

Part II. Fish-Borne Food Poisoning in Japan

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I. Introduction

From ancient times, fish and their products have been the most important animal protein source in the Japanese diet. This is attributed to the geographical location and economic factors. The surrounding waters carry an abundance of fish and other sea food. The mountainous topography, on the other hand, makes the raising of livestock precarious. The taboo on eating cattle, dating many hundreds of years back, seems to some extent to have affected eating habits, particularly in rural regions.

Fish consumption is, however, hampered by poisonings that constitute a hazard to public health. According to statistical data (Table I), more than 60% of all such outbreaks refer to fish or fish products.

Table I lists the causative agents in recent outbreaks. Surprisingly many outbreaks remain undiagnosed. Clinical and epidemiological data, including the incubation period, symptoms, prevailing seasons, etc., clearly suggest that most of these cases are of a bacterial nature.

II. Bacterial Poisonings

Salmonellas and staphylococci are most common in this group. Much attention has recently been given to cases of botulism of type E from Hokkaido (Nakamura *et al.*, 1956), other northern parts of Honshu, and the main island (Sakaguchi *et al.*, 1954). Some outbreaks can be at-

TABLE I
 OUTBREAKS OF FOOD POISONING IN RESPONSE TO CAUSATIVE AGENTS IN THE PERIOD 1957-1958

| Causative agent | 1957 | | | 1958 | | |
|-----------------------------|-------|----------|--------|-------|----------|--------|
| | Cases | Patients | Deaths | Cases | Patients | Deaths |
| Bacteria | 153 | 7,411 | 24 | 218 | 8,158 | 16 |
| <i>Salmonella</i> | 47 | 2,330 | 8 | 63 | 2,044 | 7 |
| <i>Staphylococcus</i> | 45 | 1,962 | 1 | 43 | 987 | — |
| <i>C. botulinum</i> | 3 | 49 | 9 | — | — | — |
| Unidentified | 58 | 3,070 | 6 | 112 | 5,127 | 9 |
| Chemicals | 11 | 69 | 6 | 13 | 304 | 5 |
| Methanol | 3 | 3 | 2 | 1 | 4 | 2 |
| Others | 8 | 66 | 4 | 12 | 300 | 3 |
| Naturally occurring poisons | 249 | 821 | 144 | 287 | 778 | 200 |
| Plants | 91 | 480 | 8 | 96 | 473 | 22 |
| Animals | 158 | 341 | 136 | 191 | 305 | 177 |
| Unidentified | 1,303 | 15,863 | 126 | 1,393 | 21,816 | 111 |

tributed to halophilic bacteria (Takigawa and Fujisawa, 1956). As shown in Table II, the number of outbreaks caused by the consumption of fish, shellfish, or other marine products accounts for more than 50 to 60% of the bacterial poisonings. This high frequency may be due to one or more of the following causes: (1) the preference for fish or shellfish in the raw stage. Numerous outbreaks are in fact attributed to raw fish. Some fish products, such as broiled, steamed, or fried fish paste products ("kamaboko," "hanpen," etc.) which are also consumed without further cooking are incriminated. (2) The low price of sea food as compared to other animal products. (3) The high degree of perishability combined with the time from capture to final consumption. Refrigerators are not very common, especially in rural districts. Furthermore, most people prefer fresh fish flesh to frozen. Most of the poisoning outbreaks have been due to improper handling or inefficient preservation.

III. Naturally Occurring Poisons

As to the classification of poisonings caused by naturally occurring poisons of various kinds, reference is made to Chapter 14, by Halstead. This presentation will restrict itself to some recent Japanese investigations in this field.

A. TETRAODON POISONING

Globefish, "fugu," is a favorite both in China and Japan, but numerous poisonings have been reported. In some prefectures in Japan, a cook must have a license to cook and serve this fish to the public, while in others the sale of visceral organs is prohibited. Poisoning scarcely occurs from eating globefish at a restaurant; however, more than 200 cases, with 70 deaths, of this poisoning have been reported annually from eating home-cooked globefish.

In Japan, about 13 out of 27 known species of globefish are most commonly consumed, of which only saba-fugu (*Liosaccus lunaris* Bloch and Schneider) and yaito-fugu (*L. cutanus* Gunther) are nontoxic. Symptoms and other characteristics of fish poisoning are discussed in Chapter 14, Volume I.

Several investigations of globefish poisonings have been conducted by Japanese scientists. Tani (1945) revealed that there exists a marked seasonal difference with respect to toxicity, which is highest during the spawning period from December up to March. Since most globefish are eaten during the winter, this period coincides with the peak of the poisoning risks.

