

Review Article

Yusho in Japan

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Abstract: The aim of the present paper is to summarize the history of the Yusho incidence that occurred in the western part of Japan in 1968. A strange disease was reported in October 1968. This strange disease was characterized by acne-like eruptions, pigmentation of the skin, and eye discharge, and it was named Yusho (oil disease). Through systematic epidemiological studies based on observation of initial case series, and extensive efforts to clarify causal agents by the Study Group for Yusho, it was concluded that Yusho was caused by ingestion of rice oil contaminated with PCBs and PCDFs. As of now, more than 1,800 patients, have been registered as having Yusho and around 300 are deceased. Clinical observation showed that typical symptoms of Yusho have decreased, even general fatigue, headache and numbness of extremities have still been complained by patients. No effective treatment has been found so far. Careful and systematic observation for Yusho patients and medical care services should be continued for a further understanding of Yusho.

Key words: Yusho, Chloracne, Heat transfer, PCBs, PCDFs, Dioxin, Black baby

Outbreak of a Strange Disease

The first patient, a 3 year-old girl with acne like eruptions, was brought to the outpatient clinic at the Kyushu University Hospital in June 1968¹⁾. By the end of August, 13 patients among 4 families had been referred to the same clinic with similar symptoms. Detailed observation and examinations of these patients suggested that the strange disease occurred in familiar aggregation and that ingestion of a certain commercial brand of cooking oil produced by K Company might be the cause of the occurrence of these symptoms. These cooking oils suspected by the patients were carefully examined to detect any possible chemicals that would cause this strange disease. But no specific chemicals were detected by laboratory chemical analysis.

On October 3, 1968, one of the patients reported this disease to a local health center for further investigation. On October 10, 1968, the outbreak of a strange disease was made public in a newspaper. The strange disease was

characterized by acne-like eruptions, pigmentation of the skin and increased eye discharge (Fig. 1). According to the newspaper, ingestion of a certain commercial brand of rice bran oil was suggested to be the cause.

Then, the local government of Fukuoka Prefecture established the Study Group for Yusho at Kyushu University in order to clarify causal factors of the strange disease on October 19, 1968¹⁾.

Then, the strange disease was named Yusho, meaning oil disease in Japanese. Within the Study Group for Yusho, an Epidemiologic Study Subgroup was formulated.

Epidemiological Approach

The Epidemiologic Study Subgroup headed by Prof. Kuratsune immediately made systematic epidemiological study plans to clarify causal factors related to the strange disease (Table 1).

Based on the tentative diagnostic criteria (Table 2)^{1,2)} for

Yusho proposed by the Clinical Study Subgroup, self-reported and suspected cases were screened and finally diagnosed by the Study Group for Yusho. In Fukuoka Prefecture, as of 20th January 1969, 325 cases were diagnosed as Yusho cases.

Descriptive epidemiology

As the first step of the epidemiological surveys, descriptive features of Yusho patients based on 325 cases were scrutinized. One of the most important epidemiological characteristics was a familiar aggregation. Occurrence of the strange disease reached a peak in June, July and August



Fig. 1. Acne-like eruptions and pigmentation of the skin.

1968 (Fig. 2). Geographically, these patients were not equally distributed in the Fukuoka prefecture³⁻⁵. Later it was found that most of the patients were located in Fukuoka and Nagasaki prefectures (Fig. 3). But no possible common socioeconomic nor environmental explanation was found. Also no sex nor age group differences in incidence rates among patients was observed³⁻⁵.

The uses of a certain commercial brand of rice bran oil suspected by patients was investigated. Among 325 patients, half of the patients consumed canned rice oil and the other half used bottled rice oil. A field survey of the canned rice oil showed the very exciting fact that 166 out of 170 patients who used the canned rice oil had consumed a specific oil produced or shipped by the K company on February 5 and 6, 1968 (Table 3)³⁻⁵.

Case control study

A case control study (for individual cases=121, controls=121, for household cases=69, controls=207) was carried out to find any causal factors related to the disease,

Table 1. Plan of the epidemiologic studies for Yusho

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| 1. Descriptive Epidemiology (325 Patients) |
| Distribution of Yusho Patients. |
| Use of K rice* oil by patients. |
| 2. Case Control study |
| To find possible etiologic factors |
| 3. Cohort Study |
| To examine attack rates for K rice oil consumer. |
| 4. Dose Response Relationship |

*K rice oil: a commercial brand of rice bran oil produced K Company.

