Review Article

The History and the Present of Minamata Disease
—Entering the second half a century—

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Abstract

Minamata disease is a methylmercury poisoning with neurological symptoms and caused by the daily consumption of large quantities of fish and shellfish that were heavily contaminated with the toxic chemical generated in chemical factories and then discharged into the sea. The first epidemic occurred in the southern costal area of the Yatsushiro Sea including Minamata mainly through the 1950s to the 1960s and a second in the basin of the Agano River, in the 1960s. Minamata disease is one of the most significant negative consequences associated with environmental pollution caused by industrial activity in the world. These epidemics appeared during an era in which productivity took the highest priority and little consideration was given to the environment. Minamata disease not only took many lives among residents but also caused conflicts in the local community and has left a large variety of social and political issues. There are many lessons left to learn from the experience, and persisting issues are far from abating even half a century after the first identification of the disease.

Key words Methylmercury poisoning, Environmental pollution, Causative agent, Compensation of victims, Public health policy

Occurrence of Minamata Disease

Minamata is a small town facing the Yatsushiro Sea, also called Shiranui Sea, in Kumamoto Prefecture on Kyushu Island in southern Japan (Fig. 1) and abundant in fishing resources. On a spring day in 1956, a girl of five years old in the town was found to have unusual neurological symptoms. She had convulsions and difficulties in walking and speaking. She was the first well-documented case of Minamata disease, and was officially reported with other three cases including her sister on May 1, 1956.[1]

Minamata disease is a methylmercury poisoning associated with the daily consumption of large quantities of fish and shellfish heavily contaminated with the toxic chemical. The disease shows a variety of clinical symptoms depending on the exposure level to the chemical.[2] Severe cases are characterized by Hunter-Russell syndrome that includes sensory disturbance with predominance in distal portions of the extremities, cerebellar ataxia, and bilateral concentric constriction of the visual field.[3] Among other neurological signs and symptoms are dysarthria, hearing impairment, disturbance of ocular movement, equilibrium disturbance, tremors, etc. Relatively mild cases may be associated also with some subjective complaints including paresthesia, arthralgia and myalgia of the extremities, disability using the fingers, easy stumbling and unsteadiness, ageusia, anosmia, cramp, headaches, failure of memory, insomnia, etc.

Investigation of Causative Agent and Spread of the Pollution

The company responsible for the Minamata epidemic was the chemical company Chisso. Chisso

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Fig. 1 A view of central Minamata City, the Yatsushiro Sea and flow of the Minamata River on the right side

was a predominant company with advanced technologies in Japan at the time. In the Minamata disease episode, methylmercury was generated as a byproduct in reaction chambers for manufacturing acetaldehyde that was synthesized by a hydrolysis of acetylene using mercury as a catalyst. Methylmercury, after discharging into the sea, accumulated in fish and shellfish by the absorption through the gills or digestive tracts.

Following the official identification of the first patient in 1956, research teams were organized in Kumamoto University School of Medicine and later in the Ministry of Health and Welfare (MHW). The University research group identified the causative agent within the first three years. However, the epidemiological findings were not effectively exploited to prevent the spread of the disease.

Early epidemiological studies in 1956 found 55 cases of the disease, which included 17 deaths. These studies indicated that the disease was closely associated with the consumption of fish and shellfish and suggested that it might be a kind of heavy metal poisoning. The factory waste was suspected as the source of the causative agent but it seemed difficult to prove it. Since the ingestion of marine products caught in Minamata Bay apparently caused the disease, the Kumamoto Prefecture government recommended not eating fish and shellfish of the bay in 1957, but did not actually prohibit the fishing or eating of them.

As new patients continued to be found during the summer of 1958, the Minamata fishermen's cooperative claimed compensation for damages of fishing operation in the hazardous sea area and demanded immediate elucidation of the cause of the disease. In this period Chisso intended to increase the production of acetaldehyde, for which there was much demand as a raw material of octanol, a chemical used in polyvinyl chloride manufacturing. Engineers of the company assumed that if there were any toxicity contained in the waste, it could be eliminated by dilution with a large excess amount of seawater. Chisso changed the acetaldehyde drainage channel from the waste outfall of Minamata Bay, where water tends to stay, to the mouth of Minamata River in September 1958. However, the results differed from their expectations and strengthened suspicions about the association between the factory waste and the cause of the disease. In March of the following year, patients began to appear around the Minamata River mouth area in addition to the Minamata Bay and neighboring areas. The areas in which patients appeared expanded further around every costal region of the southern Yatsushiro Sea.

