Chapter 8

Annual Health Examinations of Yusho Patients

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Since the initial outbreak of "Yusho" in the summer of 1968, health examinations have been carried out for case detection as well as for patient follow-up, in accordance with the diagnostic criteria established in 1968, and thereafter amended in 1972 and 1976 to cope with the chronic phase patients (Appendix 1. Tables 1, 2, and 3). For this follow-up study the Ministry of Health and Welfare allotted 84.5 million yen during the first ten years after the outbreak, and a total of 519.1 million yen up to 1993 (Appendix 5).

These examinations have shown that the typical signs for Yusho improved greatly in the first 10-year-period after the outbreak, but thereafter they were gradually superseded by systemic disorders, such as dullness, headache, numbness of the extremities, and so on (Toshitani, 1972; Urabe et al., 1979; Okumura, 1984; Toshitani, 1987). These features are so complicated as to be indistinguishable from those observed in the general population. In addition, persistent hypertriglyceridemia, which was observed in two-thirds of the patients at the outbreak (Okumura and Katsuki, 1969), returned to a range comparable to normal subjects by 1975 (Okumura et al., 1979; Okumura, 1984). It therefore seems unlikely that the chronic phase patients manifest abnormal findings in blood chemistry peculiar to the pathogenesis of this illness (Okumura, 1984). As a result, little attention has been paid to the laboratory findings in recent years.

In 1986, a nationwide annual health examination for Yusho was started using a standardized examination form, in order to promote patient health and to determine the health status of chronic patients. In addition, an entire data-processing system has been established in a two-year effort (Kataoka et al., 1989). We herein present the outline of this examination, and the relation of blood PCB concentration with the clinical manifestation of symptoms or signs (Hirota et al., 1991) with the laboratory findings (Hirota et al., 1993a; Hirota et al., 1993b) in Yusho patients at the chronic stage twenty years after exposure, using the information obtained from a health examination performed in 1988. These associations were not fully studied in the early years after the outbreak, because the routine analysis of blood PCBs has only been in use since 1973.

8.1. Outline of Annual Health Examination

The annual health examination involves a comprehensive checkup for internal medicine, dermatology, ophthalmology, dentistry, pediatrics, general blood chemistry, and analyses of blood PCB and PCQ concentrations. The internal medicine

examination includes an evaluation of the digestive, respiratory, circulatory, and nervous systems along with a chest X-ray, electrocardiogram, and abdominal ultrasonography. The evaluation in dermatology, ophthalmology, and dentistry mainly covers the areas related to the peculiar symptoms or signs of Yusho patients. For children born to a mother with Yusho, information on gestational toxicosis, gestational age, breast feeding, dentification, mental or physical development, etc. was also obtained in a pediatric examination.

These examinations are open not only to officially identified Yusho patients, which amount to 1,862 cases as of 1990, but also to those who regard themselves as potential victims. A total of 387 patients received the initial examination in 1986. Afterwards, this number has since decreased as follows; 291, 285, 302, 313, 273, and 269 from 1987 to 1992, respectively. Almost an equal number of males and females were examined. The number of examinees of potential victims has consistently decreased; 158, 113, 88, 73, 60, 50, and 42 from 1986 to 1992, respectively. The examinations have been annually conducted at twelve prefectures, and 65–70% of total patients examined are the residents in Fukuoka or Nagasaki Prefectures, where the outbreaks were most prominent. The age distributions of the patients examined between 1986 and 1992 consist of about 50% aged 60 or older and about 80% aged 50 or older, annually.

8.2. Symptoms or Signs

8.2.1. Subjects, Data Reduction, and Analysis

The total number of patients who underwent the 1988 health examination was 285 (143 males and 142 females). They had been notified to come in for this examination after an overnight fast and registration was voluntary, not obligatory. Of these, 259 patients (136 males and 123 females), in whom a PCB concentration in the blood had been identified, were subjected to the analysis. The peak age distribution was at ages 60–64 and comprised about 20% of all study subjects, while those aged 50–69 and 40–79 consisted of 60% and 85% of the subjects, respectively.

PCBs in the blood were analyzed by saponification with 1N NaOH ethanol solution, extraction with n-hexane, column chromatography on silica gel, and then by gas chromatography with electron capture detection (Masuda et al., 1974; Masuda and Schecter, 1992). The blood PCB concentration for the subjects ranged from 0.6–32.0 ppb (mean ± SE; 4.78 ± 0.22), and they were classified for comparison into approximate quartiles; < 2.7, 2.7+, 4.1+, and 6.1+ ppb.

