

- *Interact. Contaminated PCB from rice oil*
- 0 - *Rice incultation*
- 0 - *2000 to 3000 PPM*
- 5 - *Known the dose ratio to body weight*
- *Est. - 2 grams each - min. 0.5 gram*

Scientific a popular publication

Environmental Health Perspectives

any budget obsolescence

original study a rely on work of others

Relevance

Even contaminants in the oil?

Epidemiologic Study on Yusho, a Poisoning Caused by Ingestion of Rice Oil Contaminated with a Commercial Brand of Polychlorinated Biphenyls*

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In October, 1968, an epidemic of a peculiar skin disease similar to chloracne was reported in Fukuoka-Ken (Fukuoka prefecture), Japan. The epidemic was later proved to have spread not only over Fukuoka-Ken but also over 20 other prefectures in the western part of Japan (Fig. 1). It produced 1,057 patients according to the latest tabulation (August, 1971) by the Ministry of Welfare.

Soon after the epidemic was announced, a study group was organized by the staff of the faculties of medicine, pharmaceutical sciences, agriculture, and engineering of the Kyushu University and by the staff of the local health departments, to clarify the cause of the epidemic and to effectuate its control (1). We participated in the study group and conducted, as members of its epidemiologic study subgroup, an extensive epidemiologic investigation following the basic methodology of epidemiology (2). Fortunately, the cause of the epidemic was soon demonstrated to be the ingestion of a brand of rice oil contaminated with a commercial brand of polychlorinated biphenyls, and the disease was called "Yusho", namely oil disease.

Although our observations and experiences are confined to the Yusho patients seen in Fukuoka-Ken, we believe that reporting of them will help many people in the world who are deeply con-

cerned about the chronic deleterious effects of PCBs. The outline of our findings will, therefore, be presented, referring in addition to some other important observations reported by the clinical and chemical study subgroups of the Yusho study group and to those collected from other sources.

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Clinical Symptoms

The most common initial symptoms experi-

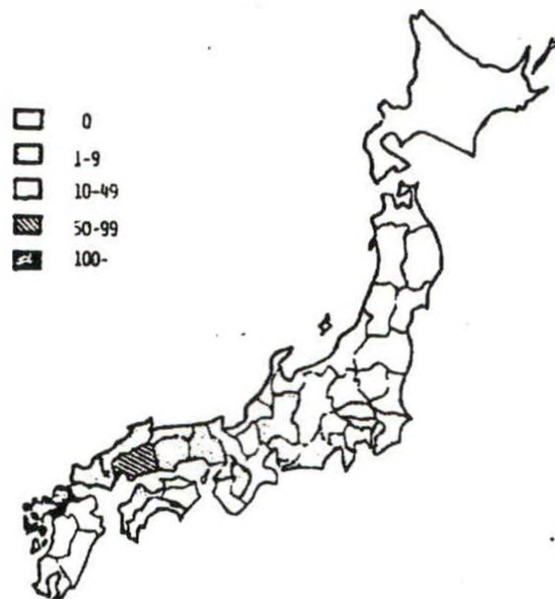


FIGURE 1. Number of patients with Yusho by prefecture.

* Prepared by Department of Public Health, Faculty of Medicine, Kyushu University, Fukuoka, Japan.

Table 1. Initial symptoms Goto et al.

Initial symptoms	Patients	
	No.	%
Swelling of upper eyelids, increased eye discharge	52	38.3
Acne-form eruption, follicular accentuation	45	33.1
Edematous swelling of limbs	9	6.6
Languishment	4	2.9
Disturbances in digestive canal	4	2.9
Numbness and other neurological signs	9	6.6
Pigmentation of skin	13	9.6
Total	136	100.0

enced by 136 patients with Yusho were increased eye discharge and swelling of upper eyelids (38.3%), followed by acne-form eruption and follicular accentuation (33.1%), and pigmentation of the skin (9.6%) (3) (Table 1). With others which appeared later, the subjective symptoms of Yusho as stated by 189 patients diagnosed up to October 31, 1968, are summarized in Table 2. Dark brown pigmentation of nails and skin, follicular accentuation, acne-form eruption, increased eye discharge, increased sweating at palms, and feeling of weakness were the most notable symptoms (2).