The research group of Kumamoto University presented, in July 1959, the organic mercury hypothesis for the etiology of Minamata disease based on pathological and clinical findings and on the fact that mercury was detected at extremely high concentrations in the sludge of Minamata Bay with a maximum of 2,000 ppm at the waste outfall. Chisso officially argued that 1) the factory had been using inorganic, but not organic, mercury as a catalyst since the 1930s without appearance of the disease, 2) Minamata disease had never been reported elsewhere in neighboring chemical plants using mercury, a common chemical, 3) although alkylmercury compounds are soluble in organic solvents, animal experiments using cats indicated that toxic agent could not be extracted from poisonous fish or shellfish with the solvents and were found to remain in insoluble fraction, and 4) the research group was unreliable, because it had been presenting other hypotheses of manganese, selenium, and thallium to that point without any success. However, the company had not mentioned at all several important facts, such as 1) the possible formation of methylmercury during the course of the chemical reaction in the synthesizing chamber containing inorganic mercury had been postulated, 2) the production of acetaldehyde had increased substantially in

the Minamata factory during the 1950s, 3) an oxidizer of the synthesizing process, manganese dioxide, was replaced by ferric sulfide in 1951, and 4) neurological signs resembling Minamata disease had been induced in the cats at the Chisso laboratory after the ingestion of not only fish and shellfish caught in the Minamata Bay but a diet mixed with the waste liquid obtained from the acetaldehyde process of the factory. The oxidizer change is now considered to affect the yield of methylmercury in the reaction chamber. Concerning the paradoxical findings on the extraction of methylmercury from biological samples, it has since been found that methylmercury covalently binds to cysteine residue of polypeptides in organisms (as mentioned below) and it cannot be extracted by organic solvents without the hydrolysis of protein.

Becoming a Social Issue

After the announcement of the methylmercury hypothesis by the research group, Minamata disease became a social problem. Fishermen's associations pushed Chisso to compensate the fishing industry, to establish a waste liquid processing facility, and to cease waste liquid drainage. The Ministry of International Trade and Industry (MITI) admonished Chisso in October 1959 to restore the drainage channel to the waste outfall of Minamata Bay and to complete the construction of a waste processing facility by the end of the year. In November 1959, more than two thousands members of fishing cooperatives gathered in Minamata from the coastal area of the Yatsushiro Sea to appeal to the Diet Investigation Team that visited Minamata. A thousand of the members then invaded the factory and at least a hundred were injured.

In December 1959, Chisso signed an agreement with fishermen's associations on fishery compensation and held a ceremony cerebrating the completion of the waste liquid processing facility "*Cyclator*". Kiichi Yoshioka, the President of Chisso, reported in the ceremony that the completion of the "*Cyclator*" had perfected the company's waste liquid management. He showed drinking a glass of the so-called "treated" water as the waste passed through the facility in front of the assembled guests including Prefecture's Governor. It was revealed many years later, however, that the main function of "*Cyclator*" was to precipitate insoluble suspended materials in water and dissolved chemicals in the waste could not be removed by the facility.

Chisso also made an agreement in December 1959 with the patients' association consisting of 78 patients and some of their families to pay an annuity of 100,000 yen as consolation money to each of adult patients. The contract, however, specified that the payments would cease if Chisso was found not to be involved in the cause of the disease, and that patients would make no further demand for compensation even if the cause of the disease was proven to be the Chisso factory waste. Chisso emphasized that the payments were made as a token of the company's sympathy for the patients, not as compensation for any damage.

The sub-committee of the Food and Sanitation Investigation Committee of MHW, including Kumamoto University research group, had carried out an investigation to elucidate the cause of Minamata disease. In November 1959, the Committee presented its official conclusion, based on the report of the sub-committee, that Minamata disease was a kind of organic mercury poisoning induced by the intake of polluted fish and shellfish caught in Minamata Bay. The Chairperson of the Committee said "although the factory waste was suspected as the cause, the further investigation of the Committee is impracticable and the matter should be entrusted to the ministries concerned". At the Cabinet meeting of November 13 in which the minister of MHW presented the report of the Committee, Hayato Ikeda, the minister of MITI (who promoted the rapid economic growth policy from 1960 to 1964 as prime minister) argued that it would be hasty to conclude that organic mercury had been discharged from the factory.

