Chapter 3

Investigation of the Cause of the "Strange Disease"

3.1. Preparations for the Investigation

Masanori Kuratsune

3.1.1. Organization of a Study Group

In view of the grave situation of the epidemic, an utmost effort had to be urgently made by all the medical professionals and health authorities in the prefecture in order to clarify the cause of the epidemic and to provide the patients with proper medical cares. Complying with Professor Higuchi's request, Professor Shibanosuke Katsuki, director of the Kyushu University Hospital, organized a study group in the hospital to meet this emergency on October 14, 1968, comprizing the staff of the hospital, of the Faculty of Pharmaceutical Sciences, Kyushu University, and of the Department of Public Health, Fukuoka Prefecture (Katsuki, 1969, 1973). It was decided to call this study group the "Study Group for YUSHO" at the first meeting of the group. This is quite strange because "Yusho" literally means "oil disease", and nothing had been proved yet at all in regard to the cause of this strange new disease. It is thus clear that the study group was already too firmly convinced of a causal association of the disease with some cooking oil. Generally speaking, a profound conviction like this could often hinder an unbiased pursuit of the cause of a disease. At any rate, the study group was thus launched and immediately decided to hospitalize the patients to the University Hospital for thorough medical examinations and proper treatments and to set up a special outpatient clinic in the hospital exclusively for them (Katsuki, 1969).

3.1.2. The Diagnostic Criteria and Tentative Therapeutic Guidelines for the Disease

The study group also prepared diagnostic criteria and tentative therapeutic guidelines for the disease at its first meeting (Katsuki, 1969; Appendix 1. Table 1). They were respectively called the Diagnostic Criteria for "Yusho" and the Tentative Therapeutic Guidelines for "Yusho". Here again, the presumptive term, "Yusho", was used even though the cause of the disease was entirely unknown yet. Neverthless, these documents were very important and interesting. The former was particularly so, primarily because it indicated the incipient clinical features of this quite unusual disease which was soon proved to have never been experienced by man, and secondarily because they served to provide us with correctly diaganosed cases which are essential for any epidmiologic investigations. These documents were immediately printed and distributed to hospitals and clinics. According to Dr.

Masayasu Goto who was a member of the study group, a particular effort was made by the group to make practitioners well understand the disease as well as the documents by holding a special seminar at the University Hospital. Furthermore, the clinicians of the study group were dispatched to several major cities to examine the patients with the disease. All these efforts allowed us to grasp unequivocal cases of this peculiar disease, greatly facilitating the epidemiologic investigations by the study group. However, it was soon realized that the diagnostic criteria had a rather grave defect from an epidemiologic point of view. The criteria say first that "these criteria can be applied only to the specific disease called Yusho . . . which is suspected to have been caused by the use of a specific brand of rice bran oil". According to these criteria, physicians will hesitate to diagnose those who did not use rice oil before, even though they may be actually affected. This will, of course, seriously disturb an impartial pursuit of the cause. This problem will later be discussed in the section 3.3.5.

3.1.3. An Announcement of Arsenic Contamination of the Rice Oil

At the first meeting of the study group that was held immediately after it was organized on October 14, 1968, a researcher from the School of Medicine, Kurume University in Fukuoka Prefecture reported on their detection of arsenic in a certain lot of Kanemi rice oil which had been used by some affected families (Katsuki, 1973). The public was immediately seized with fear. On the next day, the Department of Public Health, Fukuoka Prefecture, issued an order to prohibit the sale of Kanemi rice oil. Although the symptoms and signs of the present disease considerably differ from those of arsenic poisoning, the above announcement appeared too important to be disregarded. Several laboratories such as the Department of Hygienic and Forensic Chemistry, Faculty of Pharmaceutical Sciences and the Department of Public Health, Faculty of Medicine of Kyushu University, the Prefectural Institute of Public Health, Fukuoka Prefecture and the Kitakyushu City Institute of Public Health soon started to analyze the Kanemi rice oil used by patients for arsenic. None of these laboratories, however, could find it. These unanimously negative results were announced to the public by Professor Katsuki and Professor Hidetoshi Yoshimura, Faculty of Pharmaceutical Sciences, on October 17. Soon afterwards, the researchers at Kurume University withdrew their previous statement.

Meanwhile, a meeting was for the first time held by the Ministry of Health and Welfare in order to exchange the latest information on the epidemic in Fukuoka City on October 17. It was attended by Dr. Kiyoshi Nodzu, chief of the Division of Food Sanitation, Ministry of Health and Welfare, by doctors from universities and by health officers from the prefectures in Western Japan. Dr. Nodzu reported that

Table 3.1. Number of Notified Patients[a] by Prefecture

District	Prefecture	Number of patients
Kinki	Kyoto	20
	Osaka	71
	Hyogo	12
Chugoku	Shimane	12
	Okayama	73
	Hiroshima	94
	Yamaguchi	203
Shikoku	Tokushima	90
	Kagawa	19
	Ehime	13
	Kohchi	57
Kyushu	Fukuoka	568
	Saga	110
	Nagasaki	136
	Kumamoto	10
	Ooita	120
	Miyazaki	26
	Kagoshima	21
Total		1,655

(As of October 16, 1968)

[a]: Including doubtful cases.

more than 5,000 persons rushed to local public health centers or hospitals for fear of the disease, and about 1,600 of them were diagnosed as affected with the present disease as shown in Table 3.1. This indicates how seriously and widely the epidemic of the disease and the announcement of arsenic contamination shocked the general public.

3.1.4. Reinforcement of the Study Group

For the quick clarification of the cause of the disease, a reinforcement of the study group seemed inevitable. Professor Katsuki was visited on October 18, by two doctors, namely, Professor Hitoshi Takahashi, Toxicology Institute, Medical School, Kumamoto University, who had been engaged in the study of the treatments of Minamata Disease, and Professor Kaoru Inagami, Chairman of Food Technology, Department of Food Science and Technology, Faculty of Agriculture, Kyushu University. They were both interested in seeing patients suffering from the "strange disease" at the "Yusho" clinic (Katsuki, 1973; Inagami, 1992). Conversing with them who had been deeply impressed by seeing the miserable conditions of the patients, Professor Katsuki realized the urgent necessity of a close cooperation to be made by professionals not only of the medical field but also of

other related fields and abruptly asked Professor Inagami to join his study group. Professor Inagami declined to answer immediately but several hours later advised Professor Katsuki to organize a small chemical group to analyze the rice oil (Katsuki, 1973).

Professor Katsuki was then a member of the University Council that consisted of the representatives of all the faculties and research institutes of the university. On the morning of October 19, he visited Professor Takaaki Mizuno, president of the university, and explained the urgency of the epidemic and succeeded in getting his wholehearted support. He also immediately made contact with several council members, seeking their assistance in performing his hard task and again succeeded in getting their unanimous support. This was rather a surprise to us, because the whole school was then in an utter confusion due to a student riot which had been blazed up by an accidental crash of a U.S. jet fighter to a building of the school in early June 1968 and all the staff of the school had been obliged to make rewardless efforts to restore order in the campus, losing both time and energy to do anything else. Contrary to our expectation, many experts from various faculties and research institutes willingly joined the study group complying with the request of Professor Katsuki, and with consent of the respective faculty deans. Among them were Professor Inagami and his associates who had decided to completely suspend their own research and other activities for about ten days so that they could concentrate their efforts on the identification of toxic compounds which might be contained in the rice oil (Inagami, 1992). Without doubt, they must have thought that without such concentrated close cooperation the identification would not be achieved quickly. A multidiciplinary pursuit of the cause of the epidemic thus became feasible.