Descriptive Epidemiologic Studies

First, 325 patients seen in Fukuoka-Ken from October, 1968, to January, 1969, were analyzed in order to know their distribution characteristics. One of the most important characteristics readily noted was a distinct familiar aggregation. The 325 patients belonged to 112 families. As shown in Fig. 2 and Table 3, 99 percent of these patients were affected during 1968, while the remaining stated that they became ill in December, 1967. Fifty-five percent of the patients were concentrated in the 3 months from June to August, and no significant difference was noted between sexes in monthly distribution (Table 3). For geographical distribution of the patients, crude incidence rates of Yusho were calculated for 3 large cities and for the jurisdictional areas of the 22 local health departments of Fukuoka-Ken. Excepting 10 health departments where no cases of Yusho

were reported, the rates varied considerably from 1.0 to 58.9 per 100,000. Examination of such geographical distribution failed to indicate any common socioeconomic or environmental factor which might be associated with the disease. The 325 patients consisted of 158 males and 167 females, indicating that both sexes were equally affected. More than 90 percent of them were younger than 50 years (Table 4). Age- and sex-specific incidence rates again indicated no significant sex difference but lower risks for both males and females in the age group over 60 years (Table 5).

Analytical Epidemiologic Studies

When our study started, a commercial brand of rice oil produced by K company (abbreviated as K rice oil) in Kitakyushu-Shi (Kitakyushu city), Fukuoka-Ken, had vaguely been suspected as a possible cause of the disease, because most patients with Yusho seemed to have used it.

Table 2. Percent distribution of symptoms of Yusho reported by 189 patients examined before October 31, 1968.

Symptoms	Males (N=72)	Females (N=117)
Dark brown pigmentation of nails	83.1	73.9
Distinctive hair follicles	81.0	56.0
Increased sweating at palms	50.6	53.9
Acnelike skin eruptions	87.6	73.0
Red plaques on limbs	20.2	16.0
Itching	42.7	52.0
Pigmentation of skin	73.1	77.0
Swelling of limbs	20.2	41.0
Stiffened soles in feet and palms of hands	24.7	29.0
Pigmented mucous membrane	56.3	47.0
Increased eye discharge	84.4	63.0
Hyperemia of conjunctiva	70.4	71.9
Transient visual disturbance	56.3	53.9
Jaundice	31.2	11.0
Swelling of upper eyelids	71.9	74.0
Feeling of weakness	54.4	53.0
Numbness in limbs	37.6	29.0
Fever	16.9	19.0
Hearing difficulties	14.0	19.0
Spasm of limbs	7.9	9.0
Headache	20.2	29.0
Vomiting	23.6	13.0
Diarrhea	19.1	17.0

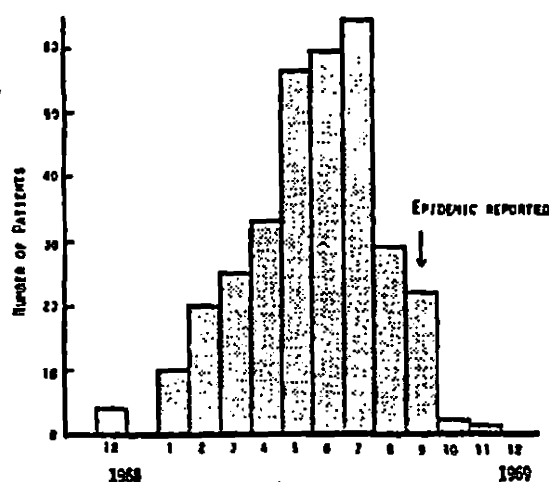


FIGURE 2. Distribution of patients by sex and month when symptoms appeared.

