Chapter 1

Outlines of Yusho

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A "strange disease" occurred involving more than 1,800 persons in Western Japan in 1968. The major symptoms and signs of the disease consisted of acneiform eruptions, pigmentation of the skin, nails and conjunctivas, increased discharge from the eyes, and numbness of the limbs. The disease was diagnosed as chloracne at the Kyushu University Hospital.

The cause of the epidemic was quickly clarified by a research team, organized by Kyushu University, to be the ingestion of a commercial brand of rice oil produced by the Kanemi Sohko Co., Ltd., because the oil was found to be contaminated with Kanechlor 400, a product of PCBs manufactured by the Kanegafuchi Chemical Industry Co., Ltd. The disease was thus named "Yusho" (oil disease).

The contamination was at first thought to be due to a leak of Kanechlor through pinholes which were found in a stainless steel pipe installed in a deodorization tank at the Kanemi rice oil plant. Heated Kanechlor had been circulated through the pipe. This possible mechanism of contamination was called the "Pinhole Theory". It was later disclosed, however, that a hole had been formed in the pipe by a welding error, leading to a heavy contamination of the rice oil with Kanechlor, and thus gave rise to the "Welding Error Theory" which is now generally accepted as the true cause.

The toxic rice oil consumed by patients contained not only PCBs, including coplanar ones, but also PCDFs, PCDDs, PCTs, PCQs, and some other related substances. The biochemical studies of the induction effect of these compounds on hepatic enzymes as well as their toxicological studies revealed that some PCDF congeners, including 2,3,4,7,8-PenCDF, exhibit a very potent acute toxicity which is proportional to the 3-methylcholanthrene-type inducibility of hepatic enzymes by the congeners. Also taking into account the amount of these congeners contained in the causal rice oil, PCDFs were considered to play an overwhelmingly important role in the pathogenesis of the disease, while the PCBs and other substances did not.

In vitro and *in vivo* metabolic studies using rats revealed that PCBs are metabolized principally through regioselective hydroxylations, each of which is catalyzed by specific cytochrome P-450 isozymes. Some PCB congeners have been shown to be converted to more toxic hydroxy-metabolites in rats. Methylsulfone metabolites and certain hydroxy-metabolites of PCBs were also detected in the tissue of patients for many years.

Pharmacological studies showed that the sharpest biological response to exposure to PCBs is the induction of hepatic enzymes as indicated e.g. by a shortening

of the hexobarbital sleeping time seen in exposed animals. Studies on hepatic biopsy specimens from one patient showed no changes by light microscopy, but definite changes were evident in electron micrographs: including a marked proliferation of the smooth-surfaced endoplasmic reticulum and a reduction of the rough-surfaced endoplasmic reticulum. Thus, hepatic enzymes seemed to have been induced in these patients.

The hepatocarcinogenicity of PCBs and PCDFs was demonstrated by our animal experiments.

The total amounts of PCBs, PCQs and PCDFs ingested by each of the patients and the amounts of these compounds ingested during the latent period before the clinical manifestations of the illness appeared were estimated. The clinical severity of the patients showed a close positive correlation with the total amounts of the rice oil consumed but not with the amount of the oil consumed per kg per day. This may thus indicate that an exposure to a highly persistent toxic agent is better represented by the total dose taken than by the dose per kg per day as is commonly believed.

The disease was found to be very hard to cure by conventional medical treatments, primarily due to the high persistency of the PCDFs remaining in the tissue of the patients.

Extensive clinical studies including autopsies have been conducted on Yusho, thus revealing a number of clinical features characteristic of the disease, and the major ones are listed below as follows:

1) Many patients complained of various subjective symptoms and showed peculiar signs such as swelling of the eyelids and meibomian glands which secreted an excess amount of a cheese-like material, acneiform skin eruptions, pigmentation of the corneal ring, conjunctiva, skin, nails, lips, gingivae and mucous membrane of the oral cavity. Over time, these symptoms and signs have either gradually improved or disappeared but some of them are still seen in certain patients even more than 25 years after the attack.
2) Histopathological studies of the skin lesions showed a marked hyperkeratosis, cystic dilatation of hair follicles and a marked increase of melanin in epidermal as well as follicular basal cells.
3) Elevated serum triglyceride levels were generally observed in the patients for a prolonged period of time, while the levels of cholesterol and phospholipid were normal. A weak but significantly positive association between the blood PCBs and serum triglyceride was observed in the patients even 20 years after the attack, although their blood PCB and serum triglyceride levels had decreased to close to normal levels.

