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ITAMAE SAN, SASHIMI
NI MUSHI, GA IMASU!

(Waiter, there's a worm in my *sashimi*!)

Texts of medical parasitology are like counter cook-books describing the ethnic and cosmopolitan gastronomic delights that serve as conveyances of infection. A steak tartare or hamburger rare may sow the seeds of beef tapeworm and toxoplasmosis. That ambrosial country sausage may produce a ten-foot-long pork tapeworm or, even worse, an acute, sometimes fatal case of trichinosis. The tourist to Asia who will "try anything once" may have a fluke (*Clonorchis*) implanted in his biliary tree or a Roto-Rooter-headed larva of the gnathostome burrowing through skin, soma, and brain after succumbing to the temptation of a dish containing raw fresh-water fish. And beware the drunken crab (uncooked fresh-water crab marinated in rice wine). That particular Asian specialty can deliver a worm (*Paragonimus*) to lung and brain. It is no wonder that medical students, a highly suggestible lot, are close to anorexia nervosa by the time they take their final exam-

ination in parasitology. For our students at the University of Hawaii school of medicine, particularly those of Japanese ancestry, only *sashimi* (raw marine fish) seems safe, and it is a sad day when I have to give the lecture on anisakiasis that will dislodge them from their last refuge of culinary comfort.

At night, lights from the small shops lining the narrow, serpentine side streets of Japanese cities beckon the passer-by. From within the restaurants, each displaying plastic pop-art models of the *spécialités de la maison*, issues a subdued conviviality of voices, with a promise of warmth. On an autumn evening, at the Season of the Chrysanthemum, a man whom we shall call Manabu Okada was making his way home through such a street after a trying day at the factory. As he passed a *sashimi* bar the thought of that fish nosh, complemented with warm saki, was irresistible. He entered through the curtained doorway and inspected the glass case on the counter which displayed slabs of raw fish and squid. Mr. Okada selected a rosy-pink piece of tuna, which the proprietor, with deft artistry, cut into thin slices. Each slice of the delicately flavored fish was dipped into a pungent sauce consisting of soy sauce, freshly grated horse-radish, and mustard powder. (A preparation of green horse-radish, *wasabi*, can be purchased at oriental food stores. I use Colman's mustard powder, adding enough mustard and horse-radish to the soy sauce to make my eyes water when I taste it.)

The inner man having been well served, Mr. Okada arrived home about 7 P.M., had a light meal, watched television for a short time, and was asleep by 9. He slept soundly until 3 A.M., when he was startled into sudden waking by an abdominal pain so keen that it was like a *seppuku* sword piercing his stomach. Somewhat con-

fused by the strangeness of the pain and the hour, he managed to stagger to the bathroom, where he agonizingly retched up blood tinged vomitus. Then he collapsed. His wife, thoroughly alarmed, called an ambulance, and Mr. Okada was rushed to a nearby hospital. The attending physician, after making certain Mr. Okada's condition was not life-threatening, began to ask questions, some of which seemed peculiar to the distressed patient. Had he eaten *sashimi* earlier that day? (Yes.) How long before the attack had he eaten *sashimi*? (About eight hours.) What kind was it? (Tuna.) How much did he eat? (One portion.) Satisfied that emergency surgery was not necessary, the doctor entered his provisional diagnosis of anisakiasis on the chart, requested a gastroenterological consultation, gave Mr. Okada a shot for his pain, and had him admitted to a medical ward.

In the late morning Mr. Okada, his pain somewhat blunted by drugs, was seen by a gastroenterologist. This specialist employed a fiber-optics gastroscope, a cunning instrument that enables the doctor to illuminate and inspect the stomach wall. The gastroscope's reconnoiter revealed the expected lesion, an ulcer approximately two inches in diameter located on the inner stomach wall. At the center of the ulcer's bloody crater a small, threadlike worm, its anterior end buried in the tissue, could be seen undulating leisurely. Still peering through the gastroscope, the doctor used a pair of remote-control pincers to pluck the worm neatly from the lesion. The laboratory parasitologist confirmed that the worm was an *Anisakis*-type larva. No one was surprised; several hundred cases similar to Mr. Okada's occur each year in Japan. Mr. Okada did not require surgical resection of his affected stomach, as some cases

do, and within a few days felt well enough to be discharged, with a caution to stay off the *sashimi*. However, like most Japanese, he was gastronomically hooked on the fish and continued to indulge in the pleasures of the flesh.

