Chapter 2
Something’s Fishy

The telephone rang early one morning at my desk at the New Jersey Poison Information and Education System. As was my habit, I was reviewing the previous day’s cases called into the poison center. It was Elvis Perez on the line. Elvis, a certified poison information specialist who was trained as a nurse and had spent the last several years fielding the telephones at the hotline for drug and poison information, had a doctor on the line with some questions that he felt I should handle. Dr. Goldsmith was calling about a 38-year-old woman who had come to his office on October 11 with what he thought were strange, unrelated complaints. She explained to him that her hands felt as if they were burning, and that she felt weak and had a metallic taste in her mouth. Dr. Goldsmith had done routine laboratory work, which did not help him make a diagnosis. When she returned to his office a week later, she was complaining of a continuation of those symptoms but now also had extreme fatigue, itching all over, excess tearing, and pain in her eyes. She was so sensitive to light that she resorted to wearing sunglasses most of the time. She had searched the Internet and asked him to check her for mercury poisoning. He read her laboratory results for me: chemistry profile normal; complete blood count normal; Lyme titer by immunoassay screening test was 1.81, but specific testing by a more precise test was negative; a blood mercury level was abnormal with a result of 29.8 μg/L (normal for environmental exposure is less than 15 and should not be greater than 15 at the end of a shift if there is an occupational exposure). We spoke about the interpretation of her results and the usual symptoms of mercury poisoning. He knew of no obvious exposure that his patient had to mercury. She was a graduate student and no member of her family worked with mercury.

We discussed the controversy regarding mercury in dental fillings and the fact that scientists are somewhat divided on whether there is enough mercury liberated from such fillings to represent any potential hazard. There is some data to suggest that soon after a filling is placed in a tooth there may be some absorption of mercury but that this appears to decrease rapidly and produces no obvious ill effects. We also discussed the fact that removal of the patient’s fillings might represent a greater risk than leaving them intact. Further, we discussed the fact that her mercury...
level may have been dietary in nature and that she should be placed on a diet free of shellfish and other fish for several days. After such a period with no fish consumption, a collection of all her urine for twenty-four hours should be analyzed for mercury to see if she really had a high mercury level in her body.

Calomel (mercurous chloride) was once a commonly used medication. It was thought to increase the flow of bile and urine and was used as the treatment for syphilis for several hundred years until its toxicity became apparent. Benjamin Franklin was reported by some to have been the source of the phrase “a night with Venus, a lifetime with Mercury.” Mercury, as mercuhydrin, was a commonly used diuretic to increase urine flow until forty years ago, when safer alternatives became available. Mercuric chloride was commonly used as a topical antiseptic solution. This preparation was dispensed in unique, dark blue-grey, irregularly shaped “pills” which were, roughly, in the shape of a coffin and were labeled with the word *poison* on one side and a skull and crossbones on the other. Mercury in its organic form, Mercurochrome, was and still is, commonly found in homes and used as an antiseptic on minor wounds. Mercury salts, as dusting powder, are frequently still used as protection against mold, etc. on seeds, particularly wheat and corn. The mistaken use of these for food preparation has led to several outbreaks of mercury poisoning, such as during the 1970s in Iraq. Acute mercury poisoning is extremely unusual today. When it does occur, it is usually the result of a suicide attempt. The symptoms of acute poisoning usually start with severe vomiting and diarrhea, which may include large quantities of blood. Loss of fluid and blood through the diarrhea may be so profound as to produce shock and rapid demise. One of the most famous outbreaks of chronic mercury poisoning occurred from the contamination of Minamata Bay in Japan with methylmercury. Two young girls were seen by physicians in Minamata City. The physicians were puzzled by their symptoms: difficulty walking, difficulty speaking, and . It was initially thought to be an infectious disease, something like polio, which occurred in epidemic proportions throughout the world at the time. Serendipitously, anecdotes of a strange phenomenon in the community began to appear. Something peculiar was happening to the wildlife and specifically to the cat population. Cats, often allowed to eat the leftover fish, developed seizures, were “going mad” and dying. Locals called it the “cat dancing disease.” This eventually led to the finding of the contamination of the bay by the industrial release of methylmercury into the bay. The contamination was devastating to the population. By the time the outbreak was uncovered and the release of mercury stopped, over 2300 individuals became afflicted and nearly half succumbed to the effects. Exposure of fetuses in utero led to a severe form of cerebral palsy, the subject of a *Life* magazine photo essay by the famous US photographer Eugene Smith entitled “Death-Flow from a Pipe.” Chronic mercury poisoning has often been the result of an occupational exposure. Hatters used mercury to cure leather into felt during the nineteenth century. Those in hat production were exposed to large quantities of liquid mercury over protracted periods of time. Such chronic occupational exposure led to such peculiar symptoms as feeling that teeth are loose in the jaw, slurred speech, memory loss, rapid swings in emotions (a person may be laughing one minute and crying the next), assorted aches and pains, tremors, and a metallic taste in the mouth. The
symptom of erratic behavior, embodied by Lewis Carroll’s Hatter character in *Alice’s Adventures in Wonderland*, has led to the phrase “mad as a hatter.” Patients often complain of difficulty paying attention and have a tremor which interferes with their handwriting.