Therefore, a thorough investigation was undertaken to determine whether the patients had actually taken such special brand of oil before being affected. This was achieved by examining lot numbers appearing on the remaining containers of the oil used by some of the patients, shipping records of K company, and purchase and sale records at wholesale oil dealers' offices and at retail stores. It was soon disclosed that

all the patients had used K rice oil, either canned (16.5 kg) or bottled (1.65 kg). Furthermore, an astonishing fact became evident: No matter where they lived, 166 of 170 patients who used only the canned K rice oil had used a very specific oil, produced or shipped by the company on February 5 and 6, 1968 (Table 6). For those who used bottled K rice oil, date of production or shipment could not be confirmed, because they had no old bottles at home. Examination of all available records concerning shipping, sale, and purchase at K company, wholesale dealers and retail stores, however, clearly indicated a possibility that 143 of 155 patients who used bottled K rice oil only had used a very specific rice oil produced or shipped from February 5 to 15, 1968. This was because such oil had been shipped to and had reached the retail stores from which they had purchased their oil (Table 6). Thus, nearly all of the patients had had a very peculiar common experience of use or possible use of a rice oil produced or shipped by one company in a specific period of time. An attack rate as high as 63.9 percent was noted for those who consumed the specific canned oil.

In an additional survey, we examined whether those who regularly used K rice oil, but did not use the specific K rice oil produced or shipped

Table 3. Distribution of patients with yusho diagnosed by January 20, 1969, by sex and month when symptoms appeared.

Month	Males		Females		Total	
	Number	Percent	Number	Percent	Number	Percent
Before 1968	2	1.3	2	1.2	4	1.2
1968						
January	0	0.0	0	0.0	0	0.0
February	4	2.5	6	3.6	10	3.1
March	8	5.1	12	7.2	20	6.2
April	15	9.3	10	6.0	25	7.7
May	18	11.4	15	9.0	33	10.2
June	23	14.6	33	19.8	56	17.2
July	27	17.1	32	19.2	59	18.1
August	34	21.5	30	18.0	64	19.7
September	17	10.8	12	7.2	29	8.9
October	8	5.1	14	8.4	22	6.8
November	1	0.6	1	0.6	2	0.6
December	1	0.6	0	0.0	1	0.3
Total	158	100.0	167	100.0	325	100.0

Table 4. Distribution of 325 patients with yusho diagnosed by January 20, 1969, by sex and age group.

Age group (years)	Males		Females		Total	
	Number	Percent	Number	Percent	Number	Percent
0-9	37	23.4	27	16.2	64	19.7
10-19	38	24.1	29	16.8	66	20.3
20-29	28	17.7	26	21.6	64	19.7
30-39	30	19.0	39	23.4	69	21.2
40-49	11	7.0	23	13.8	34	10.5
50-59	9	5.7	11	6.6	20	6.2
60-69	4	2.5	3	1.8	7	2.2
70-79	1	0.5	0	0.0	1	0.3
Total	158	100.0	167	100.0	325	100.0

in the period in question, were free of the disease or not. A group of 113 persons of 29 households living in an apartment house had purchased canned K 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 purchases were made. Their disease experience in 1968 was carefully explored through investigation of their medical records at hospitals and doctors' offices. No case of Yusho was found among them.

All these results suggested that Yusho was caused by use of the K rice oil that was produced or shipped from K company on February 5 and 6, 1968, or soon thereafter. Nevertheless, some other factors or agents might have been the primary or secondary cause of the epidemic. Therefore two case-control studies were done. In one, the per-

sonal backgrounds of the patients and matched controls were compared. In the other, the use of oil and fats in the households of the patients and the controls were compared.

121 patients and their 121 healthy controls, (53 males and 68 females) matched by age, sex, and place of residence to each of the patients, were selected and asked 60 questions concerning their occupations, medical background, general health status, habits, customs, diet, pets, and other characteristics of their lives. As shown in Table 7, only one of the 60 personal factors examined, namely habit of "eating fried food or tempura nearly every day", was significantly more commonly seen among the patients than among the controls.

In the latter case-control study, 69 households with Yusho patients were matched by place of residence with 207 control households without

Table 5. Age-specific incidence rates for Yusho, by sex of patients.

Age group (years)	Incidence rates per 100,000	
	Males	Females
0-9	11.4	8.6
10-19	8.9	6.6
20-29	9.1	10.3
30-39	9.6	11.9
40-49	6.4	9.3
50-59	5.4	7.2
60-69	3.5	2.4
70 and over	1.7	0.0
Total	8.3	8.1

Table 6. Rice oil used by Yusho patients.