Table 2. Diagnostic criteria of "Yusho" (1968)*

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| 1. Reference factors |
| 1) Consuming rice bran oil (contaminated by Kanechlor) |
| 2) Frequent familiar occurrence |
| 3) Symptom onset after April of 1968 |
| 2. Symptoms and signs |
| 1) Subjective symptoms: swelling of upper eyelids, increased discharge from eyes, loss of appetite, nausea, itching, numbness of extremities, paresthesia of feet, arthralgia, and prominent skin symptoms |
| 2) Ocular signs: hypersecretion of Meibomian glands (sebum), hyperemia and brownish pigmentation of conjunctiva, and temporary failing of eyesight |
| 3) Dermatological signs: blackening of nails, black spots in hair pores, comedo- and acne-like skin eruptions, change in skin color (abnormal pigmentation), pigmentation of mucous membranes, and excessive sweating in palms |
| 4) General findings: no obvious anemia, hepatomegaly, or splenomegaly. Occasionally observed slight fever or abnormal liver function tests, numbness or weakness of hands and feet without paresis |

*Partly simplified table published by Study Group for "Yusho"².

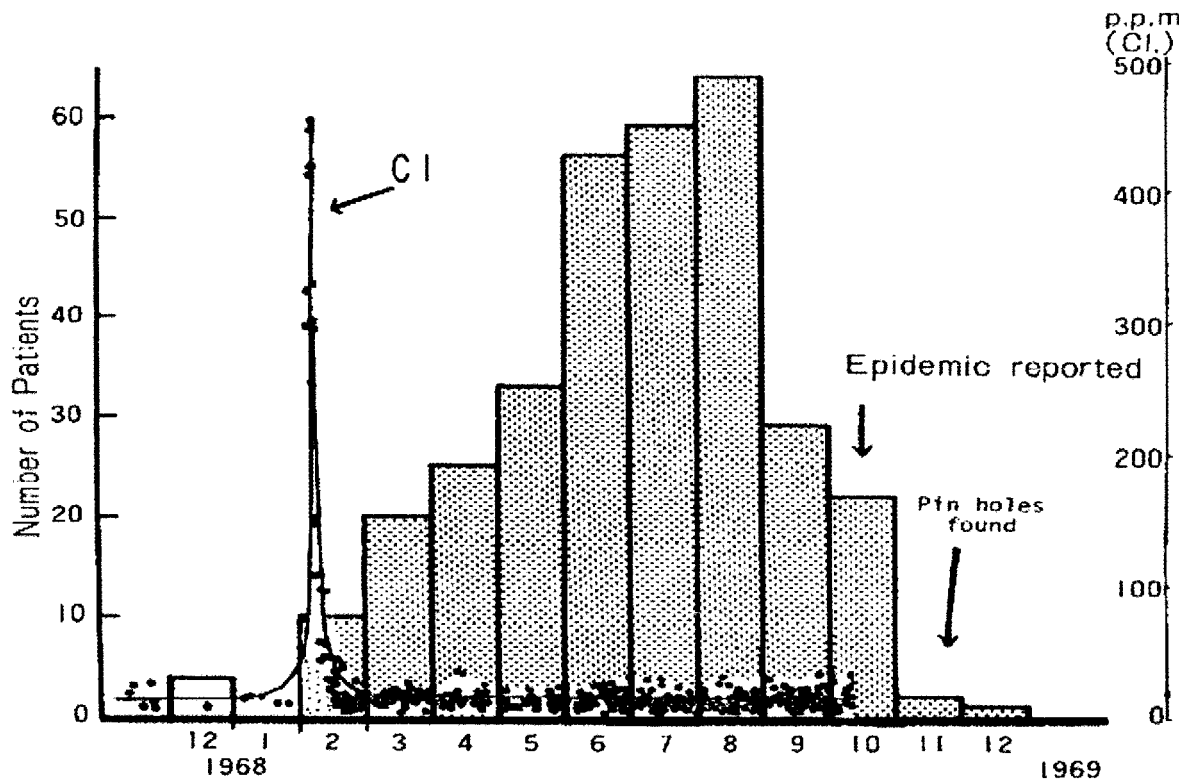


Fig. 2. Temporal distribution of patients and chlorine in bottled Kanemi rice oil. (Kuratsune, M., 1989)⁵⁾