Toxicity differs greatly with species. The muscles, as well as the milt, are generally considered nontoxic or only slightly toxic, while the ovaries

TABLE II
OUTBREAKS OF FOOD POISONING IN RESPONSE TO VARIETY OF FOODSTUFFS IN THE PERIOD 1956-1958^a

| Incriminated foodstuffs | 1956 | | | | 1957 | | | | 1958 | | | |
|--------------------------|-------|----------|--------|--|-------|----------|--------|--|-------|----------|--------|--|
| | Cases | Patients | Deaths | | Cases | Patients | Deaths | | Cases | Patients | Deaths | |
| Fish and shellfish total | 655 | 7,364 | 148 | | 729 | 6,382 | 181 | | 778 | 7,280 | 217 | |
| Shellfish | 50 | 1,131 | 2 | | 48 | 505 | 8 | | 70 | 1,201 | 3 | |
| Globefish | 127 | 185 | 107 | | 157 | 241 | 137 | | 187 | 289 | 176 | |
| Others | 478 | 6,048 | 39 | | 524 | 5,637 | 36 | | 521 | 5,790 | 38 | |
| Fish products, total | 200 | 3,197 | 32 | | 185 | 1,796 | 27 | | 225 | 4,923 | 23 | |
| Fish cakes | 106 | 1,600 | 6 | | 83 | 942 | 3 | | 123 | 3,043 | 11 | |
| Others | 94 | 1,597 | 26 | | 102 | 855 | 24 | | 102 | 1,880 | 12 | |
| Meat and meat products | 41 | 1,057 | 2 | | 36 | 1,175 | 5 | | 49 | 1,444 | 2 | |
| Egg and egg products | 15 | 301 | 6 | | 15 | 385 | 1 | | 12 | 285 | 1 | |
| Milk and dairy products | 14 | 505 | 1 | | 14 | 157 | 2 | | 12 | 541 | — | |
| Cereals | 94 | 1,772 | 9 | | 87 | 1,354 | 5 | | 81 | 1,279 | 4 | |
| Vegetables and beans | 166 | 2,207 | 19 | | 142 | 998 | 13 | | 160 | 2,256 | 24 | |
| Miscellaneous | 196 | 4,643 | 27 | | 194 | 5,387 | 26 | | 240 | 5,129 | 29 | |
| Unidentified | 284 | 7,240 | 27 | | 314 | 6,529 | 40 | | 354 | 7,919 | 34 | |
| | 1,655 | 22,286 | 271 | | 1,716 | 24,164 | 300 | | 1,911 | 31,056 | 332 | |

^a Figures cited were based on the data collected by the Food Sanitation Section, Public Health Bureau, Ministry of Welfare.

are lethal in doses as low as 2 g. of such tissue. Intestines follow the liver and ovaries in degree of toxicity. Sometimes the skin has turned out to be very dangerous and has caused poisonings. A few species seem to carry the poison in the muscle tissue. They are generally characterized by a reddish-brown skin and an extremely high toxicity. Other species with the poison chiefly in the viscera, as a rule, have a black or bluish-green skin. Quite different compounds have been isolated and been claimed to be the globefish poison (Tahara, 1910; Yokoo, 1950, 1952; Tsuda *et al.*, 1952a, b, and 1953) and there is quite some diversity of opinion as to its identity.

B. BARRACUDA POISONING

The great barracuda (*Sphyraena picuda* Bloch and Schneider) mingles with tuna in long-line fishing frequently in the tropical Pacific. An outbreak caused by this species occurred in Tokyo in 1947. Thirty people developed the typical symptoms (see Chapter 11, Part I). No deaths were recorded.

Hashimoto (1956) maintains there is a marked difference between the toxins involved in the tetraodon and the barracuda poisoning. The former attacks mainly the nerve endings, both motor and sensory, while the latter directly affects the central nerve system.

Several outbreaks have been reported from eating the liver of such species as "ishinagi" (*Stereolepis ischinagi*) (Abe *et al.*, 1957), Spanish mackerel (*Scomberomorus maculatus* A.) (Mizuta and Mizobe, 1957), and shark. In 1956, seven outbreaks of ishinagi poisoning occurred from eating the liver, in which case 21 persons developed symptoms. The poisoning is characterized by severe headache, nausea, and vomiting appearing from 30 min. to 12 hr. after ingestion. The temperature rises and some patients develop diarrhea, abdominal pain, and palpitation. In 1 to 2 days, a marked swelling appears on the face, followed by peeling of the skin, especially around the lips, nose, and neck. This peeling spreads all over the head, fingertips, arms, breast, and abdomen, and finally reaches the legs and toes. In no case is tingling or numbness recorded. Most cases recovered within 1 week, but peeling persisted. The causative agent or agents remain to be identified. The peeling may be indicative of an overdosage of vitamin A.