During the Silence

It was apparent that the organic mercury hypothesis had a significant influence not only on the chemical industries but also on government policy for industrial promotion. Further investigation on the cause was left to the new council established in February 1960 and comprised of the Economic Planning Agency, MITI, MHW, and the Fisheries Agency. The Japan Chemical Industry Association, a business community, also organized the so-called "Tamiya Committee"

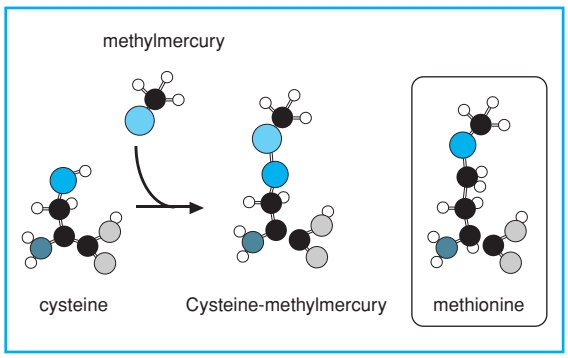

Fig. 2 Formation of cysteine-methlymercury, an analogue of methionine (after A Yasutake)

after the name of Chairperson Dr. Takeo Tamiya, the President of the Japanese Association of Medical Sciences. These committees, however, had drawn no conclusion on the cause of the disease. They gave the impression that methylmercury was only one among several different hypotheses including the degenerated amine hypothesis and that the cause of the disease had yet to be elucidated.

By the beginning of 1960s, it seemed as if the Minamata disease problem had terminated without having clarified the cause of the epidemic, after the contracts on the consolation money and the fishery compensations had been agreed, after the waste processing facility had been completed, and after the official comments of the government committee were issued. Meanwhile, Chisso increased the production of acetaldehyde in 1960 and 1961, and methylmercury pollution of the sea continued, resulting in the increase of potential patients, who were also discriminated and oppressed in the local community.

Since the mid 1950s the incidence of cerebral palsy had been extremely high among neonates in the area Minamata disease occurred. Incidences of abortion and stillbirth were also high, and the birth sex ratio indicated a significant decline of male birth during the 1950s in the district. Two girl patients who died in 1961 and 1962 were found to be fetal cases of Minamata disease after autopsy,[4] and 15 patients of cerebral palsy were certified as the cases in 1962. The occurrence of serious congenital effects by the exposure to toxic chemical in utero was unexpected, because the placental barrier had been considered to be effective in excluding most toxic chemicals from entering the fetus. It is now known that methylmercury covalently binds to cysteine, as mentioned above, to form cysteine-methylmercury, a structural analogue of an essential amino acid methionine (Fig. 2), which can effectively pass through not only the placenta but the blood-brain barrier via an amino acid transporter.[5]

A Chisso engineer successively isolated methylmercury in the waste from the acetaldehyde synthesizing process of the factory in 1961. However the company did not release the findings. In the following year, the isolation of methylmercury was published by members of Kumamoto University Research group, independently from the Chisso engineer's findings, from not only shellfish in the Minamata Bay but also the sediment of the bay. It was 1967 that the by-production of methylmercury was demonstrated in the synthesizing process.

Second Minamata Disease

In the history of public health, diseases can sometimes be eradicated before their causes are properly understood.[6] However, this was not the case with Minamata disease. The interruption of the exposure to causative agent is effective to prevent disease. From an epidemiological standpoint, it is not a necessary requirement to demonstrate strictly the causal relationship between specific agent and onset of the disease before removing the possibility of exposure. It should be argued that the delay in taking precautions to eliminate the suspected causative agent was a failure in political decision making.[7] While the causative agent of Minamata disease had not been officially accepted in spite of the research achievements and no comprehensive measure was taken to prevent the pollution from enlarging, another tragedy happened when patients of methylmercury poisoning were found along the basin of the Agano River in Niigata Prefecture in January 1965. It was the second Minamata disease epidemic. The experience in Minamata was enough for the government to take prompt measures including a medical examination involving a hair mercury survey of the inhabitants of the lower basin of the Agano River. Contraception was recommended for women who had hair mercury levels of 50 ppm