On the afternoon of October 19, a reorganized study group, namely, the "Study Group for YUSHO (Rice Oil Disease)" was launched. It was headed by Professor Katsuki as director, and by Professor Higuchi and Dr. Osamu Shimono, Director General, Department of Public Health, Fukuoka Prefeccture, as associate directors. As shown in Table 3.2, the study group consisted of three study subgroups, namely, the Clinical Study Subgroup, the Epidemiologic Study Subgroup and the Chemical Study Subgroup. The Clinical Study Subgroup included three committees, namely, the Clinical Committee, the Committee of Clinical Laboratories, and the Committee of Physical Check-up. Members of these subgroups and committees are listed in Appendix 2, Tables 1, 2 and 3. As referred to, the Chemical Study Subgroup was quite unique in its composition, comprising many non-medical experts such as those of food technology and of pharmaceutical or applied chemistry. It is also notable that the Epidemiologic Study Subgroup was set up in the study group, because at that time in Japan, the necessity of epidemiologic in-

Table 3.2. The Study Group for YUSHO[a]

Director	:	Shibanosuke Katsuki, Professor of Medicine, Director, University Hospital, Faculty of Medicine[b]
Associate Director	:	Kentaro Higuchi, Professor of Dermatology, University Hospital, Faculty of Medicine[b]
Associate Director	:	Osamu Shimono, Director General, Department of Public Health, Fukuoka Prefecture
Study Subgroups :		
Clinical Study Subgroup :		
Chief	:	Kentaro Higuchi, Professor of Dermatology, University Hospital, Faculty of Medicine[b]
Chemical Study Subgroup :		
Chief	:	Hisao Tsukamoto, Professor of Physiological Chemistry, Dean, Faculty of Pharmaceutical Sciences[b]
Epidemiologic Study Subgroup :		
Chief	:	Masanori Kuratsune, Professor of Public Health, Faculty of Medicine[b]

[a]: Organized on October 19, 1968.
[b]: Kyushu University

vestigations for clarification of the cause of diseases had been poorly understood even by medical professionals. Professor Katsuki was rather exceptional in this respect, however. He was not only an eminent clinician, but also a scientist of epidemiologic discretion, as indicated by the fact that he had already initiated a highly internationally recognized epidemiologic project, that is, Hisayama Project, a carefully designed and admirably developed cohort study of cerebrovascular and other adult diseases. We owe the establishment of the Epidemiologic Study Subgroup much to his distinguished insight into the difficult task of the study group.

At the end of the first meeting of the Study Group for YUSHO on October 19, a few researchers from Hayashikane Sangyo Co., Ltd. in Shimonoseki City in Yamaguchi Prefecture made a guest lecture on a strange epizootic which had prevailed in the Kyushu district involving more than 2 millions of chickens, from February to March in 1968 (see Appendix 6, The "Dark Oil" Incident). According to them, the affected chickens showed peculiar lesions similar to those of "chick edema disease" which occurred in the United States (Schmittle et al., 1958). They mentioned that, as revealed by an offical investigation, poultry farmers who suffered a heavy loss had used commercial formula feeds produced either by their company or by another, Tokyu Ebisu Sangyo Co.,Ltd., and both companies had used so-called "dark oil", a by-product of the rice oil production at Kanemi, as a common ingredient for the feeds. The formula feeds as well as the "dark oil" were

found to be toxic by feeding experiments but they had failed to specify the toxic agent. They also referred to the causal agent of the chick edema disease that had been determined to be 1, 2, 3, 7, 8, 9-hexachlorodibenzo-p-dioxin by Dr. Cantrell and his associates. Frankly speaking, none of us seemed to have paid much attention to this compound then, because our disease concerned appeared quite different from the chick edema disease and nobody appeared to take notice of the strong acnegenicity of the dioxins yet, although such acnegenic potency had already been discovered by a series of admirable studies conducted at the Department of Dermatology, Hamburg University Hospital as early as in 1956 (Schulz, 1957; Kimmig & Schulz, 1957). At any rate, we thus started our pursuit suspecting Kanemi's products as a possible cause of the "strange disease".

3.2. Chemical Analysis of the Rice Oil

Masanori Kuratsune and *Hidetoshi* Yoshimura

Although no detailed epidemiologic investigation had been made yet, the common consumption of Kanemi rice oil by the patients before being affected seemed to be true. The Chemical Study Subgroup, therefore, concentrated its effort to the chemical analysis of the oil. Quite a few samples of the rice oil were provided to us as the oil used by the patients through health departments, directly by patients, or from other sources. All these materials were registered and carefully preserved at the Department of Legal Medicine, Faculty of Medicine, Kyushu University, following a judicious advice by Professor Katsuki and then subjected to chemical analyses and pathological examinations. According to him, any specimens used for an elucidation of the cause of a certain disease should be kept with due legal precaution, as they could be an invaluable evidence in case of legal trials. It should be noted that he had been deeply involved in the clarification of the cause of "Minamata Disease" as a professor of Kumamoto University before he was appointed professor of medicine at Kyushu University. His precaution, therefore, must have stemmed from his hard experience in Kumamoto (Katsuki et al.,1969).

Every evening after the Chemical Study Subgroup was launched, the group members gathered and discussed fervently, exchanging their views and findings. Based upon Professor Higuchi's clinical confidence, priority was unanimously given to the pursuit of agricultural chemicals containing chlorine, which were considered to be contained in the rice oil samples used by the patients. Professor Hisao Tsukamoto, chief of the subgroup, however, was cautious enough not to miss any other types of toxic compounds such as inorganic substances as possible contaminants of the oil. Some of the members were thus assigned to a thorough analysis of the oil exclusively for toxic inorganic compounds including arsenic for precaution, although the contamination of the rice oil with arsenic had, as mentioned, been denied by our previous analyses (Tsukamoto et al.,1969).

First of all, a possible contamination of the rice oil with pentachlorophenol, a herbicide widely used for paddy fields, was highly suspected. This working hypothesis seemed quite promising, because cases of occupational chloracne had been observed by Professor Higuchi among workers who were engaged in the production of this chemical at a chemical factory in Ohmuta City (Goto and Higuchi, 1969). Professor Kaoru Inagami, a member of the subgroup, who had studied this compound before, quickly analyzed the rice oil samples and found no significant amount of the chemical in them. The most promising working hypothesis was thus

denied almost in no time, leaving all the group members at a loss for a while. Other chlorinated agricultural medicines such as DDT, hexachlorocyclohexane (BHC), dieldrin, endrin and a few others were also suspected, but none of them seemed to be acnegenic. Occupational acnegens such as chlorinated naphthalenes, nitrochlorobenzenes, machine oils, cutting oils, and some others were also suspected, but, if our memory is correct, PCBs were not discussed at the group meeting. Neither PCDDs nor PCDFs were discussed by any of us, although, as mentioned, their strong acnegenicity had been reported by Kimmig and Schulz more than ten years before.

After all the members of the subgroup jointly worked hard in the chaotic atmosphere of the campus for about ten days, a big breakthrough suddenly came along. Professor Inagami and his associates who were specialized in food technology discovered that specimens of the Kanemi rice oil used by affected families were heavily contaminated with PCBs. Visiting and inspecting the oil production plant of Kanemi, he found that Kanechlor 400 (to be abbreviated as KC-400), a commercial brand of PCB mixture of chlorine content 48%, produced by Kanegafuchi Chemical Industry Co., Ltd., had been used there as a heat transfer agent for heating the rice oil over 200°C under a reduced pressure of 3 to 4mm Hg in order to remove odorous matters from the processed oil at the final stage of production of the oil. He received a portion of the agent from Kanemi and compared its gaschromatographic peak pattern with that of the unsaponifiable fraction of the rice oil, proving a heavy contamination of the oil with KC-400. Since no analytical method specific for PCBs was available then, the concentration of KC-400 contained in the oil was estimated to be 2,000-3,000 ppm from its organochlorine content (Tsukamoto et al.,1969).

It is interesting to know how Professor Inagami attained this remarkable discovery. According to him (Inagami,1992; Inagami,1994) and to Mr. Mikio Nishimura, the Asahi (Nishimura,1972; Nishimura,1995), the story is as follows:

1) As professor of food technology, he had been engaged in the study of antioxidants contained in natural fats and oils, and his laboratory was blessed with researchers who were well experienced in such study, and with equipments necessary for it.
2) Mr. Mikio Nishimura brought to his laboratory a bottle of Kanemi rice oil used by an affected family in Kitakyushu City on October 16, 1968 before he joined the Study Group for YUSHO, and asked him to analyze it for its possible toxic contaminants. He suggested Mr. Nishimura to take the bottle to the study group, but Mr. Nishimura left it at his laboratory.
3) It was soon found that the oil contained more unsaponifiable matters than