IV. Invertebrate Poisoning

A. VENERUPIN POISONING

In March, 1942, an outbreak of peculiar poisoning occurred near Lake Hamana, Shizuoka Prefecture, due to consumption of the clam "asari" (*Venerupis semidecussata* Reeve). Three hundred and twenty-

four persons were affected, and 114 deaths (34%) occurred. In March, 1943, an essentially identical type of poisoning followed the eating of oysters (*Ostrea gigas*). In March, 1949, similar outbreaks involving 93 cases with 6 deaths (6.5%) occurred in the same district from eating "asari" and oysters. The first death ascribed to a similar shellfish poisoning occurred in 1889 in the district of Nagai-machi, Miura Peninsula. However, no case of similar poisonings has been reported from other countries. Symptoms and the isolation of the likely poisoning agent, venerupin, are discussed in Chapter 11, Part I.

In spite of a wide survey of Lake Hamana for bacteria, plankton, bottom material, or other environmental conditions, conducted by many investigators, the source of venerupin in shellfish has up to the present not been traced to its origin.

Shellfish toxicity in Lake Hamana is not on the same level throughout the year. The frequency peak has been recorded as located between March and April, followed by a rapid decrease to nontoxicity in the summer seasons. This poisoning is principally caused by clams and oysters, notwithstanding that "hamaguri" (*Meretrix meretrix lusoria* Roding) and "shiofuki" (*Macrta venerifirmis* Reeve) cultivated in the same part of Lake Hamana have never exhibited poisonous characteristics.

B. PARALYTIC SHELLFISH POISONING

Outbreaks of paralytic shellfish poisoning are quite rare in Japan. Only one incident is known and that from July, 1948, in which the clam "asari" was toxic in the district of Yanagawa, Toyohashi, Shizuoka Prefecture (Hashimoto *et al.*, 1950). There were 12 cases, including one death with symptoms of shellfish poisoning identical to those in foreign countries. *Gonyaulax catenella*, considered the primary source of this poison, did not show any bloom, as "red tide."

C. "EZOWASURE-GAI" POISONING

In 1950, an outbreak of shellfish poisoning was reported from the vicinity of Mori, Hokkaido Island, due to the eating of ezowasure-gai (*Callista brevisiphonata* Carpenter). Twenty-six people out of 115 consuming this particular species developed symptoms. No fatal case was encountered. Symptoms such as itching of the skin, nausea, blushing of the face, nettle rash, stomach ache, abdominal pain, stiffening, vomiting, asthma, and hoarseness, developed within 30 min. after ingestion of the incriminated shellfish. No relationship was established between the freshness of shellfish and the poisoning. Asano *et al.* (1950) reported that an unusual amount of choline was detected in the shellfish. He suggested that the allergy-like symptoms may have some relationship to over-

dosage of choline, abundant in the ovaries, either as choline or its esters. The amount of these compounds in the ovaries increases parallel with the state of maturity as the spawning period unfolds, and at the same time the toxicity increases.

D. "HIME-EZOBORA" POISONING (GASTROPOD)

Many outbreaks of "hime-ezobora" (*Neptunea (Barbitonia) apthritica Bernardi*), a gastropod poisoning, have occurred in the island of Hokkaido. This gastropod, known to be one of the most delicious shellfish, is widely distributed in the coastal waters of this island. The poisoning is characterized by such symptoms as headache, dizziness, nausea, vomiting, and others within 30 min. after eating these gastropods. In some cases, nettle rash develops. The causative agent has not been identified as yet but, according to Asano (1952), it appears that the poison is a physiological metabolite, as the toxic substance exists only in the salivary gland and not in other organs. Removal of the salivary gland before eating would be an effective way to prevent intoxication. The poison is soluble in water or alcohol, but insoluble in chloroform or ether. It is a heat-stable substance and seems to belong to the amines rather than to the alkaloids.