No. patients	Specifications of oil used	
	Type	Date of production or shipment
166 (51.1)	Canned	February 5 and 6, 1968
4 (1.2)	Canned	Unknown
143 (44.0)	Bottled	Unknown, but use of oil shipped from February 5 to 15, 1968, is very probable,
12 (3.7)	Bottled	Unknown
325 (100.0)		

Table 7. Results of case-control study.

Items investigated	Cases %	Controls %
Allergic to fish	5.0	7.5
Allergic to aspirin	0.0	4.2
Allergic to other drugs	7.5	6.6
Having bath facilities at home	84.7	85.5
Taking bath everyday	73.0	70.6
Having pets at home	18.3*	36.5*
Living in house smaller than 66 m ² floor space	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
Dining the same meals with families	88.8	89.6
Eat green vegetables daily	63.1	58.9
Drink milk nearly everyday	49.0	39.0
Take butter nearly everyday	22.4	24.9
Eat eggs nearly everyday	64.7	59.8
Eat fried foods or tempura nearly everyday	22.4*	11.6*
Eat foods prepared with oil nearly everyday	21.6	29.1
Eat fish nearly everyday	21.6	29.1
Take mayonnaise nearly everyday	10.8	10.8
Eat instant "rahmen" or chinese noodle nearly everyday	10.8	10.0

* $p < 0.05$.

such patients. A distinct difference was noted between the two groups only for regular use of rice-bran oil, namely 96 percent of the patients' households affirmed it while only 31 percent of the control households did (Table 8). Thus, the case-control studies clearly indicated that none of the factors tested except use of K rice oil could account for the disease.

Dose-Response Relationship

To prove a causal relationship, a definite dose-response relationship is needed. A rough estimate of the quantity of the specific K rice oil consumed by each patient and his family members was made disregarding their age, sex, amount of food intake, and possible loss of oil during and after cooking (4). Eighty of the 146 users of the specific canned

K rice oil in question were believed to have consumed, individually, less than 720 ml. For these 80 light users, the attack rate of Yusho was 88 percent, while for those who were estimated to have used more than 720 ml, it was 100 percent (Table 9). It was also demonstrated that the proportion of severe cases of Yusho clearly increased with the amount of oil consumed. While the clinical severity of the disease was not found to differ significantly between the sexes, it did differ considerably according to age, as shown in Table 10 and Fig. 3. The proportion of severe cases among those aged 13 to 29 was significantly larger than that of other age-classes. Therefore, each of the three groups of users, with different levels of oil intake, was standardized for age using the age composition of the whole 146 users as standard. The figures, however, hardly changed from those shown in Table 9. Thus, a clear dose-response relationship could be demonstrated, even though the estimates of the dose were inaccurate (4).

Toxic Agent

In view of all these epidemiologic observations, we concluded that the K rice oil of specific production or shipments had caused Yusho. Now, why was the oil toxic? The chemical study subgroup (chief: Prof. H. Tsukamoto, Faculty of Pharmaceutical Sciences, Kyushu University) demonstrated that the canned K rice oil produced or shipped on February 5, 1968, and used by some of the patients contained about 2,000 to

Table 8. Results of case-control study on oils used.

Fat or oil	Cases		Controls	
	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	64	30.9
Lard	12	17.4	38	18.4
Other oils	13	18.8	117	56.5

Cases: 69 patient households.

Controls: 207 non-patient households.

Wink of
ethics

3,000 ppm of Kanechlor 400, (Kanegafuchi Chemical Industrial Co. Ltd.) a brand of polychlorinated biphenyls (chlorine content: 48%) (5). In this discovery, Prof. K. Inagami of the Department of Food Technology, Faculty of Agriculture, Kyushu University, and his associates made most admirable contributions as members of the chemical study subgroup. The study subgroup also demonstrated that the oil was not contaminated with toxic agents such as Cu, Ni, Zn, Co, As, Hg and Pentachlorophenol. Furthermore, it found that most of the components of Kanechlor 400, particularly those corresponding to the peaks of higher retention times in the gas chromatograms, were retained in the sebum, subcutaneous fat, mesenterium, mesenteriolum, extraperitoneal adipose tissue, appendix vermiformis, heart, sternal marrow, small intestine, trachea, and other organs of patients, and can be transported into the fetus through the placenta (5,6,7). To examine whether only the K rice oil produced or shipped in the period in question was contaminated with Kanechlor, the