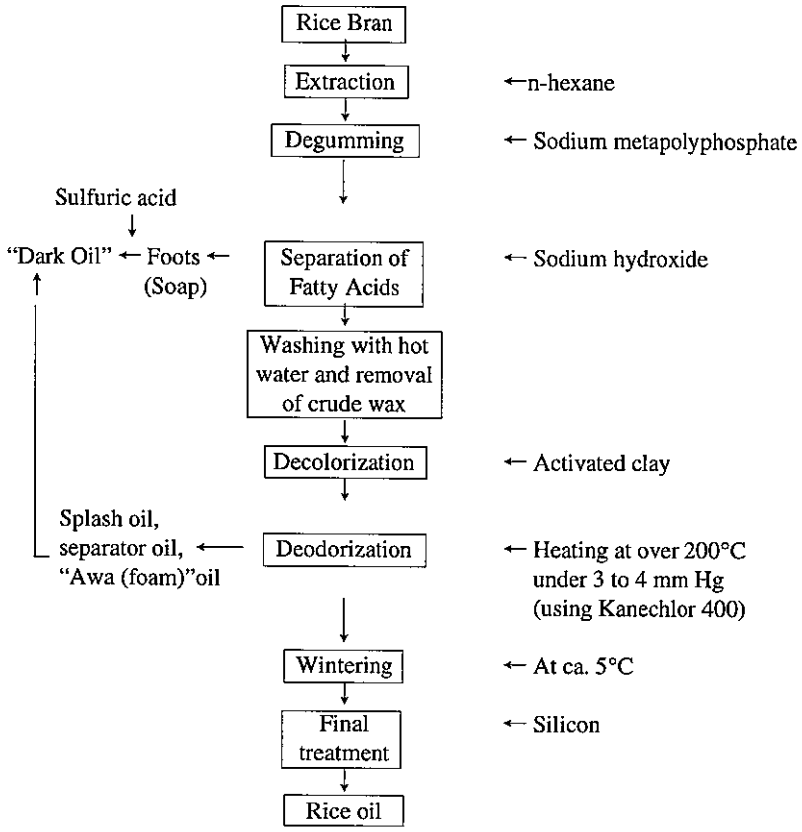

Fig. 3.1. The Flow Sheet of the Kanemi Rice Oil Production

did popular cooking oils. The unsaponifiable matters were resistant to strong acids and soluble in hexane but not in alcohol, benzene or ether, and differed from sterols and vitamin E.

4) An analysis of the unsaponifiable matters using a gaschromatograph equipped with a hydrogen flame detector that was available at his laboratory showed several unsharp irregular peaks, indicating a presence of an aggregate of similar chemical compounds.

5) At a laboratory meeting, they presumed a contamination of the oil with some polycyclic hydrocarbons (heat transfer agents or chlorinated agricultural medicines) from the above findings. Meanwhile, Professor Inagami then joined the Study Group for YUSHO at the request of Professor Katsuki.

6) In view of the finding by the Epidemiologic Study Subgroup that the patients seem to be consumers of a batch of Kanemi rice oil shipped during a very limited period of time as short as 3 days (see Section 3.3.3), he consid-

ered that any contamination, if present, must have occurred at the final stage of the production process of the rice oil (Fig. 3.1). This can be explained that if the contamination had occurred at some earlier stage such as the preparation stage of the rice bran which is the raw material for the rice oil production, the contamination must have been more widely spread in time, contaminating batches of the rice oil shipped during a period of time probably longer than 10 days. Therefore, he decided to concentrate his effort to detect any chlorine-containing compounds in the rice oil, particularly heat transfer agents that must have been used at the final stage of oil production in order to remove odorous matters.

7) To investigate such heat transfer agents that might have been used by Kanemi, he proposed to Professor Katsuki to inspect the Kanemi factory. With arrangements made by health authorities, he entered the factory on October 29 and obtained a portion of the heat transfer agent that had been used by the factory. From the next evening, his associates, and Dr. Tohru Kojima at the Department of Legal Medicine, Faculty of Medicine, Kyushu University, started to analyze four samples of the Kanemi rice oil used by patients and one sample of nontoxic rice oil, and tried to detect in them the KC-400 obtained from Kanemi. They used a gaschromatograph equipped with an electron capture detector that was then available only at the laboratory of the above department throughout the university at a good running condition under Dr. Kojima's due care. They succeeded in identifying the KC-400 in the four samples of the rice oil but not in the control rice oil. The result was notified to Professor Katsuki on October 31.

Professor Katsuki announced the above findings to the public on November 2 and indicated that they would be crucially scrutinized by the Chemical Study Subgroup soon. The subgroup met on November 4. A certain feeling of relief and satisfaction prevailed among the members and the discussion was more vivid than ever. All the findings collected till then were critically reviewed and it was concluded that the KC-400 contained in the rice oil would be the most important causal agent of the disease and the role of any inorganic substances including arsenic would be negligible. This conclusion was released to the media by Professor Katsuki and Professor Tsukamoto immediately. This was only two weeks after they started their activities. Without doubt, this quick identification of a highly probable causal agent would not have been achieved if no specialists in the food production technology like Professor Inagami and his associates had joined the study group.

By the subgroup, an examination of the sebum, skin and other tissues of the

patients for KC-400 was considered to be essential and was later conducted, yielding positive results (Tsukamoto et al., 1969). Experimental reproduction of this peculiar disease in animal models by feeding KC-400 was also thought to be essential because its pathogenicity in man seemed uncertain.

Soon after KC-400 was identified in the rice oil, Professor Hisashi Shinohara and his associates, Faculty of Engineering, Kyushu University, inspected the rice oil plant of Kanemi independently of our study group and quickly discovered pinholes in the coiled stainless steel pipe in a deodorization tank, through which heated Kanechlor had been circulated, on November 16, 1968. It appeared quite reasonable that the rice oil was contaminated with Kanechlor which leaked through these pinholes. Their discovery thus well assured our chemical findings, but questions were later raised about the validity of the pinholes as the route of contamination of the rice oil (see Section 3.4.6 and Appendix 7).

3.3. Epidemiologic Investigations of the Cause of the "Strange Disease"

MASANORI KURATSUNE

3.3.1. Preparations for the Epidemiologic Investigations

On the evening of October 19, 1968, immediately after the Epidemiologic Study Subgroup was organized, its first meeting was held to discuss and decide our principal approaches to the clarification of the cause of the disease. The major information about the epidemic that had been gathered by then was as follows:

a) The patients seemed to cluster in certain households. Most of the household members appeared to be affected regardless of age and sex.
b) Most of the affected households appeared to have used a specific canned rice oil produced by Kanemi.
c) No patients seemed to be in households that had not used the specific canned Kanemi rice oil, however close to the affected households they lived.
d) Patients seemed to live mainly in large cities such as Fukuoka, Kitakyushu and Ohmuta.

Fortunately enough, a few but competent young researchers cooperated with the subgroup, who had learned the epidemiologic principles and basic methods by reading the notable book by Professor MacMahon et al. (1960) and were eager to devote themselves to epidemiologic investigations. Much time was not needed to decide what and how we had to do. It was agreed by all of the members of the subgroup to make united efforts for the following investigations.

a) Clarification of the distribution of patients affected with this peculiar disease.
b) A thorough pursuit of the rice oil consumed by patients, from its production to personal purchase and consumption.
c) A case-control study to be conducted by interviewing patients with the disease and controls without it, in order to identify the specific cause or causes of the disease.

We also agreed that the above epidemiologic investigations should be carried out fully independent of the other study subgroups, although a good communication had to be maintained with them. We decided to continue our utmost efforts until we completed all the necessary investigations, even if the cause of the disease

might be quickly clarified by others. It actually took us more than 3 months to complete our epidemiologic investigations, without being dazzled by the brilliant success of the Chemical Study Subgroup, that is, the quick identification of KC-400 in the Kanemi rice oil used by some patients.

3.3.2. Distribution of the Patients

Elucidation of the characteristics of the distribution of a disease in terms of age, sex, time, place, etc., is basically important for epidemiologic pursuit of its cause, whatever the disease may be. It was arranged, therefore, that all the new cases of the disease would be regularly and quickly reported to the subgroup through health departments. Analyzing such reported cases, the distribution of patients could be readily determined, although it was a fairly time-consuming process, taking more than three months to collect a sufficient number of patients for such analysis. By January 20, 1969, a total of 325 patients were diagnosed by the Clinical Study Subgroup as affected with the disease. They were found from more than one thousand persons who were examined by the subgroup at the "Yusho" Outpatient Clinic of the University Hospital, or at the Visiting "Yusho" Clinic that was opened for those worrying about the disease in distant areas. The validity of the diagnosis was, without doubt, very high, because a single team of specialists diagnosed all of them following the established diagnostic criteria (Appendix 1. Table 1).