Two weeks later Dr. Goldsmith called me with the twenty-four-hour urine mercury level. This time the mercury studies of the patient, Darlene Hanson, were normal; she excreted only 6 μg of mercury in a full twenty-four hours. It was clear that her diet had been responsible for her prior abnormal tests. We spoke about other possible causes of her symptoms, and I offered to see her in consultation if she felt it necessary. Two hours later the patient called the office and we had a nice discussion about her problems. She had been in good health until vacationing with her family in the Caribbean. The family spent several weeks there during the preceding summer. The family had a grand time enjoying the activities available and became familiar with the local foods. They loved the silver snapper served there so much that they brought some of the fish home with them and froze it. On October 5, she cooked the fish for a family dinner. Her husband did not eat the fish because he thought it was too spicy, but both the patient and her daughter ate a full meal of fish, vegetable, and salad. The following day the fish was used to prepare a fish stew and the entire family ate it. She continued to eat the fish for the following days. On the day after consuming the fish, her daughter developed abdominal cramping, nausea, dizziness, and pains in both of her ankles and groin. The gastrointestinal symptoms disappeared spontaneously but the ankle pains continued off and on. On the fourth day after the fish meal, Darlene developed diarrhea, generalized aches and malaise, sweating, and the feeling of tingling of her tongue and lips. She complained of memory loss and a severe metallic taste in her mouth, which prompted her to ask for the mercury studies. She thought that she had gone a bit crazy, because she stated that soon after she developed these symptoms she noticed that hot coffee or tea seemed cold, and cold felt hot to her. We set up an appointment for the following week. This constellation sparked my interest. I had been involved in several cases just like this. The first case I became involved with occurred in the late 1970s in a physician who developed the identical symptoms after eating red snapper on a trip to the Caribbean. She became ill, while her husband did not. Yet another case involved a television producer who shared a meal of grouper with a priest after completing an educational television show; the producer became ill, the priest showed no signs of illness.

I saw Ms. Hanson on October 31. She came accompanied by her husband and daughter. On the day I saw her, she was complaining of tingling in her tongue and lips, memory loss, photophobia, and itching in her ears as well as pain in her ankles. I made the presumptive diagnosis of ciguatera fish poison.

According to the U.S. Centers for Disease Control, ciguatera is the most frequently reported food poisoning related to the ingestion of fish. It is commonly found contaminating fish that live in warm water and feed at reefs, such as in Hawaii, Florida, the Caribbean, and the Indian and South Pacific oceans. There are over 100 fish species reported to harbor the toxin responsible for the poisoning. The list includes grouper, snapper, dolphin, trigger, barracuda, parrot fish, Spanish

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mackerel, mullet, kole, and many more. The toxin is produced by a tiny microorganism known as a dinoflagellate. The small, blue-green protozoan (single-cell organism) *Gambierdiscus toxicus* and bacteria within it are thought to be responsible for the production of the toxin. The production appears to increase during times of algal blooms, such as red or green tides. These dinoflagellates are the food of smaller fish, generally herbivorous (plant-eating) fish. These fish then are the prey of larger carnivorous fish and so on up the food chain until a human ingests the fish. Generally, the larger the fish, the older the fish—and the more likely that it has ingested considerable toxin. In this way the toxin is bio-amplified and can reach toxic levels and cause illness when ingested by an unwary human. There probably are a diversity of toxins, since at least three toxins have already been identified. This helps account for variations in the clinical effects seen. The toxin is not destroyed by heat or freezing, and it is colorless, odorless, and tasteless. It does not disturb the taste of the fish. People have developed symptoms after eating fish boiled, broiled, fried, barbecued, or raw.

The toxin produces neurological and, potentially, cardiac abnormalities, by interfering with the way nerve impulses are transmitted. A normal nerve or muscle cell stays in its resting stage through several means of balancing the concentration of certain metallic ions on both sides of the cell membrane. There are a series of tiny pumps and channels which are responsible for maintaining the status quo of the cells in the body, particularly the central nervous system. Virtually every cell in the body contains what is termed the sodium-potassium ATPase pump. Sodium is pumped out of a cell and potassium is pumped in, but slightly unequally, in that more sodium ions are pumped out then potassium ions are pumped in. There is, thus, always an imbalance and a slight electrical charge across the membrane, as in a battery. When an electrical impulse, in the form of a nerve impulse, hits the cell, the pump stops functioning momentarily, resulting in sodium ions rapidly rushing into the cell and potassium ions rushing out. As the impulse passes, the pump then pumps sodium out and potassium in. The cell then returns to its resting state. If the cell is a muscle cell, the rapid movement of sodium into the cell causes the muscle to contract; if a nerve cell, the change in electrical activity allows the impulse to continue along the path of the nerve jumping to another nerve, etc. The ciguatera toxin distorts this delicate balance with the effect that the cell membrane appears to be more permeable to sodium, allowing more sodium to build up inside the cell and causes the cell to be more excitable. In a “slight of evolution,” the infected fish is missing the binding site for the toxin, and thus cannot become affected by the toxin while it becomes a depot for the toxin. The toxin accumulates in the muscles of the fish. As the fish ages and eats more toxin-contaminated smaller fish, the concentration of toxin increases. The toxin is colorless, odorless, and tasteless, so the hapless victim has no idea that he or she has become poisoned until the classical symptoms and signs develop.

