in Case 5. Bar = 1 cm.

Concerning the FDA's study of the territorial fishing waters off the Hawaiian Islands, it concluded that, because nearly all anisakine larvae were found in nonedible tissues of the fishes and invertebrates caught in local waters, the risk of infection to the consumer was probably slight[20,21]. Fishes imported to Hawaii for consumption, however, represented a more substantial problem to local conumers.

A total of 158 specimens of finfishes imported to Hawaii, representing 15 species, were examined between 1980 and 1985 (TLD, unpublished data). Of these fishes, Pacific salmon (*Oncorhynchus* spp.), cod (*Gadus* spp.), pollack (*Theragra* spp.), and "Pacific red snapper" (*Sebastes* spp.) were infected with juvenile *Anisakis simplex;* fishes in the latter 3 genera also were infected with juvenile *Pseudoterranova decipiens.* Of the imported fishes examined, salmon probably represent the greatest health risk to the people of Hawaii because of the popularity of lomi lomi salmon. Juvenile *Anisakis simplex* were found in 91% of the salmon examined. Furthermore, when 20 salmon steaks (average 150 grams) and rockfish fillets (average 150 grams per fillet) were purchased from local supermarkets and examined, all samples were positive for the potentially invasive juvenile *Anisakis simplex.* All juvenile *Anisakis simplex* found in the salmon steaks were dead; likely a result of the commercial blast-freezing process completed prior to cutting the salmon steaks[1]. However, some of the worms in the rockfish were alive.

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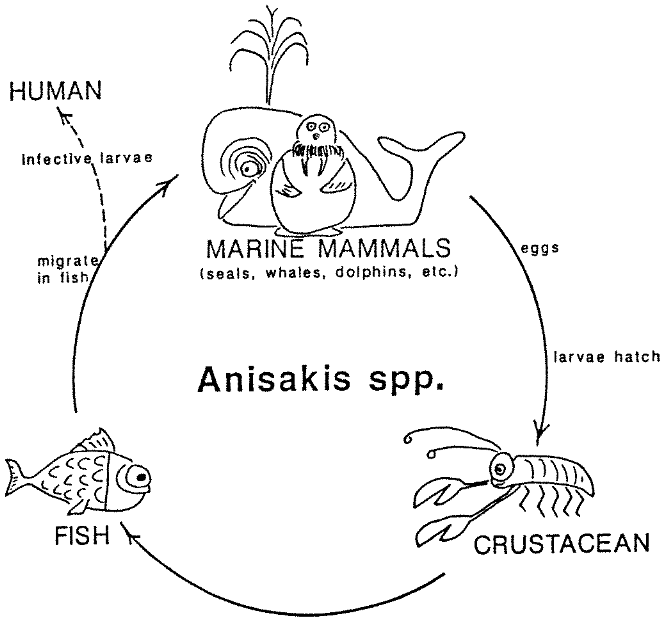

Fig. 4. Generalized life cycle of a marine ascaridoid[1]. This large group of nematodes has adults that infect the stomach or intestine of a variety of marine mammals and juveniles that encyst in fishes or crustaceans. The juvenile stage that encapsulates in fishes has been confirmed to infect humans[1].