Examination of these 325 patients demonstrated very unique features of the distribution of the disease as follows:

a) They consisted of 158 males and 167 females. Both sexes had been equally affected.
b) As indicated by incidence rates calculated by sex and by age-class, all the age-classes had been affected, although older persons showed lower rates (Table 3.3).
c) They belonged to 112 households, the average number of patients per household being 2.9. A familial clustering was evident.
d) Excepting 4 patients (1.2% of the total) who stated, according to their memory, to have been affected with the present illness in December 1967, nearly all of the patients stated that they were affected between February and October in 1968. A marked temporal clustering was noted, with a distinct peak of occurrence in summer followed by its spontaneous sharp decline, as shown in Fig. 3.2. The occurrence of patients was definitely not sporadic.
e) A large number of patients were seen in large cities such as Fukuoka and Kitakyushu and in specific areas such as Tagawa (Table 3.4). The incidence

Table 3.3. Number of Patients and Incidence Rates by Sex and Age-class (Fukuoka Prefecture, as of January 20, 1969)

Age-class	Male		Female	
	No. of patients	Incidence rate[a]	No. of patients	Incidence rate[a]
0~9	37	11.4	27	8.6
10~19	38	8.9	28	6.6
20~29	28	9.1	36	10.3
30~39	30	9.6	39	11.9
40~49	11	5.4	23	9.3
50~59	9	5.4	11	7.2
60~69	4	3.5	3	2.4
70+	1	1.7	0	0.0
Total	158	8.3	167	8.1

[a]: per 100,000

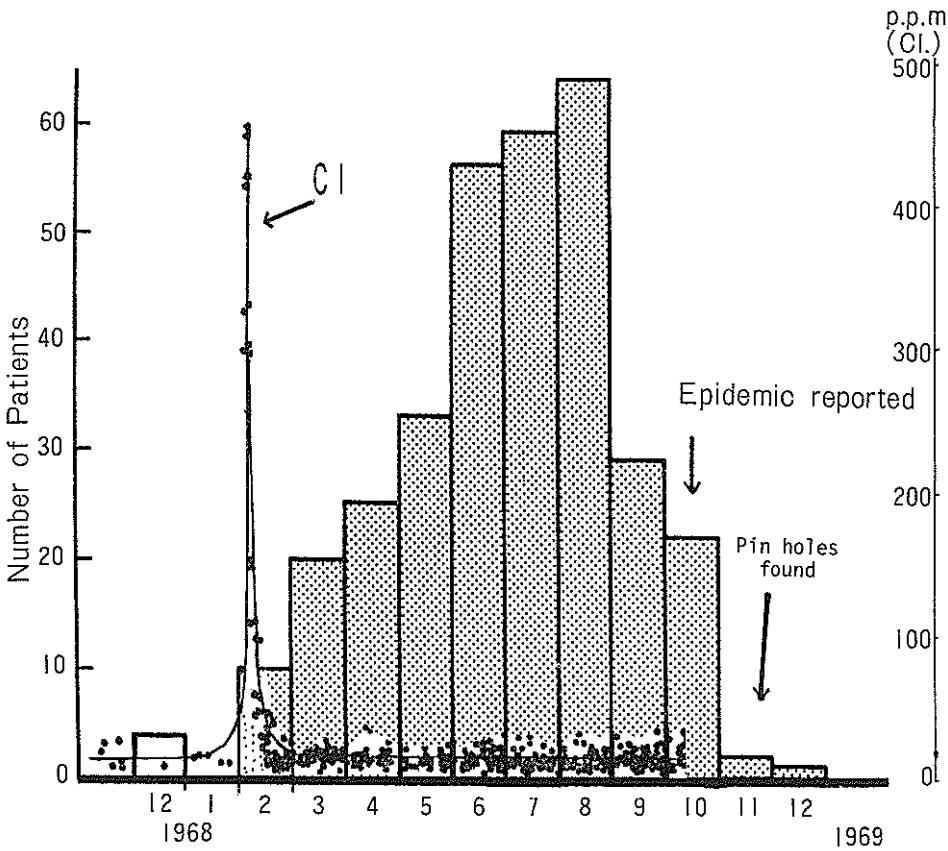

Fig. 3.2. Temporal Distribution of Patients and Chlorine in Bottled Kanemi Rice Oil (Kuratsune, M., 1989.)

Table 3.4. Number of Patients and Incidence Rates by Public Health Center (Fukuoka Prefecture, as of January 20, 1969)

Public health center	Socio-economic features	No. of patients	Incidence rate[a]
Fukuoka City	U	68	9.1
Kitakyushu City	U,I	113	10.8
Ohmuta City	U,I,C	14	7.2
Kurume	U	4	2.5
Nohgata	C	4	4.4
Iizuka	C	2	1.1
Tagawa	C	72	44.5
Miyata	C	1	2.1
Ookuma	C	2	4.8
Soeda	C	16	58.9
Kasuya	C	18	14.4
Onga	C	1	1.0
Munakata	A	4	6.6
Asakura	A	0	0.0
Chikushi	A	3	2.6
Itoshima	A	0	0.0
Mii	A	0	0.0
Mizuma	A	0	0.0
Yamato	A	3	2.1
Yame	A	0	0.0
Kuroki	A	0	0.0
Ukiha	A	0	0.0
Miyako	A	0	0.0
Chikujyo	A	0	0.0

A : Agricultural C : Coal mine
I : Industrial U : Urban
[a] : per 100,000

rate was extremely high in two specific areas, that is, Tagawa and Soeda, where coal mines used to flourish. However, such a high rate was not seen in any other coal mine areas. In agricultural areas, the disease was definitely rare.

All the above characteristics of the distribution of the patients suggested that both male and female patients, irrespective of age, must have been almost equally exposed to the causal agent or agents of this peculier disease probably at their home. A certain food poisoning was therefore suspected as the cause. Furthermore, the observed sharp temporal clustering of the patients forming a single huge peak of occurrence in summer clearly indicated that the exposure of the patients to the causal agent or agents could not be a light and sporadic one but a heavy and single

one.

3.3.3. Pursuit of the Rice Oil Used by the Patients

There were several commercial brands of rice oil available in Kyushu area at that time. Among them, only Kanemi rice oil had been strongly suspected as the cause of the disease, when the Epidemiologic Study Subgroup started its activities. It was therefore decided to thoroughly examine whether the patients had actually used any rice oil. The staff of local public health centers visited and interviewed all of the 325 patients and their inmates at their houses and asked them, using a questionnaire, of their state of health, their use of rice oil and other living conditions. Those who were known to have consumed any rice oil were further asked about the manufacturer of the oil, name of the brand, place and date of purchase, amount of the rice oil consumed, duration of the use of the oil and lot numbers stamped on the containers of the oil. Type of the containers was also asked, as there were two kinds of Kanemi rice oil available, namely, canned one (16.5 kg) and bottled one (1.65 kg).

Soon after we started our survey, we came to know that many patients with the disease had actually used a very specific Kanemi canned rice oil that was produced or shipped early February in 1968. An investigation by the Central Public Health Center, Fukuoka City, (Director: Dr. Hideo Imamura) revealed that 27 of the 31 family members of 8 employees of an electric power company who had jointly bought two cans of Kanemi rice oil from F company in Fukuoka City on February 8, 1968 and divided it among them, had been affected with the disease. Another group of families that had also jointly bought one can of the same rice oil from the same company on the same day were also found to be suffering, with 18 patients among their 27 family members. These three cans were confirmed to be a portion of 20 cans that had been shipped from Kanemi on February 6, by examining the purchase records of F company.