V. Unusual Cephalopod and Fish Intoxications

During the years 1952–1955 a series of intoxications from squid occurred in Niigata, Yamagata, and Nagano Prefectures; 785 outbreaks were reported involving a total of 2,874 persons. From June to September, 1955, there were at least 108 outbreaks, with 2,159 diseased persons in Niigata Prefecture and the islands of Miyake, Mikura, and Hachijo caused by scombroid and carangoid fishes. The actual number of persons involved is believed to have been considerably greater than indicated [see further Kawabata *et al.* (1957)].

The squid causing the outbreak is "yariika" (*Ommastrephes sloani pacificus*). One case in Yamagata Prefecture was traced to squid captured in the vicinity of Tobishima Island about 35 km. northwest of the city of Sakata. Another outbreak in Niigata Prefecture originated with squids from the waters around Sado Island. Both these islands are located in the Japanese Sea. No poisonings resulted from squid simultaneously captured near Hachinohe in Aomori Prefecture, in an area bordering the Pacific Ocean.

Mackerel scad, "muro-aji," (*Decapterus muroadsi* T. and S.) and other related "aji" (*D. lajang* and *D. macrosoma*) causing poisonings in Miyake, Mikura, and Hachijo Islands, were captured in the vicinity of Mikura Island, off the south central coast of Honshu.

The Japanese horse mackerel, "maaji," common Japanese mackerel,

"masaba," and flying fish, "tobiuwo" (*Prognichthys agoo*), were incriminated in outbreaks in Niigata Prefecture and captured along the coastal waters of that same region.

The symptomatology was essentially the same in all these cases, regardless of the poisoning species. The incubation period varied from 10 to 20 hr. The predominant symptoms consisted of nausea, vomiting, abdominal pain, diarrhea, fever (38–39 C.), headache, chills, and weakness. Most of the patients recovered within a period of about 48 hr. The largest series of fish intoxications, in which there were 4,511 known consumers and 1,113 victims developing symptoms, showed a mortality of 24.6%. In the most serious squid intoxications there were 2,202 consumers and 589 victims, or a death percentage of 27.1. Neurological symptoms were largely absent. Bacteriological examinations failed to show evidence of any of the ordinary types of bacteria known to cause food poisoning. The putrefaction was no factor in this particular series of intoxications. Iwamoto *et al.* (1957) disclosed that serum cholinesterase activity in the patients of fish-borne summer food poisoning in 1956 was lower than that in normal healthy persons. However, the etiology of these outbreaks is still unknown.

MINAMATA DISEASE

During the past few years the inhabitants of the Island of Kyushu have been afflicted with an apparently new disease resulting from the ingestion of fish or shellfish. This neurological disease was named Minamata disease for the industrial town near which the patients resided (McAlpine and Araki, 1958). The first cases appeared toward the end of 1953. Fifty-six persons were finally afflicted with the disease. This number gradually increased through 1956, when a government edict was passed to prohibit fishing in the bay. Since then, no new cases have been reported. Minamata is the site of a large artificial fertilizer factory. Prior to 1950, the effluent from the factory was poured into the sea. At the latter date, a new sewer line was built which poured the water into Minamata Bay. It was not until three years later that the first neurological disorders were seen.

The first symptom was a numbness in the extremities and sometimes around the mouth, frequently followed by slurred speech, unsteady gait, and increasing disability. Deafness and disturbances of vision, the latter being confined to constriction of the visual field, were seen in most cases. Many patients experienced difficulty in speech, insomnia, and emotional disturbances. Mental confusion and muscular incoordination occurred in all cases. Seriously affected patients showed an increased amount of amino acids in the urine and of γ -globulin in the blood.

The mortality rate was 33%. Eight patients died within 2 months after the first symptoms, while four died within the first year. The other patients remained incapacitated to varying degrees. There apparently was no recovery once the individual was afflicted with Minamata disease. In autopsies, small necrotic areas were encountered in the intestinal mucosal membrane in the viscera. The central nervous system showed cellular degeneration which was most marked in the granular layer of the cerebellum; there was a dilation of the perivascular spaces, with occasional softening, but no demyelination. There was edema, and occasionally small hemorrhages also in the spinal cord.

Fishermen and their families were mainly affected, and the evidence supports the thesis that the disease was caused by eating fish from the bay. In many instances, two or more members of the same family had the disease. In the neighboring families where this disease did not appear, fish from the local bay was consumed either not at all or in very small amounts. All ages and both sexes were equally represented. Infants were protected, probably because they were breast-fed until the age of two.