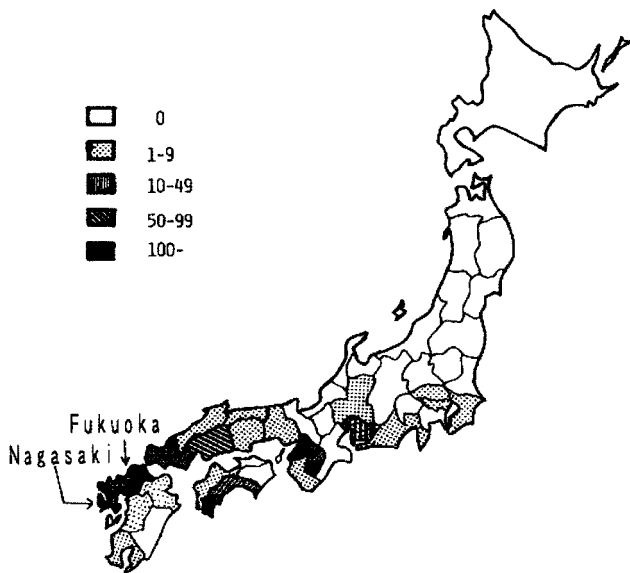


Fig. 3. Number of patients with Yusho by prefecture as of 1973. (Kuratsune, M., 1996)⁵⁾

regardless of former suspected information on the issues. Forty-seven personal items related to lifestyle (e.g. allergy, life style, drug intake, handling chemicals, dietary habits, use of cooking oil etc.) were investigated. Through this

Table 3. Use of K rice oil among 325 Yusho patients

Container		No. Patients	
Can	User of Oil Produced on 5-6 Feb, 1968	166	51.1
	Unknown	4	1.2
Bottle	Possible user of Oil Produced on 5-15 Feb, 1968	143	44.0
	Unknown	12	3.7
Total		325	100%

case control study, one distinct difference was noted between cases and controls, that is, the regular use of rice-bran oil (Table 4 and Table 5). It was suggested that causal factors might be related to the regular use of rice-bran oil, and that many other daily habits might not be of importance regarding Yusho occurrence³⁻⁵⁾.

Cohort study

In order to confirm a hypothesis that the specific oil produced in early February, 1968 might be causal, possibly exposed individuals should be identified and attack rates should be compared with non-exposed individuals. Individual consumers who used the canned rice oil, produced or shipped on February 5-6 were identified through purchase

Table 4. Results of a case-control study on habits, customs and others

Questions asked	Cases	Controls
	n=121 %	n=121 %
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*	36.5*
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*	11.6*
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

*p<0.05. (Kuratsune M, 1996, Yusho)

Table 5. Results of a case-control study on fats and oils used at home

Fat and oil	Case group (n=69)		Control group (n=207)	
	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*

*p<0.01. (Kuratsune M, 1996, Yusho)

and shipment records at the company, wholesale dealers and retail stores. Among 266 possible exposed individuals who used the specific rice oil produced and shipped on February 5–6, 1968 by the company, 170 individuals (64%) were already diagnosed and registered as Yusho³⁻⁵⁾ (Table 6).

The experience among the exposed group should be compared with that among the non-exposed group. In this context, the non-exposed group should have been regular

K rice oil users but who did not use K rice oil produced in February 1968. By the request of our study group, public health officials tried to find such a specific group. Fortunately, the non-exposed group was found to fit our study purpose. One hundred and thirty one K rice oil regular users except February's oil in an apartment house were identified. All family members were examined by the Clinical Study Sub group. It was found that no one showed the symptoms of

Table 6. Follow up of the canned rice oil dispatched in early February, 1968

Date of dispatch	User	No. canned oil	No. user	No. Yusho
1968 Feb.5	Personal (K.K)	1	25	0
Feb.5	Retail Dealer (T)	20	117	93
Feb.6	Personal (H.I)	1	32	0
Feb.6	Retail Dealer (R)	20	78	64
Feb.5,6	Retail Dealer	-31	Not identified	Not identified
Mar.1	Personal (S.M.)	1*	14	13
Total		43	266	170

*The canned oil dispatched was produced in February 1968. Attack Rate = 170/266 = 0.64.