Based on the above fact, we requested Kanemi to provide us with copies of all the shipping records of rice oil (both canned ones and bottled ones) produced during the month of February 1968 and they complied with our request. Examining these records, nearly all the shipping channels of the rice oil produced during this specific period of time as well as the date and amount of shipping came to be known in detail. Thus, the rice oil used by the patients was pursued both by interviewing them and by examining the shipping records of Kanemi. It was revealed that the canned rice oil produced or shipped on February 5 or 6, 1968 had been sold to many persons in areas other than Fukuoka City and some of the consumers of this specifically dated oil were found to be affected with the disease. This oil had

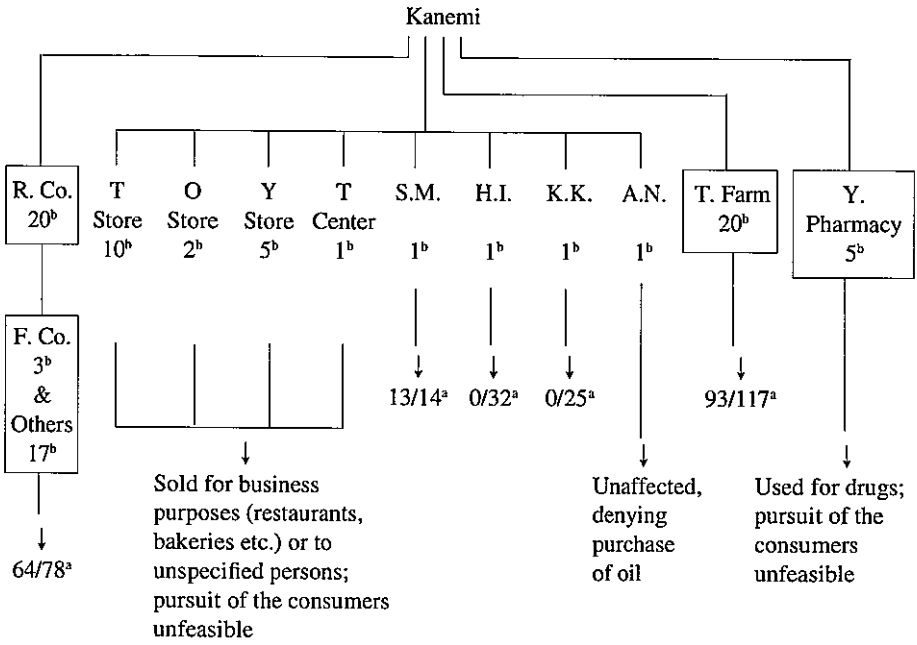

Fig. 3.3. Results of the Pursuit of the Canned Kanemi Rice Oil Shipped on February 5 or 6, 1968
[a] : Number of patients/Number of consumers of the oil.
[b] : Number of cans shipped.

also been bought by restaurants, bakeries and stores for business purposes and it was hardly possible to know whether any of their customers were affected. Fig. 3.3 gives an overview of these surveys, showing where and how much the specific canned rice oil was shipped to and how many of the consumers of the oil were affected.

It was disclosed thus that all of the 325 patients had used Kanemi rice oil either in canned form or in bottled form. It was further found that, regardless of where they lived, 166 (97.6%) of 170 patients who had used only canned Kanemi rice oil had used the very specific one, viz. the oil produced or shipped by the company on February 5 or 6, 1968, as confirmed by the lot numbers stamped on the cans of oil left at some patients' houses and by the shipping records provided by Kanemi. For the other 4 patients, their use of canned Kanemi rice oil was confirmed but the date of its production or shipping could not be determined (Fig. 3.4). An attack rate as high as 63.9% was calculated for those who had consumed the above specific canned rice oil.

The remaining 155 patients had used only bottled Kanemi rice oil for which the date of production or shipping could not be confirmed, because none of the old

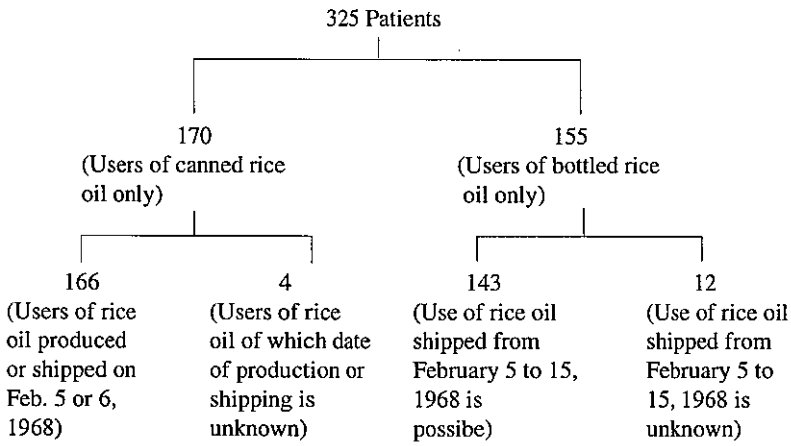

Fig. 3.4. Number of the Patients by Kind of the Kanemi Rice Oil Used

bottles that they had used were left. However, whether or not any bottled rice oil shipped by Kanemi between February 5 and 15, 1968 had reached the retail stores from which the patients used to buy their rice oil, could be investigated by examining the shipping records. It was certain that with 143 (92.3%) of these 155 patients the bottled Kanemi rice oil shipped during the above specific period of time had reached the stores where they were accustomed to buying their rice oil. For the remaining 12 patients, however, such possibility could not be confirmed (Fig. 3.4). It was quite surprising that the majority of the patients with this peculiar disease were closely associated with the consumption of such a highly specific Kanemi rice oil. The association would probably be a causal one.

Kanemi rice oil was a salad oil advertised as good for adult diseases. It was more expensive than other popular brands of salad oil produced and sold by major cooking oil manufacturers in the nation. Those who liked it often jointly bought the canned ones which were cheaper than the bottled ones and divided those among them. It was fortunate that their records of purchase and allotment had been kept well, which greatly served our purpose.

3.3.4. Risk of the Regular Users of Kanemi Rice Oil Other than the Specifically Dated One

It seemed crucially important to examine whether or not Kanemi rice oil produced or shipped at a different time from the period in question was safe. In an additional survey, we examined whether or not those who regularly used Kanemi rice oil but not the specific one were free of the disease. A group of 113 persons of 29 households living in an apartment complex had purchased canned Kanemi rice

oil as a unit from one dealer and divided it among themselves fairly regularly from December 1967 to September 1968, except for the period from January to April 1968 when no bulk purchase was made. Among them, there were 8 persons who had suffered from skin diseases from January 1967 to October 1968. The diseases were carefully explored by examining all of their medical records preserved at the hospitals and clinics which they had visited during the above period of time. No case of the present disease was found among them. It became clear, thus, that only the Kanemi rice oil produced or shipped during the specific period of time was toxic.

3.3.5. Case-control Studies

Although the above findings clearly indicated that the disease was caused by an intake of a very specific Kanemi rice oil, there still remained some possibility that certain other factors or agents might be involved as the primary or secondary cause. In order not to overlook such possibility, another type of epidemiologic investigations, that is, two case-control studies were undertaken in late October, 1968. All the health departments and public health centers in the prefecture fully cooperated with us in conducting the studies.

In one study, 121 patients and their randomly selected 121 healthy controls consisting of 53 male and 68 female unaffected persons, matched individually by age, sex, and place of residence to the patients, were asked 60 questions concerning their occupation, medical history, general health status, habits, custums, diet, pets, and other characteristics of their daily lives. These question items were selected by consulting clinicians, toxicologists, public health workers, and pharmaceutical scientists. As shown in Table 3.5, only one of the 60 personal factors examined, namely, habit of "eating deep-fried foods or *tempura* nearly everyday", was significantly more commonly seen among the patients than among the controls. This item, however, could not be considered to be the major causal factor, because those with such dietary habit composed only one fifth of the cases.

In another case-control study, 69 households with patients and 207 control households without such patients that were matched by place of residence with the patient households in a ratio of 3 control households to 1 patient household were interviewed and compared for use of fats and oils. As shown in Table 3.6, only "regular use of rice bran oil" was significantly much more commonly seen among the patient households than among the control households. Ninety-six percent of the patient households were found to have used rice bran oil (Kanemi rice oil), while only 31 percent of the control households had used the oil. Two patient households that either denied the use of "rice bran oil" or answered to be uncertain for such use at the initial interview were later found to have actually used Kanemi

Table 3.5. Results of a Case-control Study on Habits, Customs and Others

Questions asked	Case group %	Control group %
Allergic to fish	5.0	7.5
Allergic to aspirin	0.0	4.2
Allergic to other drugs	7.5	6.6
Bath facilities available at home	84.7	85.5
Bathing daily	73.0	70.6
Having a pet or pets at home	18.3[a]	36.5[a]
Living in a house with floor space smaller than 66 m^2	66.9	66.1
Handling agricultural chemicals	2.5	6.6
Taking cod liver oil	10.8	8.3
Taking vitamin pills	23.2	18.3
Taking other restorative drugs	9.1	7.5
Water supply available at home	81.3	74.7
Dining out occasionally	28.1	30.6
Taking same meals with family	88.8	89.6
Eating green vegetables daily	63.1	58.9
Drinking milk nearly everyday	49.0	39.0
Taking butter nearly everyday	22.4	24.9
Eating eggs nearly everyday	64.7	59.8
Eating deep-fried foods or *tempura* nearly everyday	22.4[a]	11.6[a]
Eating fried foods nearly everyday	21.6	29.1
Eating fish nearly everyday	21.6	29.1
Taking mayonnaise nearly everyday	10.8	10.8
Eating instant "*rahmen*" or Chinese noodle nearly everyday	10.8	10.0