The history of exposure and development of symptoms is highly variable. The diagnosis is usually made only after the full-blown neurological effects are evident. The meal usually is unremarkable. The first symptoms may be abdominal in nature: cramping, vomiting, and diarrhea. These may occur within two to six hours
but may be delayed for twenty-four hours in some circumstances. Headaches, sweating, tearing of the eyes, and pain on looking into lights are common as is numbness of the tongue, lips, and throat. A metallic taste is often reported by those affected. By far the most striking complaint is the peculiar hot–cold reversals so characteristic of this intoxication. Patients often describe pain or burning of their arms or legs. Muscle aches and weakness may occur. Occasionally, muscle weakness may be so severe that a victim is bedridden. Toxin in pregnant women affected by ciguatera may cross the placenta and produce abnormalities in the fetus. Breastfeeding mothers have been reported to contaminate their infants by nursing. There are reports of men complaining of penile discomfort after having vaginal sex with a woman suffering from symptoms of the toxin. The reverse has also been reported—that is, a woman complaining of vaginal pain and discomfort after sex with a man who harbors the toxin.

Treatment of the symptoms is not very effective. If suspected shortly after eating a meal, some toxin may be forced out through the urine. A diuretic is often prescribed to enhance urinary flow. The most often reportedly used is mannitol, a sugar which remains in the blood stream rather than being distributed into the tissues and draws water from the tissues into the plasma volume and increases urine tubular flow. It is unlikely that the toxin can be removed after twenty-four hours. Amitriptyline has been reported, in some cases, to be successful in reversing some of the symptoms. This drug appears to block the channels through which sodium moves, the sodium channel, and thus closes the path that the sodium ions move through. The list of other therapies tried and techniques used to remove toxin is very long, suggesting that no one approach has stood the test of time. This may be secondary to the fact that there is usually a mixture of toxins involved rather than a single one. The symptoms are usually self-limited. Recovery may not be complete for many years. Repeated exposure to the toxin seems to amplify the disability.

I gave Ms. Hanson a prescription for amitriptyline, an anti-depressant medication which has sodium-channel-blocking effects and has been found effective in similar cases. She was given an appointment to return the following week, and I asked her to bring some of the remaining fish with her so that it could be sent out for analysis.

The following week she was still complaining of the tingling of her tongue and joint pains. She continued to have problems concentrating but her appetite had improved. I increased her dose of medication and made a follow-up appointment for the following week.

The next week found her in much better spirits. She had been able to go to the supermarket and picked up a cold soda which felt cold to her. She stated that although she was still forgetful, her mind seemed less foggy.

At the one month follow-up visit, she was complaining of side effects of the drug: blurred vision, dry mouth, problems urinating, and constipation. Over the next months I adjusted her dose depending on her symptoms and the presence of side effects. The hot–cold reversals disappeared as did the joint pains. She continued to have “up and down” days.

Two years later she was able to stop the medication.
The fish sample that she gave to me was sent to the laboratory of Dr. Yoshitsugi Hokama, Professor of Pathology at the University of Hawaii at Manoa. The laboratory reported that two pieces of fish tested positive for ciguatoxin on an immunoassay. The fish was subjected to chemical breakdown so that it could be administered in liquid form and in a controlled concentration to experimental mice and guinea pigs. The extract killed the mice rapidly. On an experimental guinea-pig model in which the heart of the animal was treated with the extract, the heart rate dropped and the force of the contraction of the heart muscle decreased. Both of these effects were prevented by a substance which is thought to have the exact opposite effect of ciguatera.

There is a test available to detect toxin in fish before it is sold to the user. Unfortunately it is not yet widely used. Since the age of the fish is related to the potential for contamination, it may be advisable to limit fish intake to smaller, younger fish. I only chance eating a full fillet rather than part of a fish. Eating fish during a red or green algal bloom may not be wise.

We are told to decrease our intake of beef to prevent coronary heart disease, chicken may give us salmonella poisoning, vegetables and fruit may be contaminated with viral hepatitis, etc. From this experience, it may not be safe to turn to fish. That doesn’t leave much choice. I suppose all we can do is be vigilant and hope that if we become sick, there will be a knowledgeable physician to make the diagnosis and intervene to prevent a long-term disability.

Suggested Reading

Medical Toxicology: Antidotes and Anecdotes
Marcus, S.M.
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