Table 7. Follow up of the canned rice oil dispatched during the periods except February, 1968

Date of purchase	No. can	No. user	No. patients
1967 Dec.	2		
1968 May	4		
Jun.	1	113 persons	None
Jul.	1	29 households*	
Aug.	1		
Sept.	1		

*Residents in a apartment house.

Yusho (Table 7). These cohort type studies showed that the attack rate among exposed persons was 64%, on the other hand, no cases were observed among non-exposed.

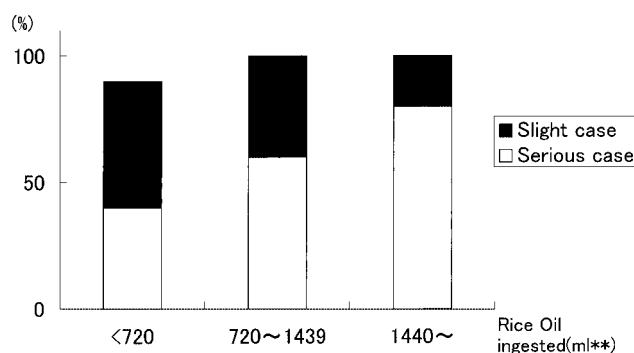
Dose-response relationship

It should be pertinent or preferable to show dose-response relationship in order to strengthen the hypothesis stated above. As imagined, it would not be an easy task to estimate the amount of the K rice oil consumed by each individual in the past. Fortunately, the amount of household consumption of the specific oil had already been investigated by the information of ① lot numbers of the canned rice oil, ② Amount of the K rice oil purchased, and ③ Amount of the K rice oil that remained.

The amount of household consumption was proportionally distributed to each family member, according to age, sex, and frequency of a home meal in a week. The individual amount of the K rice oil intake was then estimated among only users of February's canned rice oil^{6, 7)}.

Then, dose response relationship has been observed (Fig. 4), even under many conditions to estimate individual intake of the rice oil.

In summary, the results obtained by the epidemiological studies showed the following very important evidence.

**Fig. 4. Dose response relationship*.**

*: Canned rice oil (5,6 Feb., 1968) users only. **: No consideration for sex and age.

1. Descriptive epidemiology showed ① that Yusho incidents occurred in 1968, peaked in June through August (one peak epidemic) ② that Yusho has familiar aggregation ③ that there were no differences in attack rates among gender, and age group.
2. Case Control Study
Only the regular rice oil use was suggested, as possible factors
3. Cohort Study
Exposed to February's K rice oil had a high risk of 64% compared to zero among non exposed.
4. Dose Response Relationship
Positive relationship between estimated individual amounts of the rice oil intake and caseness and severity of Yusho.

Based on the epidemiological evidence stated above, it might be concluded that Yusho might be caused by the ingestion of the K rice oil produced in early February 1968 at the K company.

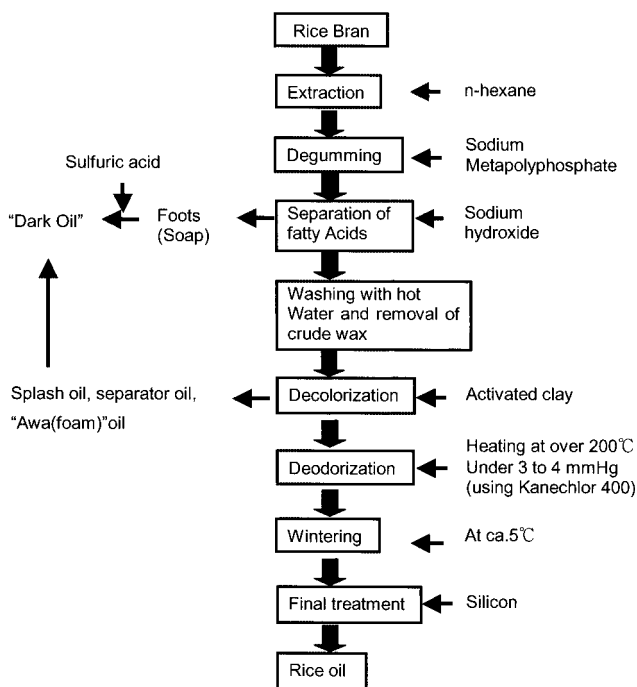


Fig. 5. The flow sheet of the K rice oil production.