Information on the symptoms or signs corresponding to or related to the diag-

nostic criteria for Yusho at the chronic phase was obtained from the standardized examination form. A total of 32 items were selected and included; general fatigue, headache, cough, sputum, abdominal pain, diarrhea, numbness in extremities, troubles with menstruation, abnormal breath sounds, hepatomegaly, splenomegaly, paresthesia in extremities, and abdominal ultrasonography, from the examinations in internal medicine; liability to suppuration, comedones (face, auricle, trunk, and other regions), acneiform eruptions (face, genital region, gluteal region, trunk, and other regions), pigmentation (face, fingernails, toenails, and other regions), and deformity of nails, from the dermatology examinations; and hypersebum, pigmentation in palpebral conjunctiva, and cystic degeneration or hypersecretion of the Meibomian gland, from the ophthalmology examinations.

The standardized form indicates the results by a semi-quantitative scale for most of the examination items, e.g., –, +, and ++ for subjective symptoms; –, ±, +, ++, and +++ for signs in the skin or eyes. Then each result was classified into two categories for analysis; absence/presence, i.e., – / +, ++ or –, ± / +, ++, +++, respectively.

The results of each examination were summarized into a two by four contingency table, i.e., two categories of each symptom or sign based on four levels of blood PCBs. Then, the distributions of the subjects at the four levels of blood PCBs were compared between two categories with or without each symptom or sign, using the Kolmogorov-Smirnov (K-S) test and Mann-Whitney test. Since similar results were obtained from the two tests, only the results of K-S test are shown hereinafter. Concerning the symptoms or signs for which statistically significant difference was observed or suggested by the K-S test, the odds ratio and its 95% confidence interval (95% CI) were calculated at each level of blood PCBs with a reference category of the lowest level. In addition, the test for trend with increasing blood PCB level was performed using the Mantel-extension method.

8.2.2. *Manifestation of Symptoms or Signs, and the Association with Blood PCBs*

The frequency of each symptom or sign is shown in Table 8.1. The proportions of those with subjective symptoms in internal medicine (No. 1–8) ranged 19% for troubles with menstruation to 76% for general fatigue. The symptoms for which the proportion exceeded 60% were general fatigue, headache, and numbness in extremities. Abnormal findings in abdominal ultrasonography (No. 13) were present in 34% of the examinees. As for the dermatology examinations, comedones or acneiform eruptions in specific regions (No. 15–17, and 19–22) were observed in 7–12% and 4–6% of the subjects, respectively. The proportions of the subjects with positive signs in the eyes (No. 29–32) ranged from 4% for pigmenta-

Table 8.1. The Frequency of Symptoms or Signs either Corresponding or Related to the Diagnostic Criteria for Yusho at the Chronic Stage

	Symptom or sign	Proportion (%)	
Internal medicine			
1.	General fatigue	76.1	(194/255)[a]
2.	Headache	67.3	(173/257)
3.	Cough	51.0	(131/257)
4.	Sputum	52.0	(133/256)
5.	Abdominal pain	43.2	(111/257)
6.	Diarrhea	42.0	(108/257)
7.	Numbness in the extremities	61.9	(159/257)
8.	Troubles with menstruation	19.3	(16/83)
9.	Abnormal breath sounds	2.7	(7/257)
10.	Hepatomegaly	7.8	(20/257)
11.	Splenomegaly	0.0	(0/256)
12.	Paresthesia in extremities	7.5	(19/253)
13.	Abdominal ultrasonography	33.7	(60/178)
Dermatology			
14.	Liability to suppuration	16.6	(41/247)
15.	Comedones in the face	12.1	(31/256)
16.	in the auricles	7.4	(19/256)
17.	in the trunk	11.8	(30/254)
18.	in other regions	2.9	(4/139)
19.	Acneiform eruptions in the face	4.7	(12/255)
20.	in the genital regions	4.7	(12/256)
21.	in the gluteal regions	3.5	(9/255)
22.	in the trunk	6.3	(16/255)
23.	in other regions	1.5	(2/136)
24.	Pigmentation in the face	2.7	(7/256)
25.	in the fingernails	2.3	(6/256)
26.	in the toenails	6.3	(16/256)
27.	in other regions	0.0	(0/132)
28.	Deformity of nails	10.3	(26/253)
Ophthalmology			
29.	Hypersebum	15.3	(38/249)
30.	Pigmentation in palpebral conjunctiva	4.4	(11/248)
31	Meibomian gland, cystic degeneration	12.0	(30/249)
32.	hypersecretion	4.6	(9/196)

[a]: The number of subjects with symptoms or signs in the numerator, and the number of total subjects examined in the denominator.

