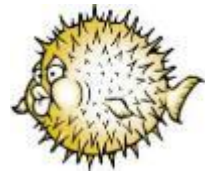


FUGU : SUSHI TO DIE FOR

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Japanese cuisine is renowned for its emphasis on seafood of innumerable varieties. From **uni** (raw sea urchin gonads) to **konowata** (fermented sea slug intestines) to **shirako** (cod sperm) to the ever-present **unagi** (freshwater eel), Japan's obsession with sea creatures and all their innards is a hallmark of its unique and, to some Western palates, bizarre cuisine. But nothing exceeds in strangeness the Japanese penchant for the world's deadliest feast: the highly poisonous pufferfish, known in Japan as **fugu**. While Dave Barry may indeed be correct in his candid observation that "This is one fish that Mother Nature is telling us to leave way the hell underwater," the Japanese apparently think otherwise. For better or worse, fugu is a part of Japanese culinary culture and in fact its consumption is on the increase in recent years, with over 10,000 tons of fugu consumed annually. In this short document we will explore the fascinating biological, medical, and culinary aspects of this uniquely Japanese repast, sometimes referred to as "Japan's culinary Russian roulette."

BIOLOGY: THE HOST AND ITS TOXIN

The pufferfish, also known as the globefish or blowfish, comprises a family of over 120 species of fish in the order *Tetraodontiformes*. "Tetraodont-" means "four teeth" and derives from the presence of four large, protuberant, often fused teeth forming a beak-like mouth in these fish. The "beak" is used for cracking mollusks, scraping coral, and general reef-grazing. Technically, the pufferfish itself is not actually poisonous, but it lives in symbiosis with bacteria which produce the world's most lethal toxin, **tetrodotoxin (TTX)**. Pufferfish grown in a laboratory do not contain TTX. In their natural environment the fish ingest several species of TTX-producing bacteria, which is then concentrated in the skin and other organs of the pufferfish, serving as a protective mechanism for the fish. If a predator takes a bite of a pufferfish, particularly its skin, it will regret it. Yet the pufferfish itself doesn't die from all the TTX in its system, because it is completely immune to TTX. TTX is an ancient toxin and the association of the pufferfish and the TTX-producing bacteria is a good one for both species: the pufferfish gets a powerful protective mechanism and the bacteria get a nice safe place to live, eat, and reproduce. Such is the wisdom of nature. TTX actually exists in many marine species, including the blue-ringed octopus, the porcupine fish, some gastropod mollusks, and horseshoe crabs. It also can be found in several amphibians including Atelopid frogs found commonly in Costa Rica and the California newt. The blue-ringed octopus, native to Australian waters, uses TTX quite offensively: it concentrates TTX in its salivary glands and injects it as a deadly venom into its prey. In the pufferfish, tissue concentrations of TTX are highly variable and seasonal, with peak levels being found from May through September. So if you are dying (forgive me....) to try fugu, please wait until mid-winter.

On a milligram for milligram basis, TTX is 10,000 times as potent as cyanide. One mg of TTX, an amount which would easily fit on the head of a pin, is a fatal dose for an adult human being. TTX is a heat-stable toxin, *i.e.*, it is not affected or inactivated by cooking (and the Japanese eat fugu both raw and cooked- see below). It is the deadliest of a large family of lethal marine biotoxins, a family which includes saxitoxin (the toxin associated with paralytic shellfish poisoning) and ciguatera toxin, a less potent toxin commonly associated with ciguatera poisoning worldwide from eating reef fish which have fed on tiny dinoflagellates containing the poison. TTX is concentrated primarily in the skin, liver, gonads, and intestines of the pufferfish. It is not present in the flesh. This is why careful preparation of fugu is the key to survival. TTX is tasteless, colorless and odorless, adding to its menace. Its lethality results from its very specific and extremely tight binding to the sodium channel receptor on nerve membranes. It blocks sodium flux across the cell membrane of nerves and effectively turns off nerve conduction. It poisons all nerves, including motor nerves that allow us to breathe and to move, sensory nerves, and autonomic nerves that control vital functions such as blood pressure and heart rate. Millions of years ago the pufferfish fortuitously evolved a "mutant" sodium receptor to which TTX cannot bind, hence its immunity to the toxin. This became a key survival trait.