Causal Agent

Through systematic epidemiological surveys, it was suggested that the K rice oil produced in early February contained some toxic agents. What is the causal agent for Yusho? When the Yusho outbreak was opened to the public in October 1968, a manager of the suspected company where the rice oil consumed by the Yusho patients was produced, showed a production flow chart of the rice oil (Fig. 5). According to this flow chart, possible contaminants in the final oil products that remained had been carefully analyzed. Besides, suspected causal agents such as, Pentachlorophenol (PCP), Chlorinated Naphtalene, Machine oil, Nitro chlorobenzen, Coal Tar, Pesticides (chlorinated), Organo chlorines, etc. were analyzed. But no suspected chemicals were detected.

Prof. Inagami, an expert on Food Production Engineering at the Faculty of Agriculture, Kyushu University got an idea from the oil production flow chart. He became interested in chemical substances for heat transfer. In the deodorization process, crude oil should be heated up to 200°C under 3–4 mmHg, low atmospheric pressure (Fig. 5). He questioned the chemical substance for the heat transfer. He was told that Kanechlor 400 (Commercial name for Polychlorinated Biphenyls majoring Tetra Chlorinated Biphenyls) was used for heat transfer⁵⁾. It was also suggested that heat transfer

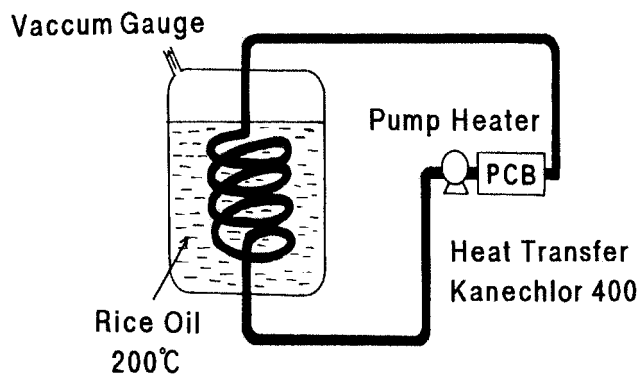


Fig. 6. Deodorization process for rice oil production. (Kuratsune)

(Kanechlor 400) in a closed circuit pipe had leaked into the rice oil during the deodorizing process (Fig. 6).

He began to analyze the remaining oil consumed by the patients and found that the oil was contaminated with PCBs^{5, 8)}. Later, subcutaneous fatty tissues from a Yusho patient was biopsied and examined. PCBs was also detected in the fatty tissues.

To confirm this contamination of PCBs in the K rice oil product, a series of the same K rice oil collected randomly by the health authorities were examined chronologically. Only February's bottled rice oil had an unusual high peak of chlorine content. This evidence by chemical analysis strongly supported the epidemiological conclusion (Fig. 2).

In 1969, the Yusho Study Group then concluded that Yusho was caused by ingestion of the K rice oil contaminated with PCBs⁵⁾.

This conclusion, however, was questioned regarding the following points as follows:

1. In 1971, Dr. R. W. Risebrough, Univ. of California, Berkeley asked Prof. Kuratsune whether Yusho was caused by PCBs alone or together with PCDFs or PCDDs which might be contained in Kanechlor400⁵⁾.
2. No similar dermatological lesions as human being could be produced by pure PCBs or by Kanechlor400 in an animal model.
3. Yusho patients showed severe clinical symptoms, even their blood PCBs level was rather low. On the other hand, workers exposed to PCBs showed almost no clinical symptoms, even their blood PCBs level was rather high (Table 8).

These fact forced members of the Study Group to consider other chemical agents together with PCBs as causal agents for Yusho.

In 1975, 1976, and 1977, Dr. Nagayama detected a significant amount of PCDFs in the toxic rice oil consumed

Table 8. Discrepancy between blood PCBs level and clinical manifestation

Groups	Blood PCBs	Clinical manifestation
Yusho patients	6 ppb	Severe
Workers with occupational exposure	45 ppb	mild or normal

Kashimoto *et al.* (1983).