Table 8.2. The Distribution of Subjects with or without Selected Symptoms or Signs Based on the Blood PCB Level, and the Results of the Kolmogorov-Smirnov Test

Symptom or sign and category	No. of subjects by PCB level (ppb)					K-S[a] test
	< 2.7	2.7+	4.1+	6.1+	Total	
General fatigue						
Presence	39 (20)[b]	60 (51)	53 (78)	42 (100)	194	
Absence	26 (43)	17 (71)	9 (85)	9 (100)	61	$p < 0.01$
Headache						
Presence	33 (19)	62 (55)	44 (80)	34 (100)	173	
Absence	32 (38)	16 (57)	19 (80)	17 (100)	84	$p < 0.02$
Numbness in extremities						
Presence	28 (18)	53 (51)	43 (78)	35 (100)	159	
Absence	37 (38)	25 (63)	20 (84)	16 (100)	98	$p < 0.01$
Abnormal breath sounds						
Presence	0 (0)	1 (14)	5 (86)	1 (100)	7	
Absence	65 (26)	77 (57)	58 (80)	50 (100)	250	$p < 0.10$
Comedones in the face						
Presence	5 (16)	8 (42)	5 (58)	13 (100)	31	
Absence	59 (26)	70 (57)	58 (83)	38 (100)	225	$p < 0.05$
Comedones in the trunk						
Presence	2 (7)	8 (33)	8 (60)	12 (100)	30	
Absence	62 (28)	69 (59)	54 (83)	39 (100)	224	$p < 0.05$
Acneiform eruptions in the genital region						
Presence	1 (8)	2 (25)	6 (75)	3 (100)	12	
Absence	63 (26)	76 (57)	57 (80)	48 (100)	244	$p < 0.10$

[a]: Kolmogorov-Smirnov test, one-sided test. [b]: Cumulative relative frequency (%) in parenthesis.

tion in palpebral conjunctiva to 15% for hypersebum.

Table 8.2. shows the distributions of subjects at four levels of blood PCBs, along with the results of the K-S test. Between the groups with or without each symptom or sign, significant differences in the cumulative relative frequencies based on the blood PCB level were observed for general fatigue ($p < 0.01$); headache ($p < 0.02$); numbness in the extremities ($p < 0.01$); and comedones in the face ($p < 0.05$) and trunk ($p < 0.05$). The differences were also suggested for abnormal breath sounds; and acneiform eruptions in the genital region, but were statistically insignificant. The symptoms or signs not mentioned in Table 8.2. showed no significant or suggestive differences according to the K-S test.

The odds ratios at each level of blood PCBs and the results of the test for trend are shown in Table 8.3. For general fatigue, the odds ratios at blood PCB levels of 2.7+, 4.1+, and 6.1+ ppb were 2.35, 3.63, and 3.11, respectively. For numbness in the extremities, the corresponding odds ratios were 2.80, 2.84, and 2.89, respec-