chemical study subgroup analyzed 109 samples of the bottled rice oil which had been shipped between October, 1967, and October, 1968. Gas chromatographic analysis revealed that a significant contamination of the bottled oil was limited only to those produced or shipped between February 7 to 10, 1968 (5). No analysis could be made of the bottled K rice oil produced or shipped on February 5 and 6 because of the lack of samples. Similarly, 479 random samples of bottled K rice oil were analyzed for chlorine content by the X-ray fluorescence method with a count meter. Again, only the samples of February 7 to 10 contained a large amount of chlorine (maximum 462 ppm). None of the oils shipped in other months were contaminated with more than a trace amount of chlorine. Thus, the results of chemical studies completely coincided with those achieved by epidemiologic approaches. By the way, the Kanechlor had been used at the K Company in the equipment for heating the processed oil at a reduced pressure in order to remove the odorous matters of the rice oil (Fig. 4). It is

Amount of oil used (ml)	Age	Number of patients by clinical grade			
		Non-affected	Light*	Severe*	Total
<720	0-12	3 (16.7)	13 (72.2)	2 (11.1)	18 (100.0)
	13-29	2 (8.3)	7 (29.2)	15 (62.5)	24 (100.0)
	30-	5 (13.1)	19 (50.0)	14 (36.9)	38 (100.0)
	Total	10 (12.5)	39 (48.8)	31 (38.7)	80 (100.0)
720-1440	0-12	0 (0)	5 (50.0)	5 (50.0)	10 (100.0)
	13-29	0 (0)	1 (6.7)	14 (93.3)	15 (100.0)
	30-	0 (0)	8 (40.0)	12 (60.0)	20 (100.0)
	Total	0 (0)	14 (31.2)	31 (68.8)	45 (100.0)

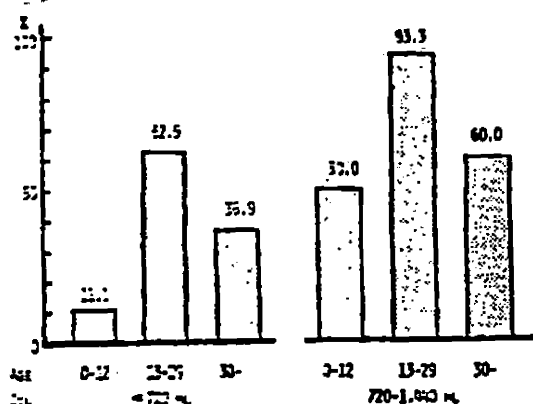


FIGURE 3. Percentage of severe cases of Yusho by age.

believed that it must have leaked from the heating pipe and contaminated the oil, because small openings were discovered in the old pipe.

Amount of Kanechlor 400 Ingested by Patients

One hundred forty-six patients who were proved to have used the contaminated canned K rice oil of February 5 and 6 by our investigation were used for the estimation of the amount of Kanechlor 400 ingested. As stated, the approximate amount of the oil consumed could be calculated for each of the patients. It was on average about 500 ml. Since the concentration of Kanechlor 400 in the oil was 2,000 to 3,000 ppm, the average amount of Kanechlor 400 ingested by a patient was estimated to be about 2 g (4). Similarly, the minimum dose of Kanechlor 400 consumed by a patient was estimated to be about 0.5 g.