While human anisakiasis remains a public-health problem in Japan, it has also been discovered, relatively recently, elsewhere. There is an international aspect to the trail of anisakiasis not unlike that of certain other parasites and the diseases they cause. For example, *Paragonimus westermani*, a trematode responsible for a serious lung disease in Asia, was first seen in a Bengal tiger that had expired in the Amsterdam zoo in 1887. Two years later Japanese doctors discovered the same parasite in the lungs of patients who had died of a pulmonary disease thought to be tuberculosis. The history of Mr. Okada's worm involved the same unlikely Dutch-Japanese connection. It began in 1955, when a fifty-one-year-old citizen of Rotterdam was suddenly seized by abdominal cramps so violent that he was rushed to a hospital, where emergency surgery was performed. When the surgeon exposed the abdominal cavity, the cause of the attack was revealed—an angry, bleeding ulcer, approximately two inches in diameter, in the ileal region of the small intestine. The offending lesion was excised, the wound closed, and the patient returned to the postoperative ward, where he made an uneventful recovery.

Only later, when the pathologist examined the preserved tissue specimen, was it discovered that this ulcer was far different from the "normal" gastrointestinal ulcers occurring in Holland. From the center of the inflamed, eroded tissue a 1½-inch worm protruded. Examination showed the worm to be a larval nematode

of undetermined genus and species. At the time this was considered to be one of those isolated episodes in which a larval stage of an animal parasite makes an abnormal foray into human tissue, and the case was dismissed.

But over the next five years individuals with the same complaint of acute abdominal pain of sudden onset, and with no previous history of intestinal disease, began to appear in the emergency rooms of Dutch hospitals. Between 1956 and 1960 sixteen such cases were admitted to hospital. Eleven of them went to surgery, and in each of these, a larval worm was found in the swollen, hemorrhagic intestinal wall. Clearly, a new disease had appeared on the Dutch medical scene. Several obvious questions had to be answered if the disease was to be understood and controlled. First, the nature of the parasite—its taxonomic status and its life cycle—had to be identified. Second, a determination had to be made as to whether it was truly an infection new to man, caused by one of those pathogens (such as *Babesia microti* and the Ebola-fever virus) that from time to time appear, as if suddenly and mysteriously spewed forth from an epidemiological maelstrom. Alternatively, it could be an infection that had occurred in Holland before 1955 but had gone unrecognized as to cause.

Identification of the worm proved to be more difficult than expected. In the immature stages the species of nematode parasites are not readily identified, because they lack the morphological landmarks of the adult that most parasitologists are familiar with. For this reason, or because the material didn't fall into the hands of the right expert, the parasite remained a taxonomic enigma until 1960. In that year some of the larval worms obtained from patients were examined by P. H. Van Thiel, a Dutch parasitologist familiar with the nema-

todes of both humans and marine animals. Van Thiel made the startling pronouncement that the larvae were *Anisakis*. The discovery was startling because *Anisakis* adults are parasites within the intestinal tract of marine mammals (porpoises and whales) and their larvae, during the course of the obligatory life cycle, are present in marine fish. The pieces of the epidemiological puzzle finally fell into place when another Dutch parasitologist, C. F. A. Bruijning, noted that the larval worms from humans with anisakiasis were identical to those parasitizing the herring caught in the North Sea.

The appropriate questions could now be asked of old and new patients with a confirmed diagnosis of anisakiasis. Had they eaten herring before their attack? If so, how had the herring been prepared? How long was the interval between eating the fish and the onset of abdominal pain? There was a unanimity of response that gave unmistakable evidence as to the source of the infection. All patients had eaten a lightly salted, uncooked herring locally known as green herring. Abdominal colic usually began about twenty-four hours after the meal, although in some cases the time interval was as short as four hours and in others as long as three days.

It was now assumed that this was a disease new to Holland, and the intriguing problem remained of what had caused its relatively sudden appearance. Though a new infection, such as anisakiasis, seems to arise from the void, there is always a reason for it—a new set of conditions that has brought the pathogen to humans. As far as can be determined, the two factors responsible for human anisakiasis in Holland were the introduction of a new way of preparing herring and a change in the traditional manner of processing the newly caught fish. Green herring was first placed on the market during the

early 1950s. My Dutch friends tell me that their countrymen took to this raw, salted snack like Americans took to pizza. At about the same time that green herring was being introduced for public consumption, the traditional practice of eviscerating the fish while still at sea gave way to that of cleaning the fish ashore. The fish were iced after being caught, and often several days passed before they were brought to port and processed. In some fish, the larvae of the potentially pathogenic anisakid worms are naturally present in the flesh, but in herring, most of the anisakid larvae are normally located in the tissues of the intestinal tract, so the former custom of gutting the fresh herring immediately had rendered them fit for consumption even in the raw state. But now, as the iced fish cooled, some of the larvae were prodded into a migratory movement to seek the somewhat warmer protection of the musculature. Thus the green herring was now more likely to contain a worm.