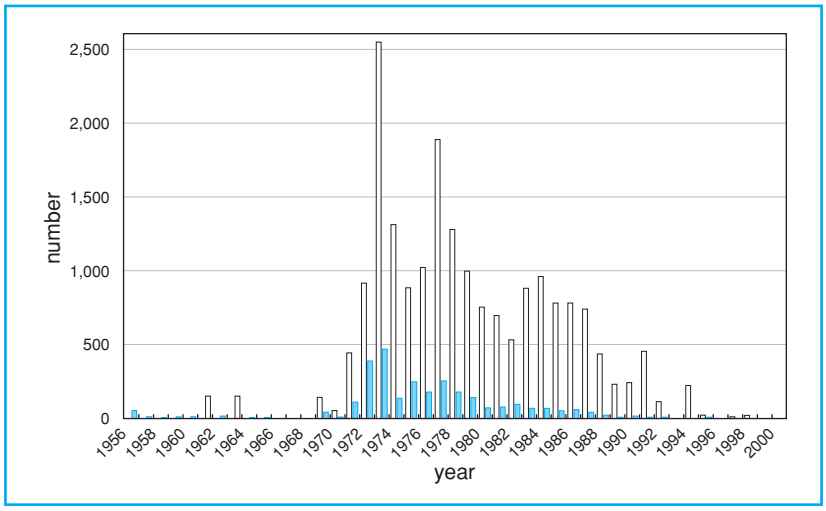

Fig. 3 Number of application (white bar) for the official certification and of certified patient (blue bar) of Minamata disease (up to 2000)

or higher to prevent fetal cases. Showa Denko's Kanose factory located on the upper Agano River, which had been synthesizing acetaldehyde until January 1965, was suspected as the most plausible source of methylmercury in the basin.[8]

By the mid 1960s in Japan, air and water pollution, known as *kogai* (public hazard), had become a serious problem as the negative consequences of the rapid growth of the heavy and chemical industries.[9] The Basic Law for Environmental Pollution Control was established in 1967. The central government had recognized that identifying a cause, instead of leaving it ambiguous, might help to settle the problems. The government had to determine whether Minamata disease was associated with environmental pollution that was under the jurisdiction of the law. In September 1968, the government presented a collective view on the two epidemics of Minamata disease and stated that the causative agent in Kumamoto was methylmercury discharged from Chisso Minamata factory and that the waste of Showa Denko's Kanose factory had substantially caused the methylmercury pollution in Niigata. Twelve years had already passed since the first recognition of the patient in 1956.

Compensation and Relief

Officially certified patients are eligible to receive compensation from the companies responsible. The total number of certified patients was 111 in Yatsushiro Sea area and 32 in Niigata by 1968, year of the government's announcement. After four years struggles in lawsuits, the Niigata and Kumamoto District Courts in 1971 and 1973 respectively, ruled that full responsibility for Minamata disease lay with the companies. The Kumamoto District Court also voided, because of a violation of public order, the consolation money agreement that specified for patients to renounce making claim for further compensation. It had become apparent that damages should not be tolerated even among a small number of residents as an acceptable cost for achievements in economic development as a whole. Company compensation was legally justified. Applications for certification of Minamata disease then increased since the 1970s (Fig. 3). It should be noted that the apparent increase in the number of patients and applications during the period does not indicate an actual increase in the onset of the disease but acceleration of making applications by pre-existing patients. The total number of certified cases was 2,955 by 2005 in the Yatsushiro Sea costal areas and the basin of the Agano River as shown in Table 1. Fig. 4 indicates the change in the number of living patients who receive compensation from Chisso, with the decrease in the number over

Table 1 Number of Minamata disease patients, recipients of official relief services and applicants for the certification as of 2005 (including deceased cases)

Total number of officially certified patients	2,955
Kumamoto Prefecture*	1,775
Kagoshima Prefecture*	490
Niigata Prefecture*	690
Recipients of the Medical Task of the Comprehensive Measure of Minamata disease (since 1992)	c.a.12,700
Patients manifesting health effects of methylmercury that were recognized by the ruling of the Supreme Court in 2004	58
Applicants for certification (before judgment)	>3,300

*: Patients of Kumamoto and Kagoshima Prefectures were residents of the costal area of the Yatsushiro Sea, and patients of Niigata Prefecture were in the basin of the Agano River.