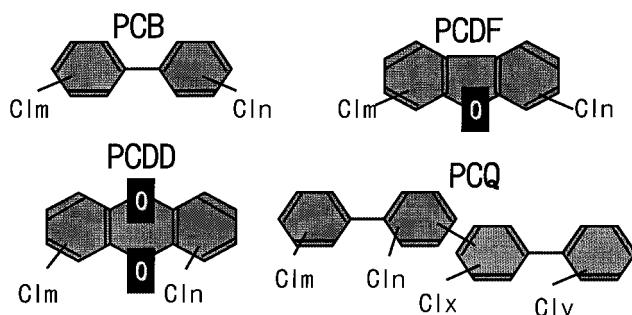


Fig. 7. PCB related chemical substances.

by patients as well as in the tissues of Yusho patients⁹⁻¹¹). Further investigation showed that the most important causal agents for Yusho were PCDFs, but not PCBs⁵) (Fig. 7).

In 1990, coplanar PCBs, PCDFs and PCDDs have been classified into “the group of dioxin” by the Japanese Government. Therefore, terminology of chemical substances for dioxin should be carefully identified according to definition.

Mortality among Yusho patients

In 1971, it was reported that a 48-year-old female died from liver cell carcinoma, 2 years and 10 months after the onset of Yusho⁵). Among Taiwan Yucheng patients, 24 cases died during a 4-year follow up period. Among the deceased, mortality from liver cancer, liver cirrhosis and other liver disease had increased¹²). In 1991, it was also reported that there was a substantial elevation in the mortality rate for chronic liver disease and cirrhosis (SMR=2.7)¹³).

It is important to describe mortality experiences among Yusho patients in order to prepare medical care services for patients and to understand the effect of ingestion of K rice oil contaminated with PCBs and PCDFs.

The first preliminary report on mortality due to Yusho published in 1986 was based on 120 deaths (79 males, 41 females) among Yusho patients¹⁴). Only among male patients, was an increased mortality risk for total cancer (SMR=3.26), liver cancer (SMR=5.59) and lung cancer (SMR=3.26) observed, when compared with the Japanese male population

mortality¹⁴).

Ikeda and Yoshimura⁵) reported that the mortality of Yusho patients up to 1990 was 200 deaths during about 17 years after onset. Again among male patients, SMRs for all malignancy (SMR=1.55) and liver cancer (SMR=3.36) were significantly elevated (Table 9). An extended follow up study has been continuing by the author and his colleagues.

Recently, extended follow up surveys up to 1996 were analyzed. It seems that SMR for liver cancer tends to decrease gradually, although a pertinent explanation for this observation is still unknown¹⁵). These observations regarding Yusho patients suggested that liver cancer deaths should be carefully observed.

Time Trend of Symptoms among Yusho Patients

Since the outbreak of Yusho, medical care services and health examination have been carried out by the Study Group of Yusho. Nationwide annual health examination for Yusho was organized using a standardized examination form and data-processing system¹⁶). The annual health examination for Yusho patients are rather comprehensive, including internal medicine, dermatology, ophthalmology, dentistry pediatrics, (recently gynecology has been added), general blood chemistry, analyses of blood PCBs and PCQs concentration (PCDFs from 2002), chest X-ray, electrocardiogram, and abdominal ultrasonography.

Subjective symptoms of the examinees are also recorded at the annual health check up.

Changes of subjective symptoms during 5 years (1988–93) are shown in Table 10^{5,17}), even Yusho patients examined and analyzed for the data were limited.

Among 31 subjective symptoms, 60% or more patients complained general fatigue, headache, and numbness in the extremities. On the other hand, typical signs such as acne-like eruption, pigmentation appeared to have decreased^{5,17}).