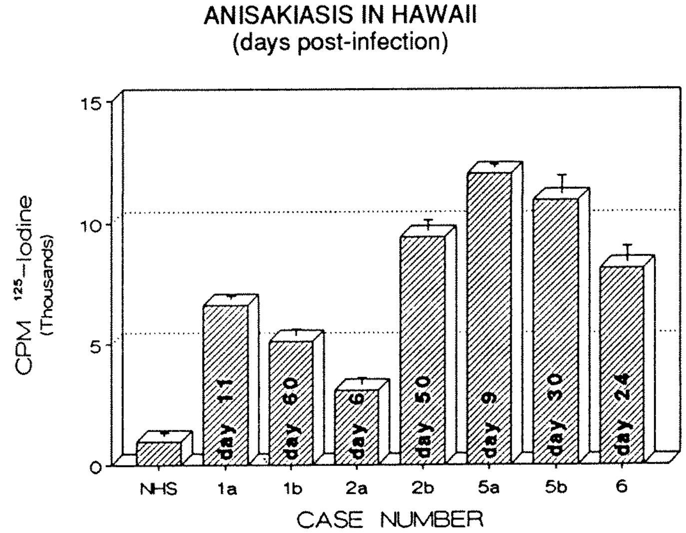

Fig. 5. Radioallergosorbent test results detecting *Anisakis*-specific IgE antibodies from patient's sera. Number within bars refer to the day serum was drawn post-infection. Case numbers correspond with those in Table 1.

Hawaiian cases

The majority of cases in the U.S. result from eating raw Pacific salmon (*Oncorhynchus* spp.) or rockfish (*Sebastes* spp.); juvenile *Anisakis simplex* are most commonly implicated. Most Hawaiian cases of anisakiasis are transmitted by salmon (Table 1) and all worms recovered from patients in Hawaii have been identified as *Anisakis simplex*.

Table 1 shows the salient facts concerning the known suspected and confirmed cases of human anisakiasis in Hawaii. A juvenile *Anisakis simplex* was removed with the aid of an endoscope from each of the patients in Cases 1-5. Cases 5-7 represented a single family; wife, husband, and child, respectively. All developed similar acute gastric pain one hour following ingestion of the same sashimi meal. Case 6 subsequently was confirmed by serologic testing (Fig. 5). No serum was collected from the child, but we believe he was infected.

A reliable and practical diagnostic assay currently utilized is the radioallergosorbent assay (RAST)[3-5,9,22]. The assay is based on increased IgE titers associated with helminthic infections. Briefly, the RAST determines the level of parasite-specific IgE in the patient's serum. *Anisakis simplex* antigens were coupled to cyanogen bromide-activated beads and reacted with the sera. I^{125}-labled antihuman IgE antibodies were used to detect bound IgE and the data are expressed as counts per minute (cpm). The sera were tested against antigen of *Ascaris suum* to rule out infection with this closely related parasite.

Figure 5 depicts relative *Anisakis*-specific IgE levels from Case 1a,b (days 11 and 60 post-infection), Case 2a,b (days 6 and 50), Case 5a,b (days 9 and 30), and Case 6 (day 24). Patients in Cases 1, 2, and 5 showed an increase in *Anisakis*-specific IgE levels even after the juvenile worms were removed. This was expected. Our data demonstrate that *Anisakis*-specific IgE levels rapidly increase following infection, appear to peak near 30 days post-infection, and gradually decrease. How long these levels remain elevated is unknown; however, one case report from San Francisco, California, demonstrated that the IgE levels remain nearly 3-fold higher than normal 6 months later[3].

Cases 1 and 2 are unique because they represent the same patient. There have been conflicting opinions in the scientific literature with regard to whether or not the "double hit" theory is valid for anisakiasis. This theory holds that the second infection with a juvenile *Anisakis simplex* will invoke an anamnestic eosinophilic inflammation measurably greater than observed during the first or primary infection. Our patient represents the first reported case of reinfection and allowed us the opportunity to compare the human reponses with a challenge.

Subjective findings compiled in Case 2 suggested the validity of the "double hit" theory. The patient stated that the second exposure was substantially more painful and severe as compared with the initial infection. During the esophagogastroduodenoscopy for the second occurrence, we noted that the inflamed area extended a greater distance from the point of worm penetration and that the erosion was deeper.