4) Definite abnormalities in common liver tests were hardly seen, apart from a slightly elevated level of alkaline phosphatase in the early stages. The serum bilirubin levels, however, were found to be significantly lowered when examined several years after being affected.
5) Many patients complained of stubborn neurological symptoms over a period of years. However, no symptoms or signs that indicated the involvement of the cerebellum, spinal cord or cranial nerves were seen. A slowing of the sensory nerve conduction velocity was seen in some early patients, whereas the motor nerve conduction velocity was within the normal range.
6) About 40% of the patients were found to suffer from chronic bronchitis, when examined about 2 years after being poisoned. PCBs and their sulfur-containing metabolites were detected in the lung and sputum of many patients. PCDFs were also found to selectively affect the Clara cells of the lung.
7) Both humoral and cellular immunities were found to be impaired in the patients.
8) Dark colored babies were borne by affected mothers. Parchment-like desquamation of the skin, dark brown pigmentation of the mucous membranes, increased discharge from the conjunctiva and eruption of teeth at birth, but no acneiform eruptions were seen among these babies. The pigmentation faded within several months. Most of them were small-for-gestational-age (SGA) babies. One baby was observed to suffer from Yusho and was considered to have been affected exclusively by breast feeding from a mother with Yusho.
9) The affected children showed clinical manifestations similar to those seen in the adult patients. In adddition, growth appeared to be disturbed in boys.
10) Pigmentation of the gingival and buccal mucosa was seen in most of the patients, only faded very gradually, and persisted for more than 20 years in about 15 percent of the patients. The pigmented mucosa contained a high concentration of PCBs and even when the mucosa was surgically removed, the pigmentation recurred within a year. This demonstrates that the current pigmentation of the oral mucosa does not represent any remains of the old pigmentation but indicates a new pigmentation caused by the PCBs, PCDFs and other related compounds remaining in the mucosa and other tissue. Besides pigmentation, a retarded eruption of the permanent teeth and anomalies in the number of teeth and in the shape of the root were also seen among the patients.
11) These patients even now have a much higher concentration of PCQs and PCDFs in the blood and other tissues than do unaffected persons. The gaschromatographic pattern of PCBs retained in the blood and other tissues

of the patients, particularly those of the severely affected, distinctly differ from the corresponding pattern seen in normal persons and has hardly altered over the past years. These facts have thus been utilized for the differential diagnosis of the disease.

In view of the high toxicity as well as hepatocarcinogenicity of PCDFs, it is essential for the patients to excrete all the PCDFs retained in their tissue as soon as possible. Extensive animal and clinical experiments were conducted for this purpose. Although a fasting cure was found to be effective, the development of less drastic but more effective methods to accelerate the excretion was thought to be highly desirable. Therefore, clinical experiments on the oral administration of cholestyramine together with rice bran fiber have been undertaken in both Japan and Taiwan, to accurately determine the amount of each PCDF congener excreted in the feces of subject patients. These interesting but extremely laborious clinical trials demonstrated that the above administration was effective, and its improved application for Yusho patients is now under investigation.

A cohort analysis of the deaths seen among the patients demonstrated a significant excess mortality for malignant neoplasms at all sites, for cancer of the liver and for cancer of the respiratory system in males, while no such excess was noted in females.

After the outbreak of Yusho, various administrative actions were taken by the Ministry of Health and Welfare and other ministries. The regulations for the production of cooking oils and fat by the government were strengthened; new standards for the regulation of PCB residues in common foods and in the environment were set; and the production, use and import of PCBs were banned. A new law to regulate the production of new chemical substances with a high persistency and chronic toxicity similar to those of PCBs was also enacted.

The victims of Yusho filed civil suits for damages. Accepting the so-called "Pinhole Theory" as the cause of the contamination of the rice oil, the courts found Kanemi to have been negligent in using Kanechlor and in processing the rice oil and found Kanegafuchi liable for failing to provide sufficient information concerning the toxicity and corrosiveness of PCBs, and thus ordered the company to pay substantial damages to the plaintiffs. Later, a high court accepted the "Welding Error Theory" and judged Kanegafuchi not to be guilty. The Supreme Court thus recommended the parties to enter into a compromise and they finally agreed to it about 20 years after the outbreak of the incident.