[a]: $p < 0.05$

Table 3.6. Results of a Case-control Study on Fats and Oils Used at Home

Fat and oil	Case group		Control group	
	No. of households	%	No. of households	%
Butter	35	50.7	105	50.7
Margarine	44	63.8	127	61.4
Sesame oil	21	30.5	85	41.1
Rape-seed oil	10	14.5	77	37.2
Rice bran oil	66	95.7[a]	64	30.9[a]
Lard	12	17.4	38	18.4
Other oils	13	18.8[a]	117	56.5[a]

Case group : 69 households with patients.
Control group : 207 households without patients.
[a]: $p < 0.01$

rice oil through reinterviews. (They had misunderstood that "Kanemi rice oil" was not "rice bran oil".) Accordingly, all of the 69 households with patients were confirmed to have been regular users of Kanemi rice oil. These results clearly indicated that the use of the rice oil was closely associated with the present disease. The validity of such association, however, was not readily evaluated, because of the defect involved in our Diagnostic Criteria for "Yusho".

As mentioned, "the use of a specific brand of rice oil" had been designated as an important referential condition for the diagnosis of the "strange disease"(see Appendix 1. Table 1). Those who denied or answered to be uncertain for "the use of rice oil" would not have been diagnosed as affected with "Yusho". It may be a matter of course, therefore, that the proportion of households using some rice oil was much larger in the case group than in the control group. Similarly, it was reasonably expected that more users of Kanemi rice oil were seen in the case group than in the control group, as far as the present diagnostic criteria were applied. Therefore, the above results might be just an artifact and no one could be sure whether the use of the rice oil is truely associated with the disease. Neverthless, the present case-control studies were considered to be significant because they demonstrated that none of the numerous factors tested, other than "the use of rice bran oil" and "eating deep-fried foods or *tempura* nearly everyday", were associated with the disease at all. Such denial of the hypothetical factors other than the use of rice bran oil was, without doubt, very significant for our purpose.

In the above case-control studies, the early symptoms and signs experienced by the patients were also investigated. As shown in Table 3.7, acneiform skin eruptions, increased eye discharge, dark-brown nail pigmentation, pigmentation of the skin and swelling of the upper eyelids were the most common ones, while jaundice, spasms of the limbs and fever were experienced by rather few patients.

All the above epidemiologic findings were published in detail by Kuratsune et al., in 1969 and 1972.

3.3.6. Dose-response Relationship

To prove a causal relationship, demonstration of a dose-response relationship was needed. Although estimating the personal consumption of bottled Kanemi rice oil was hardly possible, a rough estimate of such consumption of the specific canned rice oil could be made for individual patients, disregarding their age, sex, amount of food intake, and possible loss of the oil during and after cooking. Eighty of the 146 users of the specific canned Kanemi rice oil in question were thought to have consumed, individually, less than 720 ml of the oil. For these 80 light users, the prevalence rate of the disease was 88 percent, while for those who were estimated to have used more than 720 ml, it was 100 percent (Table 3.8). It was also

Table 3.7. Frequency of the Early Subjective Symptoms and Signs in Yusho Patients[a]

Symptoms and signs	Percent	
	Males (n = 89)	Females (n = 100)
Dark-brown nail pigmentation	83.1	75.0
Distinctive hair follicles	64.0	56.0
Increased sweating at the palm	50.6	55.0
Acneiform skin eruptions	87.6	82.0
Itching	42.7	52.0
Pigmentation of the skin	75.3	72.0
Swelling of the limbs	20.2	41.0
Pigmented mucous membrane	56.2	47.0
Increased eye discharge	88.8	83.0
Hyperemia of the conjunctiva	70.8	71.0
Transient visual disturbance	56.2	55.0
Jaundice	11.2	11.0
Swelling of the upper eyelids	71.9	74.0
Feeling of weakness	58.4	52.0
Numbness of the limbs	32.6	39.0
Fever	16.9	19.0
Hearing difficulties	18.0	19.0
Spasms of the limbs	7.9	8.0
Headaches	30.3	39.0
Vomiting	23.6	28.0
Diarrhea	19.1	17.0

[a] : As of October 31, 1968.

Kuratsune, M. et al., 1969; Kuratsune, M. et al., 1972; Kuratsune,M., 1989.

Table 3.8. Relationship between the Amount of Kanemi Rice Oil Used by Patients and Clinical Severity

Amount of oil used	Non-affected		Light cases		Severe cases		Total	
	No.	%	No.	%	No.	%	No.	%
Less than 720 ml	10	12.0	39	49.0	31	39.0	80	100.0
720~1,440 ml	0	0.0	14	31.0	31	69.0	45	100.0
More than 1,440 ml	0	0.0	3	14.0	18	86.0	21	100.0

demonstrated that the prevalence rate of severe cases clearly increased with the amount of oil consumed. Thus, a dose-response relationship was evident. Since the clinical severity of the disease differs significantly by age, the above prevalence rates were standardized for age using the age composition of the whole 146 patients as standard, but the relationship seen hardly changed (Yoshimura, 1971).

3.3.7. Temporal Distribution of PCBs in Kanemi Rice Oil

To examine if only the Kanemi rice oil produced or shipped in the period in question is contaminated with KC-400, the Chemical Study Subgroup analyzed 109 samples of the bottled rice oil which had been shipped between October 1967 and October 1968. A gaschromatographic analysis revealed that a significant contamination of the bottled oil was limited only to those produced or shipped from February 7 to 10, 1968 (Tsukamoto et al.,1969). No analysis could be made of the bottled rice oil produced or shipped on February 5 and 6 because of lack of samples.

In an additional analysis, 479 samples of the bottled rice oil randomly selected by the Epidemiologic Study Subgroup from many oil bottles which had been seized by health authorities were examined for chlorine content by the X-ray fluorescence method using a count meter. Such an instrument was not available at Kyushu University then, but one was running in a good condition at the Research Laboratory of Kyushu Electric Power Co., Inc. Complying with Professor Katsuki's request, the company kindly allowed us to use the instrument for our purpose. Under supervision of Professor Keihei Ueno, Faculty of Engineering, Kyushu University, who was a member of the Chemical Study Subgroup and with technical assistance of Dr. Kenjiro Yanagase, chief investigator at the Research Laboratory, analysis was made with due attention to the possible contamination of the sample materials with sodium chloride, revealing again that only the samples produced or shipped from February 7 to 10 contained a large amount of chlorine (maximum 462 ppm) as shown in Fig. 3.2 (Kuratsune, 1989). The results of these chemical studies completely coincided with those from the epidemiologic investigations.

3.4. Conclusions and Aftermath

MASANORI KURATSUNE

3.4.1. Conclusions

All the above findings obtained by clinical, chemical and epidemiological investigations unanimously and unequivocally proved that the "strange disease" was a food poisoning caused by the ingestion of a specifically dated Kanemi rice oil contaminated with KC-400, a commercial mixture of PCBs. Luckily enough, the name "Yusho" overhastily given to the "strange disease" as early as at the beginning of the present investigation was proved to be right. The disease was anew named "Yusho (Chlorobiphenyls Poisoning)" (Katsuki, 1969).

After the successful clarification of the cause of the disease, our fresh efforts were begun to develop the best cure for the disease, reorganizing the "Study Group for YUSHO" to the "Study Group for the Therapy of Chlorobiphenyls Poisoning" which was headed by Professor Higuchi, in April 1969 (Higuchi, 1971) (see Appendix 3).

3.4.2. Acnegenicity of KC-400 in Man

As to the cause of Yusho, everything appeared to have become clear but there still remained a few questions to be answered. One of them was about the acnegenicity of KC-400 in man. KC-400 had been known to be a mixture of pure PCB congeners, containing very little contaminants. Our literal investigation failed to find any definite evidence for the acnegenicity of such pure PCBs in man or in animals, although some authors had reported on acne seen among workers who inhaled the vapor of Aroclor (a U.S. brand of PCB mixture) (Meigs et al., 1954). Feeding experiments either of the KC-400 obtained from Kanemi or of the rice oil used by patients were therefore undertaken using conventional mice, nude mice or squirrel monkeys but the skin lesions characteristic of the present disease were poorly reproduced (Inagami et al.,1969; Nishizumi et al.,1969). These facts made us nervous about the pathogenicity of KC-400 in man. It was fortunate, however, that Dr. Ichiro Hara, chief of the Division of Occupational Hygiene, Osaka Prefectural Institute of Public Health, was kind enough to inform us that he had seen acneiform eruptions among workers exposed to Kanechlors in a factory producing electric condensers. This information well assured us of the human acnegenicity of KC-400. We asked him to publish his observation and he soon complied (Hara, 1969, 1985).