The results of the RAST strengthened the validity of a heightened response. Figure 5 illustrates that *Anisakis*-specific IgE levels at day 50 post-infection in Case 2 were nearly 2-fold greater as compared with day 60 in Case 1 (9,430 versus 5,116 cpms, respectively). Furthermore, the reinfection sera (Case 2) represented the only incident wherein the IgE levels continued to rise dramatically 7 weeks later. This is a significant contrast with Cases 1 and 5, as well as with a report of 9 cases of acute gastric anisakiasis in Japan[23]. In that report, RAST results showed that the IgE response was measurable by day 1, increased rapidly for 3 to 5 weeks, and then gradually decreased. Those findings were similar to our Cases 1 and 5. We speculate that the continued rise in IgE levels in Case 2

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Table 1. Case history highlights of anisakiasis occurring in Hawaii

Case No.	Date (m/yr)*	Location of Parasite	Interval Between Ingestion and Expression of Symptoms	Raw Seafood Implicated	References
1	8/84	Stomach	11 hours	Pacific Salmon	9
2	10/86	Stomach	1 hour	Pacific Salmon	This Report
3	1986	Stomach	No data	Ahi and Aku	3,28
4	1986	Duodenum	No data	Imported Squid	3,28
5	8/89	Stomach	1 hour	Pacific Salmon	This Report
6	8/89	Not Examined**,+	1 hour	Pacific Salmon	This Report
7	8/89	Not Examined**,†	1 hour	Pacific Salmon	This Report

*Month omitted if not available.
**Endoscope not used
+Confirmed by serologic testing
†Suspected infection (see text).

was a function of an infection of a previously sensitized patient.

An argument could be made that the worm penetrated more aggressively in the second infection; therefore, the signs and symptoms were more profound and that sensitization had no bearing on the event. The patient in Case 5, for example, was presumably infected once only, yet by day 9 exhibited a greater response compared with day 50 PI (12,037 versus 9,430 cpm, respectively) for Case 2, as measured in our RAST assay. Further controlled laboratory experimentation is necessary in order to address this issue.

The reinfection of a patient certainly demonstrates that some individuals have difficulty breaking ingrained habits. This patient was well-educated and, following her first infection, received counseling on the disease and its mode of transmission. Knowledge of the disease allowed her to evaluate the risk, risks which she subsequently took and eventually suffered the consequences. Clearly, eradication of seafood-transmitted parasitic diseases in the U.S. solely by means of public education will be a formidable task.

Six of the cases in Hawaii occurred as a result of meals prepared at home. This is predictable because of the amount of seafood consumed at home, lack of awareness by consumers of the risks of infection and the difficulty with observing juvenile worms in the fish's flesh. We found, for example, that careful dissection and "candling" of a fillet was not effective in removing all worms. Subsequent digestion in our laboratory usually yielded additional nematodes.

All cases of anisakiasis in Hawaii, however, did not result from home-prepared meals. A local sushi bar has been linked to the transmission in Case 4 (Table 1)[24]. Commercially-prepared products in Hawaii also may serve as conveyances of parasites. For example, 5 1-pint containers of the commercially-prepared lomi lomi salmon were purchased from a major supermarket chain in Hawaii; on examination, two living nematodes and numerous worm fragments of juvenile *Anisakis simplex* were recovered[9].

Other seafood-associated nematode infection

One other marine nematode from a fish has infected persons in Hawaii. In that case, an adult philometrid nematode infected a fisherman while he was filleting a fish[25]. This accidental infection probably could not have occurred had the fisherman not had an open cut or lesion on his hand. As he filleted the infected fish (papio, jackfish), contact between the marine nematode and the broken skin must have occurred. The worm had penetrated 25 mm into the patient's hand within 3 hours; a 1.1 cm portion of this nematode protruded from the lesion. Surgical removal was necessary.

Prevention and education

Such parasitic helminths are extremely sensitive to temperature extremes. The heat from thorough cooking or adequate freezing will kill the worms in the fish tissues. Obviously, there are instances where cooking a product is not desired. The FDA, therefore, released an interpretation (Part 6; Chapter 01; No. 2-403) in 1987 which suggests that finfishes, bivalve mollusks (scallops), gastropods (abalone), cephalopods (octopus and squids), and crustaceans (lobsters and crabs) that are not cooked throughout to 140°F (60°C) or above, must be blast-frozen to -31°F (-35°C) or below for 15 hours[11] or regularly frozen to -10°F (-23°C) or below for 7 days[26] before sale or serving in ready-to-eat form. Clams, mussels and oysters are specifically excluded from this ruling because of existing controls imposed by states under the provisions of the National Shellfish Sanitation Program. Juvenile worms may survive certain industrial- and home-processing regimens involving marinating, brining, or cold-smoking.