Babies Born to Patients and Non-affected Wives of Patients

Thirteen women consisting of 11 with Yusho and 2 unaffected wives of patients were shown to have delivered 10 live born and two stillborn babies from February 15 to December 31, 1968 (5,10,11). As shown in Table 11, nine of them had unusually grayish, dark-brown stained skin and similar pigmentation of the gingiva and nails was noted in five of them. Increased eye discharge was also notable in most of them. Histological examination of a stillborn fetus showed a marked

hyperkeratosis and atrophy of epidermis and cystic dilatation of hair follicle, especially at the head. A marked increase of melanin pigments in the basal cells of epidermis was also noted (9). Since no such symptoms at birth or stillbirth has been experienced in Japan during the period in which their incidence among the patients was extremely high, and also since none of the mothers had had any unusual experiences, for instance, in use of drugs or in health status, these unusual phenomena could be considered to have been caused by ingestion of the contaminated oil. However, a clear dose-response relationship between the oil consumption and such phenomena could not be shown because of the limited number of cases. The amount of the contaminated oil consumed during pregnancy ranged from 0.3 to

Offered for further conclusion?

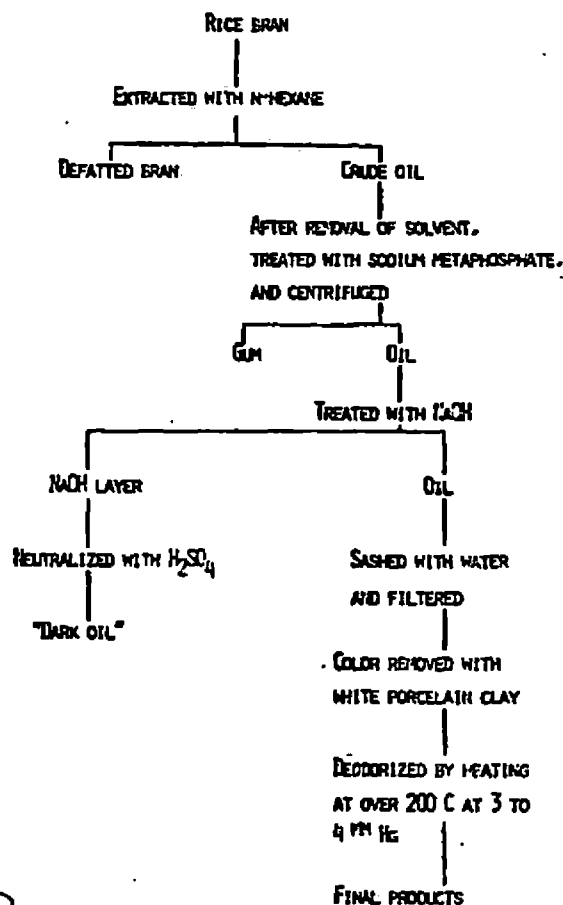


FIGURE 4. Flow sheet of rice oil production.

Table 11. Babies born to patients and unaffected wives of patients and their use of K rice oil.

Mother No.	Age	Amount of oil used during pregnancy (L)	Pregnancy period when oil used	Grade of clinical severity of mother	Delivery	Sex of baby	Small-for-date	Stained skin	Stained gingiva	Stained nail	Increased eye discharge	Neonatal jaundice
1	28	0.3	3rd trimester	2	Normal	M	No	?	-	-	-	+
2	24	?	?	3	Normal	F	No	+	-	-	+	+
3	22	1.4	Later half of 2nd trimester	Normal	Forcep	M	No	?	-	-	+	++
4	27	0.7	2nd trimester	1	Normal	M	Yes	+	+	-	+	?
5	26	0.7	1st trimester	3	Normal	F	No	+	+	+	+	+
6	29	1.4	Later half of 2nd trimester	3	Normal	M	No	+	-	+	+	+
7	30	1.1	Whole	1	Normal	M	Yes	+	-	-	+	?
8	23	?	Whole	3	Normal	M	30	+	-	-	+	+
9	33	?	?	?	Caesarean section	M	Yes	+	+	+	+	?
10	29	0.3	Early half of 2nd trimester	Normal	Normal	F	No	?	-	-	-	+
11	26	?	?	2	Normal	M	No	+	+	+	+	+
12	33	2.6	Early half of 2nd trimester	4	Stillbirth	?	?	+	?	?	?	?
13	25	?	?	3	Stillbirth	F	Yes	+	?	?	?	?