3.4.3. A Question about the Possible Contaminants of KC-400

A few years later, another question was raised from abroad in regard to the pertinence of our conclusion that Yusho is a poisoning by PCBs. In 1971, Dr. R. W. Risebrough, Institute of Marine Resources, University of California, Berkeley wrote to M. Kuratsune, inquiring whether Yusho was caused by PCBs alone or together with PCDFs or PCDDs which might be contained in KC-400. He referred to the extreme toxicity of these possible contaminants, citing the works by Schulz (1957), Kimmig & Schulz (1957) and Vos et al.(1970).

The letter was forwarded to Professor Kiyoshi Tanaka, then chief of the Study Group for the Therapy of "Yusho" (Kyushu University) for his information. The reaction of the group appeared to be rather cool, however. Since an application of pure crystalline of 3,4,3′,4′-tetrachlorobiphenyl to the ear of rabbits caused dermal lesions histologically identical to those produced by applying KC-400, the question that the possible contaminants such as PCDFs or PCDDs in KC-400 might be involved in the pathogenesis of Yusho seemed to be deniable (Komatsu and Kikuchi, 1972; Tanaka, 1972).

Realizing the gravity of the question, however, Kuratsune and his associates, Drs. Junya Nagayama and Yoshito Masuda, reanalyzed the toxic rice oil and KC-400 for these possible contaminants which would be, if present, negligibly small in amount in view of the reputable high purity of KC-400. Contrary to our expectation, a significant amount of PCDFs was shown to be contained in the toxic rice oil as well as in the tissues of patients with Yusho (Nagayama, et al., 1975, 1976, and 1977). Subsequent investigations even demonstrated that the most important causal agents for Yusho were PCDFs but not PCBs (see Chapters 4 and 6). Thus, Dr. Risebrough's inquiry was revealed to have been quite to the point.

3.4.4. Yusho in Nagasaki Prefecture

Soon after the cause of the epidemic of the "strange disease" in Fukuoka Prefecture was clarified, the cause of a similar epidemic which had been prevailing in Nagasaki Prefecture was also disclosed to be the ingestion of a certain batch of Kanemi rice oil. According to the information provided by Dr. Kikuo Ohtsuka, then chief of the Section of Environmental Hygiene, Department of Public Health, Nagasaki Prefecture, an extensive epidemiologic survey was conducted under the united efforts of all the staff of the department on the dietary habits and other living conditions of the affected persons (Ohtsuka, 1969, 1995). The survey revealed that most of the more than 500 patients affected by the disease in the prefecture were residents of certain remote areas such as Tamanoura and Naru Towns on the Goto Islands, 100 km west of Nagasaki City. Another surprising fact was found that as

many as 100 cans of Kanemi rice oil shipped by the company on February 9 and 10, 1968 had reached these specific remote areas. Unfortunately, no analysis of the oil for PCBs was made, because no portion of the rice oil used had been left when the survey was made. However, it can be reasonably expected that the oil must have been significantly contaminated with PCBs as described in Section 3.3.7 and shown in Fig. 3.2.

Incidentally, use of any brand of rice oil for cooking had been highly recommended for better health at the health centers throughout the prefecture before the present incident occurred and the patients in the above two towns are known to have for the first time bought the above specifically dated rice oil, giving credit to the official recommendation. In order to relieve these unfortunate victims, the Study Group for Yusho in Nagasaki and the Department of Public Health, Nagasaki Prefecture, have cooperated in research as well as in providing them with proper health care over the past years (see Appendix 3).

3.4.5. Collaboration with the Researchers and Others Involved in Yucheng

In March 1979, the incident of Yucheng which was so similar to Yusho in many aspects occurred in Taiwan, Republic of China. Dr. Shu-Tao Hsu, director of the Bureau of Communicable Disease Control, Department of Health, Executive Yuan, Republic of China, proved in October 1979, with the cooperation of Professor Shun-ichi Yamamoto and Associate Professor Gen Ohi, the Department of Hygiene, Faculty of Medicine, Tokyo University, that the incident was due to the ingestion of a commercial brand of rice oil contaminated wth PCBs (Hsu et al., 1985). At the end of November 1979, Dr. Shu-Tao Hsu visited us to explain the incident and to know about Yusho. To comply with his request, Professor Yoshito Masuda, Daiichi College of Pharmaceutical Sciences, assisted him by analyzing for PCBs various materials such as the blood of patients with Yucheng, the rice oil used by them, the soil collected from the plant of the rice oil's maker and the blood of workers at the plant, demonstrating abnormally high levels of PCBs in all of these materials. Since then, our close collaboration with the researchers, physicians and health administrators involved in Yucheng has been maintained.

As an example, Professor Masuda was invited by the government of Republic of China to train chemists there for the analysis of PCBs soon after the cause of Yucheng was disclosed. Dr. Motoo Imamura was also invited to apply his fasting cure to the patients in 1981 and 1982 (see Chapter 9.3). In order to exchange information, several researchers on Yucheng were invited to the "Japan-U.S.A. Joint Seminar on Toxicity of Chlorinated Biphenyls, Dibenzofurans, Dibenzodioxins and Related Compounds" which was held by Professor Norton Nelson, New York University, and myself as coordinators, in Fukuoka City in April, 1983

(Japan-U.S.A. Joint Seminar, 1985). Incidentally, the late Professor Nelson was so deeply concerned about Yusho that he came to Fukuoka several times to visit some Yusho patients at home and to encourage us by giving invaluable advices. More recently, in close cooperation with Professor Chen-Chin Hsu, Superintendent, National Cheng Kung University Hospital and other researchers, clinical trials were made on Yucheng patients in order to examine the possible therapeutic effect of the oral administration of rice bran fiber and cholestylamine, which had been initially developed by Dr. Takao Iida and his associates, Fukuoka Institute of Health and Environmental Sciences. To our great pleasure, these extremely difficult trials have been found to be quite successful (see Chapter 9.2). Without doubt, close mutual cooperation is vitally important to learn as much as possible from these two truly miserable but so valuable incidents of human disaster and to mitigate the tortures of the victims.

3.4.6. The Mechanism of Contamination of the Rice Oil

There are two opposing theories in regard to the mechanism of the contamination of the rice oil with KC-400, that is, the "Pinhole Theory" and the"Welding Error Theory".

a) The "Pinhole Theory"

On November 6, 1968, soon after the discovery of the contamination by the Study Group, the Mayor of Kitakyushu City where Kanemi was located requested Professor Hisashi Shinohara and Associate Professor Tsuyoshi Munakata, Faculty of Engineering, and Associate Professors Yoshihiro Kohda and Masao Sanbuichi, Faculty of Agriculture, Kyushu University, to investigate the rice oil plant of Kanemi in order to clarify the mechanism of the contamination. Since KC-400 had been used as a heat transfer agent for heating the processed rice oil to over 200°C under a reduced pressure ca. 3 mm Hg in six deodorization tanks at the final stage of the manufacturing process of the oil (Fig. 3.1), they closely inspected the tanks. Tank No.6 was thought particularly important because this old tank had been repaired at the end of 1967 and its reuse had begun at the beginning of February in 1968, just the time when the contaminated rice oil was known to have been produced or shipped according to the epidemiologic surveys. By introducing a compressed air at 5 kg/cm^2 into the coiled stainless steel pipe in the tank, through which heated Kanechlor had been circulated, they found 3 pinholes in the pipe on November 16, 1968 (see Fig. 3.5 for the construction of the tank). The largest hole was as large as 2 mm × 7 mm (Fukuoka High Court, 1986).