Table 8.3. Odds Ratios and Dose-response Relation for Selected Symptoms or Signs

Symptom or sign	PCB level (ppb)	Odds ratio	95% CI	p-value	Trend
General fatigue	< 2.7	1.00			
	2.7+	2.35	1.14–4.87	$p < 0.05$	
	4.1+	3.63	1.70–9.07	$p < 0.01$	$p < 0.005$
	6.1+	3.11	1.32–7.34	$p < 0.01$	
Headache	< 2.7	1.00			
	2.7+	3.76	1.83–7.71	$p < 0.01$	
	4.1+	2.25	1.09–4.62	$p < 0.05$	$p > 0.100$
	6.1+	1.94	0.91–4.14	$p < 0.10$	
Numbness	< 2.7	1.00			
in extremities	2.7+	2.80	1.42–5.52	$p < 0.01$	
	4.1+	2.84	1.39–5.82	$p < 0.01$	$p < 0.005$
	6.1+	2.89	1.35–6.19	$p < 0.01$	
Abnormal	< 4.1[a]	1.00			
breath sounds	4.1+	12.24	2.17–68.99	$p < 0.01$	$p > 0.100$
	6.1+	2.84	0.19–41.37	$p > 0.10$	
Comedones	< 2.7	1.00			
in the face	2.7+	1.35	0.42–4.35	$p > 0.10$	
	4.1+	1.02	0.28–3.72	$p > 0.10$	$p < 0.025$
	6.1+	4.04	1.40–11.65	$p < 0.01$	
Comedones	< 2.7	1.00			
in the trunk	2.7+	3.59	0.80–16.17	$p < 0.10$	
	4.1+	4.59	1.05–20.13	$p < 0.05$	$p < 0.005$
	6.1+	9.54	2.51–36.26	$p < 0.01$	
Acneiform	< 2.7	1.00			
eruptions	2.7+	1.66	0.15–18.42	$p > 0.10$	
in the genital	4.1+	6.63	1.00–44.07	$p < 0.05$	$p < 0.100$
region	6.1+	3.94	0.46–33.74	$p > 0.10$	

[a]: Since the number of subjects with abnormal breath sounds at a blood PCB level of less than 2.7 ppb was zero, two levels of < 2.7 and 2.7–4.1 ppb were combined for the reference.

tively. For comedones, they were 1.35, 1.02, and 4.04 in the face; and 3.59, 4.59, and 9.54 in the trunk, respectively. Thus, an increase in odds ratio with an increasing blood PCB level was evident for general fatigue (test for trend; $p < 0.005$); numbness in the extremities ($p < 0.005$); and comedones in the face ($p < 0.025$) and in the trunk ($p < 0.005$). For general fatigue and numbness in extremities, a distinctive increase in the odds ratio was observed at a blood PCB level of 2.7 ppb, but no linear increasing trend for the former symptom was evident at the upper two levels. In addition, the odds ratio for comedones in the face and trunk clearly increased at 6.1 ppb. Although a significant increase in odds ratio at some of blood

PCB levels was found for headache, abnormal breath sounds, and acneiform eruptions in genital region, the trend was not statistically significant.

As a whole, the symptoms or signs for which significant results were obtained both in the K-S test and in the test for trend were; general fatigue; numbness in the extremities; and comedones in the face and trunk. An association with blood PCBs was also suggested for headache; abnormal breath sounds; and acneiform eruptions in genital region, but was statistically insignificant.

8.3. Blood Chemistry

8.3.1. Data Reduction and Analysis

The relation with blood PCB concentration was investigated for triglyceride, γ-GTP (γ-glutamyl transpeptidase), total-bilirubin and conjugated-bilirubin in the serum, which were measured by an autoanalyzer. Abnormal findings in these test items are listed in the diagnostic criteria for the chronic phase patients. The associations were assessed using the analysis of variance (ANOVA).

Since the results of ANOVA indicated a close correlation between blood PCBs and serum triglyceride, this association was further explored in detail. First, the blood PCBs and serum triglyceride were analyzed for statistical analysis after logarithmic transformation, because the distributions of these two variables were skewed and a departure from the "norm" seemed evident. Then the relation was assessed using a correlation and multiple regression analysis. Second, to precisely examine this relation considering the effects of other factors, the mean values of triglyceride adjusted for two potential confounders, i.e., age and sex, were calculated and compared among four PCB levels, by the analysis of covariance. The significant different test of adjusted mean values between two PCB categories was performed by the Fisher's least significant difference method. These calculations were conducted using the Statistical Analysis System (SAS) (SAS Institute, 1985). The mean and its 95% confidence interval (95% CI) for PCBs and triglyceride were presented in the original scale by taking the antilogarithm.