Yusho patients complained more of general subjective symptoms, compared to typical symptom for Yusho such as acne like eruption, pigmentation, hypersebum etc. Besides, subjective symptoms of general fatigue and numbness of extremities showed a clear dose-response relationship with

Table 9. The observed and expected number of deaths and SMR (O/E) by cause of death (all patients) - follow up to 1990

Cause of death	Male		Female	
	Observed	O/E	Observed	O/E
Total	127	1.18	73	0.90
Malignant neoplasms	45	1.55*	13	0.68
Esophagus	2	1.43	1	3.29
Stomach	10	1.12	1	0.20
Rectum, sigmoid colon and anus	2	1.67	0	0.00
Liver	12	3.36*	3	2.26
Pancreas	2	1.36	1	0.99
Lung, trachea and bronchus	9	1.81	0	0.00
Breast	–	–	1	0.77
Uterus	–	–	2	1.31
Leukaemia	2	2.57	0	0.00

*Original table was simplified. (Ikeda and Yoshimura, 1996)

Table 10. Time trend of % positive of symptoms and signs among Yusho

Symptom or sign	1988*	1993**
1 General fatigue	76.1	69.7
2 Headache	67.3	58.0
3 Cough	51.0	49.6
4 Sputum	52.0	45.1
5 Abdominal pain	43.2	34.5
6 Numbness in the extremities	61.9	58.6
7 Trouble with menstruation	19.3	14.1
8 Abnormal breath sounds	2.7	1.2
9 Hepatomegaly	7.8	3.4
10 Splenomegaly	0	0.4
11 Paresthesia in extremities	7.5	6.3
12 Abdominal ultrasonography	33.7	48.0
13 Liability to suppuration	16.6	16.2
14 Comedones in the face	12.1	8.8
15 in the auricles	7.4	8.0
16 in the trunk	11.8	12.2
17 in other regions	2.9	2.0
18 Acneiform eruptions in the face	4.7	7.8
19 in the genital regions	4.7	4.2
20 in the gluteal regions	3.5	7.3
21 in the trunk	6.3	10.3
22 in other regions	1.5	0.5
23 Pigmentation in the face	2.7	4.6
24 in the fingernails	2.3	6.1
25 in the toenails	6.3	6.1
26 in other regions	0	4.6
27 Deformity of nails	10.3	10.4
28 Hypersebum	15.3	20.8
29 Pigmentation in palpebral conjunctiva	4.4	7.8
30 Meibomian gland, cystic degeneration	12.0	17.3
31 hypersecretion	4.6	12.7

*% positive among examined (n=257). **% positive among examined (n=264). (Hirota et al., 1996)

blood PCB levels⁵).

At outbreak of Yusho, typical Yusho patients were extensively examined by the Study Group for Yusho. Yusho patients did not show any typical abnormal chemical blood findings except serum triglyceride. Serum triglyceride was high in the 1970's, but recently this finding is starting to fade.

Recently, it is quite difficult to assess the time trend of symptoms and signs related to Yusho, because of a lack of systematic observations.

Black Babies (Cola Colored Babies)

Unusual still births and live births with abnormal pigmentation of baby skin (grayish dark brown) were observed by obstetricians in 1968. In Fukuoka, epidemiological studies showed that 13 women (10 Yusho patients, 2 not registered, 1 unspecified) in Yusho families had given 11 live births and 2 still births during February-December, 1968. Ten had shown the characteristic grayish darkbrown pigmented skin at birth¹⁸. The majority of the babies were small for-dates¹⁸.

Clinicians in Nagasaki also observed the same phenomenon as in Fukuoka. Up to this moment, no evidence has been obtained in regard to the possible retardation in physical and mental activities of the babies¹⁸. Peculiar pigmentation of baby skin gradually disappeared¹⁹.

Later, it was confirmed that PCBs and PCDFs were transferred through poisoned females to their fetuses via placenta and breast milk^{20, 21}).

It has also been reported that by 7 years after exposure,

the 13 children were seen to be apathetic and dull with low IQs in the 1970s²²). No systematic follow up studies have been reported on the growth and development of the black babies in Japan, although observation of the black babies should be carefully made to determine future countermeasures.

A low male to female sex ratio at birth was reported among children born to men exposed to 2378 TCDD after the Seveso accident²³). At the Yusho incidence, no such phenomenon was observed²⁴).

Growth of school children with Yusho was evaluated based on height and weight gain before and after the outbreak, that is, from 1967 through 1971. It was suggested that the growth of school children with Yusho was disturbed just after the Yusho incidence but their subsequent growth tended to recover to the level of healthy controls^{25,26}).

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