On December 26, 1968, Professors Shinohara and Munakata were commissioned to reexamine the tank and to give an expert opinion on the mechanism of the

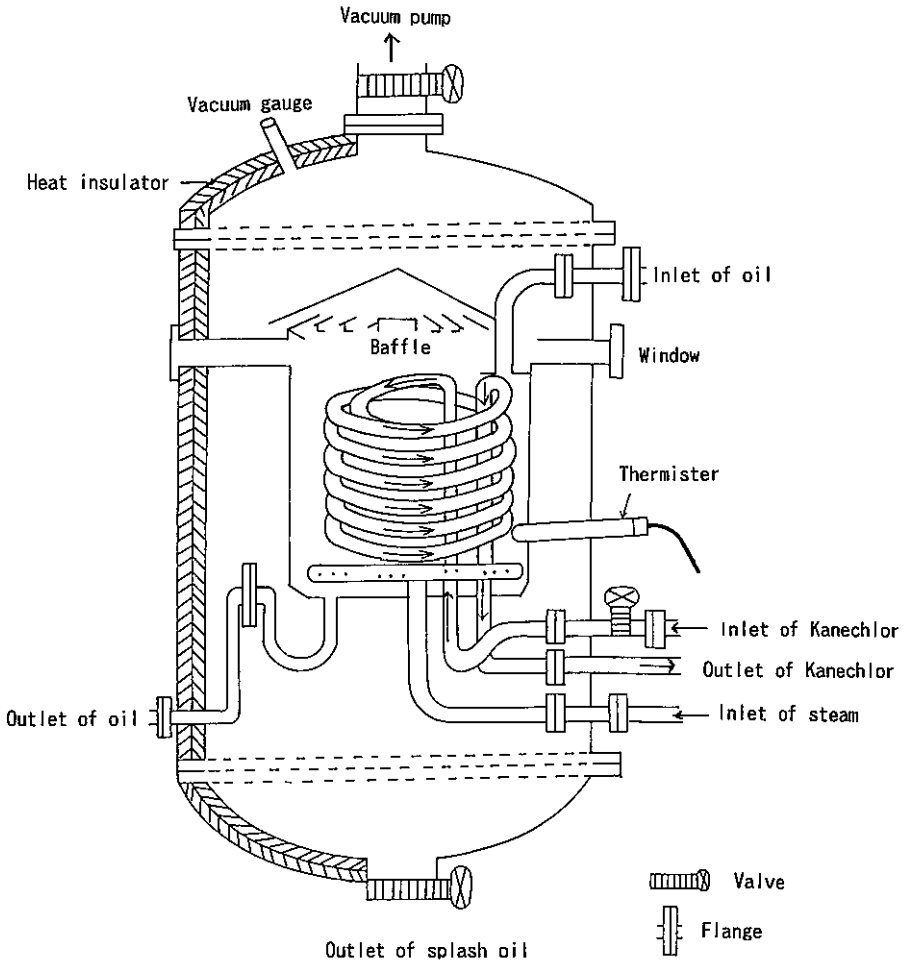

Fig. 3.5. The Structure of the Deodorization Tank for Rice Oil Production (Prepared from the Materials Provided by Kanegafuchi)

contamination by the chief of the Kokura Police Station in Kitakyushu City. They reconfirmed the three pinholes and their associate, Associate Professor Youichi Tokunaga, Faculty of Engineering, Kyushu University, also found many small perforating holes filled with tarry materials by examining the pipe near the above 3 holes by X-ray photography and microscopy. Scrutinizing the possibility of spontaneous opening of holes in the pipe as well as closing of such holes, by repeating on-the-spot experiments and metallographical and metallurgical examinations, and by analyzing the plugs of the holes, they very prudently reached a conclusion that neither of the above two possibilities were small and that the amount of Kanechlor contained in the toxic rice oil could be explained by a possible leak

through the holes in the pipe of the tank No. 6. They also admitted that no one could be sure whether such holes actually existed at the time in question, about 10 months before. The holes were thought to have been formed by corrosion of the stainless steel pipe due to acids generated from heated KC-400. This conclusion was accepted as the most reasonable mechanism of the contamination of the rice oil by the Kokura Branch Office of the Fukuoka District Public Prosecutors Office, and Kanemi, thereby, was prosecuted by the Office. The conlusion also gave rise to a popular "Pinhole Theory". The theory was later adopted by the courts for the civil damage suits filed by several groups of victims of Yusho. Quite a few people, however, were opposed to it, asserting that serious weak points were involved in it (Jinriki, 1980; Kato, 1979 and 1985; Kuratsune, 1985; Fukuoka High Court, 1986). Notable three of the weak points are as follows:

1) There is no evidence that the pinholes found in November 1968 actually existed when the Kanechlor leaked for a very short period of time at the beginning of February 1968, as admitted by Professor Shinohara and his associates.

2) According to the Fukuoka High Court (1986), the estimated total amount of Kanechlor that leaked during the short period of time in February 1968 was about 280 kg. The holes, if present, must have been very large, otherwise such a large and quick leak would not have occurred. The probability of quick spontaneous formation of such a big hole or holes followed by its or their spontaneous, simultaneous, quick and complete closing must be very small. The probability must be even smaller, if we consider that the acids which corroded the pipe were left to exert their corrosive action continuously.

3) If any leak of KC-400 had occurred through small pin-holes, the contamination of the rice oil would have been slight and the outbreak of poisoning would have been small and sporadic, just contrary to the epidemiologic findings as described in Section 3.3.2.

b) The "Welding Error Theory"

Accepting the "Pinhole Theory", several civil decisions found Kanegafuchi guilty of negligence and ordered the company to pay a huge amount of damages to the plaintiffs (Appendix 7). In October 1979, Kanegafuchi began to assert at a civil trial that the contamination of the rice oil is not through the pinholes but due to a welding error. Taking into account both an allegation made by Ms. Yachiyo Kato, an elder sister of the president of Kanemi who had casted grave doubt on the "Pinhole Theory" (Kato, 1979) and a confession made by a former chief of the deodorization plant of Kanemi, Kanegafuchi insisted that a hole was carelessly formed by an employee of Kanemi in the coil of stainless steel pipe of the deodor-

ization tank No. 1 when he was welding the tank in order to install a thermister in it; a large amount of Kanechlor leaked through the hole, contaminating the processed rice oil; noticing the contamination but expecting possible removal of the Kanechlor that leaked, Kanemi subjected the contaminated oil to deodorization, and shipped it without carefully examining its safety. This mechanism of contamination was called the "Welding Error Theory" and accepted by the Fukuoka High Court that denied the "Pinhole Theory". The Supreme Court thus recommended the parties to enter into a compromise and they finally agreed to it (see Appendix 7). The fierce dispute that had been made on the mechanism of the contamination between the plaintiffs and the defendants then rapidly and completely ebbed away, indicating that the "Welding Error Theory" was correct.

3.4.7. Grief and Agony of the Patients

Although the cause of Yusho was quite quickly clarified, the disease was soon found to be extremely hard to cure. Some clinicians optimistically stated soon after the outbreak of the epidemic that a considerable recovery would be expected within a couple of years. However, the opposite was the case in spite of their devoted efforts to relieve the patients from the tortures (see Chapter 7). Furthermore, to our great regret, there were a few clinicians who were distrusted by some patients (Kamino, 1972). According to the patients, those clinicians were not kind enough to care for these physically, mentally, socially and yet entirely unreasonably injured victims with deep sympathy but rather cooly treated the victims with a mere scientific interest. In addition, in view of the fact that the patients had clustered in certain households involving even children as already described, the disease should have been suspected to be a food poisoning, but none of the physicians practising in the prefecture reported the disease as a possible food poisoning to public health centers, despite such requirement made by the Food Sanitation Law. If they had reported the occurrence of the "strange disease" at the early stage of the epidemic, the disaster could have been considerably diminished.

Owing to the above facts, some of the patients began to distrust not only such clinicians but also the study group itself. They did not want to become a subject for "human experiments" by cooperating with the group. Their grief, agony and anger were also intensified by thoughtless attitudes to them of some people who did not well understand them. Mr. Ryuzou Kamino, one of the patients,wrote at the beginning of a paragraph entitled "A Struggle against the Disdain of Man" in a book, that "Please understand what really tortures us is not PCBs but man" (Kamino, 1972). This heart-rending cry teaches us that nobody but the victims themselves could understand their real grief.

Thus, it is unfortunately true that the atmosphere around the patients and the

study group was not a very cooperative one at least for a while. Even so, the members of the study group continued their devoted efforts, to the best of their ability, in order to mitigate the suffering of the patients. Gratefully enough, some of the patients have been so kind as to encourage the study group by subjecting themselves willingly to "human experiments" whenever they were asked by the group to do so (see Chapters 9.2 and 9.3). Without their hearty self-sacrifice, our devotion would not have lasted for years.

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