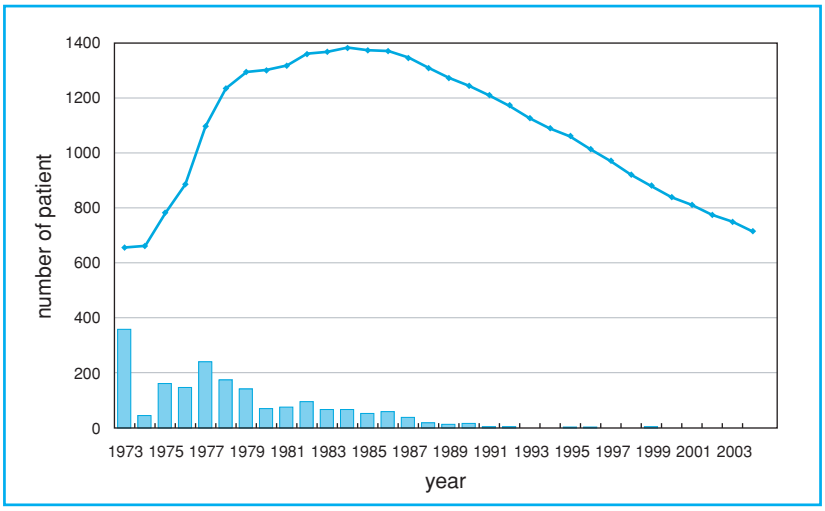

Fig. 4 Changes in the number of survived patients (solid line), who were officially certified as Minamata disease and receive compensation from Chisso
Solid bar indicates number of new certification. Data were taken by courtesy of Chisso Corp.

the decade indicating the aging of patients and about 700 still alive in 2004. The certification of Minamata disease has been conducted by the official Certification Boards on Minamata disease according to the medical criteria laid out by Ministry of the Environment. Only about 15% of applications have been certified as Minamata disease (c.a. 12% in Yatsushiro Sea costal areas, and c.a. 32% in the basin of the Agano River). Several lawsuits had been filed between 1973 and 1988 by plaintiffs including patients whose applications had been rejected, seeking to claim compensation from the companies responsible and from the governments.

There are two main difficulties concerning the evaluation of adverse health effects induced by methylmercury exposure at moderate or low doses. First, as methylmercury has a relatively short biological half life in the human body, 70–90 days on average,[10] it is difficult to assess the past exposure dose of the chemical using biological samples taken from residents. Second, most complaints of Minamata disease are subjective and may not be free from bias, especially given the possibility of linkage with compensation for the patients. Few large-scale epidemio-

logical surveys have therefore been conducted to investigate the association of methylmercury exposure and adverse health outcomes among residents in the polluted areas.

While the plaintiffs were becoming noticeably older, agreements were successively achieved for out of court settlements among almost all patient groups, companies responsible and governments in 1995. Inhabitants suffering from a part of the neurological signs specified in the criteria for Minamata disease certification, in which specific combinations of two or more symptoms are required for the certification, acquired official support including medical expenses and a lump sum payment. As many as 12,300 cases became recipients of aid in 1997 (the Medical Task of the Comprehensive Measure of Minamata disease in Table 1). In 2004, on the other hand, the Supreme Court gave a ruling on Kansai lawsuit, the only trial that had rejected the acceptance of the settlement in 1995, and identified the responsibility of governments for their failure to prevent the expanded spread of Minamata disease. More than 3,600 applications have been made for patient certification during about one year following the ruling, and some of the applicants (690 by the end of 2005) filed another case in 2005 aimed at securing compensation through the legal system.

The Present Issues

There are some discrepancies between the medical criteria for certification of Minamata disease of Ministry of the Environment and the borderline symptoms adopted by order of the Supreme Court,[11,14] and the significant controversy still exists concerning the diagnosis of Minamata disease. However, discussions are also necessary from the standpoint of how to construct the compensation system for a large variety of adverse health effects among residents including nonspecific symptoms associated with exposure to moderate or low doses of the chemical.

Memorial events are being prepared in Minamata and its neighboring areas by the governments, patient organizations, and citizens to commemorate 2006, which is fifty years since the first identification of the disease. On the other hand, there is increasing anxiety on physical conditions among aged patients particularly of fetal cases, who are mostly 40 years of age or older.[12] There is much to learn from the experience of Minamata disease, which has caused a variety of issues including social conflicts.[13] The negative consequences are far from abating even half a century after the first appearance of the problem.

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