When Japanese physicians read the Dutch publications, they realized that some of the patients they had seen over the years with similar symptoms could have had anisakiasis. Certainly, for sheer tonnage of raw fish consumed, no other people rival the Japanese. The first parasitological diagnosis of human anisakiasis in Japan was made in 1965. This was followed, within a few years, by almost five hundred more confirmed cases. Peculiar stomach lesions of unknown cause had been reported in the Japanese medical journals since 1940. Now that pathologists knew what to look for, they re-examined the tissue sections made from these patients' lesions, and this retrospective review brought to light several hundred more cases.

The recognition that nematode parasites of marine

animals could cause human disease stimulated a renewed effort to study the taxonomy, life cycles, host relationships, pathogenicity, and immunology of these worms. We are at mid-point in this research, and as at most research mid-points, there is considerably more confusion than at the beginning or the conclusion. There is, however, general agreement that all of the larvae recovered from the human cases are anisakine parasites. Anisakines are a large group of nematodes belonging to the same family as the ascarid of man, *Ascaris lumbricoides*, and the ascarid of canines, *Toxocara canis*. There are about twenty-four genera of anisakines; the exact number depends on whether the classification being used is that of a "lumper," a taxonomist who regards variants with minor morphological differences as belonging to a single species, or a "splitter," one who regards these minor morphological differences as indications of separate species. Adult anisakines are found in fish, reptiles, birds, and mammals, with different genera normally parasitizing different hosts.

The exact species of the larvae recovered from humans remains uncertain, and there is disagreement even on their genera. Working one's way through the taxonomy of these parasites is like being in a complex labyrinth whose exit has yet to be constructed. The Dutch cases, as well as most of the Japanese, seem to have been due to one or more species of *Anisakis*, the ascarid worm of porpoises and fish-eating whales. In addition, some of the larvae from cases in Japan and elsewhere have been identified as being a species of *Phocanema*, an anisakine parasite normally residing in seals. Experimental studies tend to confirm that only the larvae of "marine mammal" anisakines are capable of invading the tissues of an abnormal host, such as

humans. When various kinds of larval anisakines were introduced into the stomachs of rats only those of "marine mammal" species were subsequently found to have penetrated the stomach wall.

The developmental cycles of all "marine mammal" anisakines appear to be similar. The adult female's eggs are shed, along with the host's feces, into the sea. The number of eggs produced daily is not known, but her "human" cousin, *Ascaris lumbricoides*, is a fecund marvel, laying 200,000 eggs each day of her life. The eggs sink to the sea floor, and within a few weeks a larva develops inside each one. When embryonation is completed, the larva emerges into the marine world. If the developmental journey is to continue, the larva must be eaten by the first intermediate host, a shrimp. The larva penetrates the shrimp's digestive tract and comes to lie in the body cavity, where it molts, grows, and awaits the next fateful event that will allow it to progress along the life cycle. This occurs when a fish or squid devours the infected shrimp. The larva bores through the stomach wall of the fish to become immured in the tissues. A few worms may penetrate to the viscera or musculature. In the fish the larva molts again, to become the infective stage. If a larger predatory fish eats the infected fish, the larva merely transfers to the new host. In this way the infective larva can be serially passed along the food chain a seemingly indefinite number of times—from squid to fish, or fish to squid, or fish to fish—without undergoing any further maturation. The final event in the cycle takes place when a marine mammal consumes the infected fish or squid. The larva escapes from the digested intermediate host and attaches itself to the stomach wall of the marine mammal, where it grows into a sexually mature adult.

Anisakid larvae have been found in fish from virtually all the world's briny waters—from tropical and arctic seas, from the Atlantic and the Pacific. A great variety of fish are parasitized, with the species of fish and the species of infecting worm depending on the nature of the fish and mammal population in the marine habitat in question. In coastal North Atlantic waters, where seals are relatively plentiful, pollack and cod are frequently infected with the "seal" worm, *Phocanema*. In the waters bordering Holland many herring are infected with the "porpoise" parasite, *Anisakis*. A recent outbreak of human anisakiasis in the Nantes region of France is believed to have been caused by the regional gastronomic specialty, raw sardines. All sorts of fish caught off both American coasts have been found to be infected—salmon, flounder, croaker, and mackerel, to name a few. When Dr. George Jackson and his colleagues at the Food and Drug Administration surveyed the fish sold in Washington, D.C. markets, they examined 1,010 fish belonging to twenty genera and twenty-three species and recovered 6,547 parasitic nematodes.