The factor causing the neurological disturbances is unknown. It appears to be heat-stable, since some of the individuals who developed the disease ate nothing but cooked fish. Cats, crows, and possibly also such animals as pigs and dogs, appeared to be susceptible to a similar disease. The brains of ten cats that died of this condition showed changes similar to those observed in the human material. The disease could readily be produced by feeding fish from the bay during 2 to 4 weeks to cats (Anonymous, 1959).

Although the fish from the bay and effluents from the local factory showed increased amounts of manganese, selenium, and copper, the manifestations of the disease are not those normally associated with the toxicity of these elements. A large amount of biological and biochemical work has to be done before the factors causing this disease can be safely recognized.

VI. Allergy-like Poisonings

Allergy-like poisonings (Kawabata *et al.*, 1955a) develop in many fish and shellfish cases. Several such outbreaks are attributed to dried fish products such as "samma-sakuraboshi" (dried, seasoned saury). Attention was first drawn to these allergy-like food poisonings in 1951, when mass outbreaks occurred in Tokyo, and numerous consumers were affected. Since then, similar cases have been reported from many places, and several research workers have been greatly concerned with this disease.

The causative agent was for a long time identified with histamine. However, Aiiso (1954) recently demonstrated that although the same amount of histamine as 450–500 mg.% contained in the material of “samma-sakuraboshi,” responsible for an outbreak in Hiroshima, did not produce any symptoms among human volunteers, this same fish product actually produced symptoms. From this fact, the following conclusion was drawn. There may have been some other poison or poisons in the incriminated material in addition to histamine, which occurred in unusual amount, or else there may have been some substance which may have intensified the histamine activity. Miyaki and Hayashi (1954) assumed that the poisoning might be caused by such a combined effect. They mentioned trimethylamine oxide, trimethylamine, phosphorylcholine, agmatine, etc., as such substances. Kawabata *et al.* (1955b, c) also investigated similar materials independently and confirmed the marked difference between the amount of histamine actually analyzed by a chemical method and that estimated from the rate of contraction of a strip of guinea pig intestine by means of the Magnus’ method. The presence of a specific vagus stimulant, tentatively designated as “saurine” was assumed by Kawabata *et al.* (1955c). Unusual amounts of histamine were, however, also demonstrated. For a further discussion of this histamine problem, see Volume I, Chapter 10; an account is given there of the existence of special bacteria that may produce histamine.

VII. Fish-borne (Type E) Botulism

It was generally believed that *Clostridium botulinum* did not exist in Japan. No epidemiological or clinical cases of botulism had ever been recorded. In addition, a wide soil survey had failed to detect such spores.

The first known outbreak of type E botulism was reported in May, 1951, from Iwanai, Hokkaido Island, caused by the eating of “izushi.” Fourteen persons developed symptoms and four died. Nakamura *et al.* (1956) isolated the causative bacteria as a type E *C. botulinum*.

One year later, two similar poisonings occurred on the island of Hokkaido; in both cases type E organisms were isolated. Since 1951, when the first case was reported by Nakamura *et al.*, the total number of such type E poisonings have amounted to 22, in which 168 persons were affected, of whom 50, or 31%, died (Komatsu *et al.*, 1958).

It is worth noting that all these Japanese cases refer to type E. As to the specifics of this class of poisonings reference is made to Chapter 11, Part I, by Shewan.

Nakamura *et al.* (1956) disclosed that type E is widely distributed in the soil, coastal sand, etc. They found its frequency to range from 0.4%

(one out of 247 soil samples from various districts in Hokkaido) to 4.0% (2 out of 40 samples of coastal sand by the Sea of Okhotsk).

Recent work in various laboratories indicates that type E toxin production in fish does not depend simply on appropriate temperatures and pH conditions but is specifically affected by such factors as the mutational phase of invading organisms, the presence of other bacterial contamination and the possible action of nonbacterial enzymes. With regard to mutational phases of type E, Dolman (1957b) revealed that there are three distinct phases: the heavily sporulating ("OS"); toxigenic ("TOX"); proteolytic ("TP") ones among type E organisms; the combination of "TOX" and "TP" greatly affects the toxic potency in the fish. Furthermore, Sakaguchi and Tohyama (1955) established the presence of a fellow contaminant, a proteolytic strain of the genus *Clostridium*, which promotes toxin production when grown together in mixed culture with a weakly toxigenic type E strain. The activation of type E toxin by trypsin was reported by Duff (1956). This indicates the possibility that the type E toxin could be activated in the digestive tracts of human victims. Proteolytic enzymes originating in fish organs or tissues may also increase the amount of toxin produced prior to consumption.

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