(continued)

TTX is a complex molecule and no other molecule known on this earth binds as tightly and irreversibly to nerve membrane receptors as TTX. The TTX molecule is so complex that Dr. Robert Woodward of Harvard won the Nobel Prize in Chemistry in 1965 for the synthesis of TTX. Unlike most snake venoms and many other toxins, there is no antitoxin or other antidote to TTX, although recent research using TTX-antibodies to neutralize the poison in mice may someday lead to a specific treatment.

CLINICAL ASPECTS

The first symptoms of TTX poisoning usually occur 10-45 minutes after ingestion and include tingling and numbness in the tongue, lips, face, and extremities. Shortly thereafter, headache, nausea/vomiting, and stomach pain may develop. This is the good stage. The bad or second stage then follows rapidly and is characterized by increasing weakness and paralysis, including inability to talk and ultimately inability to breathe, circulatory collapse, convulsions, coma, and death. Because there is no antidote, treatment is supportive, including most importantly cardiopulmonary support and seizure control. I would venture to guess that anyone experiencing even the early stages of TTX toxicity would have to agree with Dave Barry...

FUGU CUISINE

Now that you are probably quite eager to try fugu, here is an overview of just how the Japanese eat it (the "why" is something I will leave to minds greater than mine to figure out). Fugu is generally served three ways:

Fugusashi is an elegant fugu carpaccio. The fugu is sliced paper thin so as to be translucent and is often artistically arranged to look like the petals of a flower or the feathers of a bird. It is eaten raw with a ponzu (citrus and soy) sauce.

Fugu-hirazake are toasted fugu fins served in a glass of sake. This is beginner's fugu.

Fugu-chiri is a fugu hotpot made with fugu and vegetables in a **dashi** broth.

*Fugu should be eaten only if it has been prepared by certified, licensed fugu chefs. A meal at a fugu restaurant is quite expensive and usually involves all three of the above courses (assuming you survive the first two). About 20 to 50 do-it-yourselfers preparing their own fugu die each year in Japan. About 50 to 100 non-fatal cases occur every year among the do-it-yourselfers. This is in stark contrast to the exceedingly rare cases of toxicity associated with preparation by licensed fugu preparers and licensed chefs. There has been only one documented case of a person killed in a fugu restaurant in the last 60 years- a celebrity by the name of Mitsugoro Bando. Mr. Bando was a well-known Kabuki actor who in 1975 insisted on living dangerously by eating the pufferfish liver, the ultimate forbidden delicacy. He died of TTX poisoning shortly thereafter. The fugu chef was convicted of involuntary manslaughter, and a law was then passed forbidding the eating of fugu liver. So I therefore would ask you all to please respect Japanese law and *do not eat fugu liver while in Japan*. Fugu consumption understandably fell off a bit for a few years after the Bando incident, but there has since been a resurgence under the new, tighter regulations. Another celebrated case of fugu toxicity occurred in the United States in 2006. A California chef brought home some pre-packaged ready-to-eat fugu from a trip to Japan and shared it with two fellow chefs. Each person ate ¼ to ½ ounce of fugu, a piece about the size of a quarter. All three came down with acute TTX poisoning and were rushed to the hospital where they had their stomachs pumped (gastric lavage with activated charcoal) and they all gradually recovered. In the CDC's report on this incident, they felt that these three individuals only survived because they ate very small quantities of fugu and had immediate emergency treatment. Note that personal importation of fugu into the USA is prohibited by U.S. Customs. The individual in the above case did not declare his fugu. Let this be a lesson to you all to *always declare your fugu* (at which time it will be confiscated by Customs). Customs and the FDA, in conjunction with the Japanese Ministry of Health, do permit the importation of specially-processed, certified fugu to licensed fugu restaurants in the USA. Blowfish Sushi in San Francisco was one such establishment - but it closed for good during the COVID shutdown. But fugu is easy to find in Japan, in restaurants, fish markets, and even in most supermarket. *Bon appetit!**