Those who dine on fish that has been baked, broiled, braised, or fried run no risk of contracting anisakiasis. Both cooking and freezing kill the parasite. The Dutch brought a rapid end to the outbreak of the infection by enacting legislation that required all herring to be frozen before being marketed. Such legislation is impossible in Japan. *Sashimi* cannot be prepared from frozen fish, and the Japanese would not forgo their deeply entrenched taste for raw fish in return for freedom from a disease that affects "only" several hundred people each year. At any rate, the variety of fish consumed as *sashimi* is too great for any legislation to be effective. In the United States, five cases of human anisakiasis

have been documented, even though most Americans would, like my wife, classify raw fish as "funny food."

For some unknown reason, these North American cases have tended to be clinically much more benign than the infections experienced elsewhere. In fact, the first instance of American anisakiasis was discovered by chance, in 1972, when a seventy-six-year-old Massachusetts man required surgery to correct, by bypass graft, an aneurysm of the iliac artery (the blood vessel that runs along the small intestine). The diseased, atherosclerotic portion of artery was placed in a bottle of formalin after it had been removed, and nothing unusual was noted at the time. Later, when the tissue was about to be processed for histological sectioning, a three-inch-long worm was found in the bottle. The worm was subsequently identified as the larval stage of a species of *Phocanema*. How this man acquired the infection is somewhat of a mystery; he claimed that he ate fish infrequently and then only when it was well cooked. Nor did he have any abdominal complaints prior to surgery. Finding the worm was considered fortuitous, for there was no evidence that it had played any role in causing the aneurysm.

The other four American cases were even stranger in that the patients themselves coughed up and extracted the worms. A man in California who had eaten *sashimi* prepared from white sea bass purchased from a Marin County fish market felt a peculiar tingling sensation in the back of his throat ten days after this meal. He coughed, put his fingers in his mouth, and drew out a live, wriggling three-inch-long worm. A lady in Nova Scotia had a similar experience four hours after eating an undercooked cod fillet. So did an Ecuadorian lady living in New York, after preparing and eating *ceviche*,

an Ecuadorian dish of marinated raw fish. All of these "throat" worms have been identified as the larval stage of the "seal" anisakine, *Phocanema*.

This variation in pathogenicity is perplexing. Do the different species of anisakine have different invasive potential, or is diversity among the human hosts involved? The only such diversity that has been suggested so far is in the amount of gastric juice, with the Japanese tending to have somewhat less than others. It is believed that the larval worms burrow better in less acidic conditions. Nor do we have, as yet, a full appreciation of the entire clinical orchestration of anisakiasis. Are there many asymptomatic infections like that of the man with the aneurysm, whose parasite was found only by chance? The answer to this problem will probably not be forthcoming until a specific serological test to detect these silent infections is perfected.

At the other end of the clinical spectrum, a study carried out by Sapporo Medical College's surgery department has some alarming implications, at least for Japan. This group studied the tissue sections, obtained during surgery, of patients diagnosed as having acute regional ileitis or Crohn's disease, whose cause(s) are currently unknown. After careful re-examination of this material, they concluded that at least half of the cases had been misdiagnosed. It was their opinion that the histological picture in these instances was more compatible with anisakiasis than with the intestinal disease originally identified. In fact, all or part of the worm was actually seen microscopically in the tissues of 140 out of 876 patients who had been diagnosed as having acute regional ileitis.

There is also much to be learned about the pathogenesis of what is considered to be typical intestinal and gas-

tric anisakiasis. Since the human is an abnormal host, the larva that burrows into the wall of the digestive tract eventually dies without reaching sexual maturity. But while the intruder lives, it elicits an intensity of inflammatory response and a size of ulcerative lesion out of all proportion to its own relative minuteness. The esophagus of *Anisakis* has a large glandular portion, and secretions from it may be responsible for these untoward effects. But this is still speculative; secretions are yet to be isolated, characterized, and tested for pathogenic activity.

It would be some small comfort to be assured that humans have already acquired their full lot of parasites and other pathogens. At least there would be no surprises, and medical science could go about dealing with the old familiars. However, every so often a new germ or worm comes along to shake this complacency. And I must admit that the scientists present at the "birth" of a new human infection experience a special sense of excitement. As far as anisakiasis goes, those of us who like raw fish will continue eating our favorite preparations, worm or no worm. I had dinner last night at the home of a friend, a vivacious lady from the Cook Islands. She served Tahitian marinated fish—*poisson cru*—and I went back for seconds. It was delicious.