The United States is not the only country to require freezing as a means of increasing the consumers margin of safety in seafood zoonoses. The Netherlands established legislative regulations in 1967 which mandated that fresh herring should be frozen to at least -20°C for 24 hours before being released to the public. These regulations, known as "The Green Herring Laws," have resulted in the disappearance of human anisakiasis from The Netherlands. According to the World Health Organization, prior to these regulations, that country had 300 cases per annum[12]. The European Economic Community (EEC) in 1988 considered a draft regulation requiring freezing of fishes similar to the one in The Netherlands[1]. Japan has no freezing regulations or policy with regard to prevention of anisakiasis; however, it is common practice in Japan to freeze Pacific salmon in order to kill the potentially invasive worms[1].

Despite the evident success of freezing regulations as demonstrated in other countries, this does not convince everyone. The Hawaii Seafood Promotion Committee (HSPC), for example, initiated a campaign to protest the FDA's suggestion that all fishes intended to be served raw or partially-cooked should be frozen. The HSPC acknowledged the possible health risks associated with the raw consumption of some fishes, such as Pacific salmon and Pacific rockfishes, and conceded that the freezing of these fishes may be prudent, but it asserted that freezing of tuna is not necessary. It believes tuna is "safe to eat raw" and states that tuna has never been implicated in the transmission of anisakiasis. The patient in Case 3 (Table 1) could take exception to this statement.

A seafood connection with parasitic diseases in Hawaii clearly has been established and clinicians and physicians need to become more aware of this association. The risk of people in Hawaii becoming infected with these parasites from seafood products are extremely low; however, this risk increases slightly if imported fresh fishes raw or partially cooked are eaten. Prevention of these diseases, therefore, is probably best accomplished by providing continuous, accurate, and responsible information to the public concerning the health risks of eating raw fishery products; by advising the seafood industry of potential problems and methods of addressing them properly; and by promoting awareness within the medical community.

Education of these groups must be continuous for at least two reasons. First, as demonstrated in our reinfection case, raw seafoods comprise a normal and irrevocable part of the diet for some individuals. These habits are ingrained and continual reenforcement of the risk appears to be necessary. Second, as we continue to exploit the abundance of species of ocean fishes and invertebrates as a food source, new marine parasites, some of which will be capable of infecting humans, will be encountered. Thus, the catch-of-the-future also may have within it a catch-22 situation.

We suggest that anisakiasis be considered in the differential diagnosis of patients presenting with acute, sporadic, abdominal pain, especially if these patients have a recent history of eating raw or undercooked seafood products. Inquiring as to the recent eating habits of a patient may represent a critical consideration in achieving a correct diagnosis. Should anisakiasis or other parasitic disease be suspected, we would appreciate being contacted.

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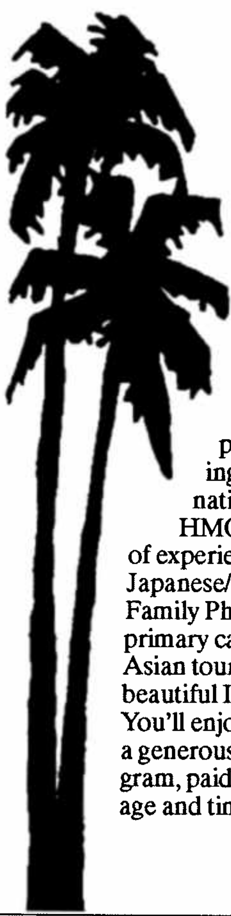

HUMAN ANISAKIASIS *(Continued from page 15)*

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