Table 12. Prognosis of patients with Yusho.*

Grade of clinical severity**	Clinical conditions			
	Improved	Stational	Worsened	Total
0	16 (66.7)	6 (25.0)	2 (8.3)	24 (100.0)
1	30 (51.7)	16 (27.6)	12 (20.7)	58 (100.0)
2	23 (52.3)	16 (38.4)	5 (11.4)	44 (100.0)
3	12 (52.2)	10 (43.5)	1 (4.3)	23 (100.0)
4	0 (0)	10 (100.0)	0 (0)	10 (100.0)
Total	81 (50.9)	58 (36.5)	20 (12.6)	159 (100.0)

* Calculated from the figures reported by Toshitani and Kitamura.

** 0: Physical complaints without skin-lesions.

1: Pigmentation of the skin and the mucous membrane.

2: Comedo formation.

3: Acneform eruptions.

4: Extensive distribution of acneform eruptions.

2.6 liters (Table 11) (8). Twelve of 13 fetuses were smaller than the national standards, and 4 of them were small-for-dates babies (8,10). As they grew older, the stain in their skin gradually faded (11). No evidence has so far been obtained with regard to any physical and mental retardation of the babies, but we suggest that a particularly careful and prolonged follow-up observation should be maintained for their future (8).

Growth of Affected Children

To examine whether Yusho disturbs children's growth, the affected school children, 23 boys and 19 girls, were compared in 1967, 1968, and 1969 with their 719 healthy classmates matched by sex. The gains of the affected boys in both height and weight decreased significantly after the poisoning, while the affected girls showed no definite change in this respect (12).

Current State of Patients

More than 3 years have passed since the epidemic was reported. It is a heart-breaking fact that many patients with Yusho are still tortured by the sickness because no curative treatments have been discovered yet. In summer of 1970, a mass clinical examination of the Yusho patients was carried out in Fukuoka-Ken, and the clinical state of the patients examined were compared with their previous findings observed in summer of 1969. As shown in Table 12, about a half of the 159 patients, for whom the comparison was feasible, were shown to have clinically improved signs, while the remaining half showed no such favorable signs, and more than 10 percent of the patients were even worsening (13). It should be noted, furthermore, that even many of those who appeared to be clinically improving had several serious complaints, such as persistent headache, general fatigue and feeling of weakness, numbness in limbs, weight loss, and others (14). All these facts clearly indicate that recovery from Yusho is extremely difficult. To cure them as quickly as possible and to prevent another epidemic of Yusho, all possible world-wide cooperative efforts are highly desired.

From the middle of February to the end of March, 1968, an epizootic of a strange disease closely resembling chick edema disease occurred

involving more than two million chickens in the western part of Japan (15,18). More than 400,000 chickens were reported to have died. The disease was characterized by such clinical signs as labored breathing, droopiness, ruffled feathers, high mortality and decreased egg production (15,18). Autopsy revealed a marked subcutaneous edema, hydropericardium, ascites, and pulmonary edema, muscular ecchymosis in the thorax or inside of the thigh, and yellowish mottled appearance of the liver (15,17,18). An epizootiological investigation demonstrated that the disease was caused by feeding chickens with specific lots of commercial brands of formula chicken feeds manufactured by two companies. In view of the fact that the K rice oil used by Yusho patients had been contaminated with Kanechlor 400, the toxic feeds were analyzed for chlorinated hydrocarbons and proved to contain Kanechlor 400 (16,19,20). The experimental reproduction of the disease by administering this chemical mixture was successful (16,20,21). The reason the chicken feeds were contaminated with Kanechlor 400 could be reasonably understood by the following facts: both of the chicken feed manufacturers had been using "Dark oil" produced by the K company (Fig. 3) as an ingredient of their formula feeds, and they had actually used "Dark oil" purchased from the company from February 6 to 27, 1968. The remaining sample of "Dark oil," used for production of the toxic formula feeds, was also shown to contain about 1,300 ppm of Kanechlor 400 (16,20). Thus, it became clear that both the epidemic of Yusho and the epizootic of the disease among chickens had been very closely associated, being caused by intake of the oils contaminated with Kanechlor 400. It is very unfortunate, however, that the epidemic of Yusho could not have been prevented even though a large scale epizootic of such an unusual chicken disease had preceded the incidence of Yusho by more than 6 months.

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