8.3.2. Association with Blood PCBs

The subjects with a blood test exceeding the normal range were numbered 68 (26.3%) for triglyceride (normal range; 35–150 mg/dl); 24 (9.3%) for γ-GTP (≤ 50 IU/l); 5 (1.9%) for total-bilirubin (≤ 1.2 mg/dl); and 3 (1.2%) for conjugated-bilirubin (≤ 0.4 mg/dl). A significant difference among the four levels of blood PCBs was observed only for triglyceride (F-value; 3.62, $p < 0.025$), but not for γ-GTP (0.65, $p > 0.1$), total-bilirubin (1.19, $p > 0.1$), nor conjugated-bilirubin (0.86,

Table 8.4. Distribution of Study Subjects and the Mean Serum Triglyceride Level Based on the Blood PCB Concentration

Blood PCBs (ppb)	No. of subjects (%)	Triglyceride (mg/dl)[a]
< 2.7	66 (25.5)	107.8 ± 8.1
2.7+	78 (30.1)	137.1 ± 9.5
4.1+	64 (24.7)	144.5 ± 13.1
6.1+	51 (19.7)	165.7 ± 18.5

$F = 3.617$ ($p < 0.025$) in ANOVA. [a]: mean ± SE.

Table 8.5. The Relation between Blood PCBs and Serum Triglyceride

No. of subjects (Male/Female)	259 (136/123)
Blood PCBs (ppb)	
Geometric mean	3.84 (3.54 : 4.17)
Serum triglyceride (mg/dl)	
Geometric mean	114.3 (106.6 : 122.6)
Correlation analysis	
Between PCBs and triglyceride	
Pearson's coefficient	0.22 (0.10 : 0.33)
Spearman's coefficient	0.20 (0.08 : 0.31)
Between sex and triglyceride	
Pearson's coefficient	−0.13 (−0.25 : −0.01)
Spearman's coefficient	−0.10 (−0.22 : −0.02)
Between age and triglyceride	
Pearson's coefficient	0.17 (0.05 : 0.28)
Spearman's coefficient	0.12 (0.002 : 0.24)
Multiple regression analysis	
Correlation coefficient	0.26 (0.15 : 0.37)
Partial regression coefficient	
Intercept	4.530 ($p = 0.000$)
PCBs	0.154 ($p = 0.006$)
Sex	−0.137 ($p = 0.050$)
Age	0.004 ($p = 0.166$)

The values of PCBs and triglyceride were evaluated by a statistical analysis after logarithmic transformation. In the regression analysis, sex was coded for male and female as 1 and 2, respectively.

The values in parenthesis, if not otherwise specified, are the 95% confidence intervals.

Table 8.6. The Crude and Adjusted Mean Values of Serum Triglyceride (mg/dl) by Blood PCBs

PCB level (ppb)	No. of subjects (%)	Crude value	Adjusted value[a]
		Mean (95% CI)	Mean (95% CI)
< 2.7	66 (25.5)	94.8 (82.7–108.6)	98.4 (85.2–113.6)
2.7+	78 (30.1)	117.4 (103.5–133.1)	117.8 (102.5–135.4)
4.1+	64 (24.7)	120.2 (104.6–138.0)	117.8 (104.0–133.5)
6.1+	51 (19.7)	131.4 (112.5–153.5)	127.7 (109.1–149.3)

The values of PCBs and triglyceride were evaluated by a statistical analysis after logarithmic transformation.

Comparison among the four PCB levels; $F = 3.67$ ($p = 0.013$) in crude values, and $F = 2.01$ ($p = 0.113$) in adjusted values.

[a]: Adjusted for age and sex by the analysis of covariance.

$p > 0.1$), in ANOVA. The mean values of triglyceride increased in a dose-dependent manner from the lowest to highest quartile of blood PCB concentrations; 107.8, 137.1, 144.5, and 165.7 mg/dl (Table 8.4.).

Then, the association between these two variables was analyzed in detail. As shown in Table 8.5., a weak but statistically significant correlation of blood PCBs with serum triglyceride was observed in both Pearson's and Spearman's correlation coefficients, as were in those of sex or age with triglyceride. The correlation analysis also showed significant Pearson's and Spearman's coefficients between PCBs and age; 0.37 (95% CI; 0.26 : 0.47) and 0.30 (0.19 : 0.41), but not between PCBs and sex; –0.02 (–0.14 : 0.10) and –0.05 (–0.17 : 0.07), respectively. In a multiple regression analysis with triglyceride as dependent variable and PCBs, sex, and age as explanatory variable, a partial regression coefficient was statistically significant for PCBs and sex but not for age. Although correlation or regression analysis assesses the linear trend between the two variables, no significant difference was indicated for serum triglyceride by blood PCBs.

Therefore, the mean serum triglyceride based on the blood PCB level was calculated, for comparison, adjusting age and sex by the analysis of covariance (Table 8.6.). The adjusted mean values of serum triglyceride revealed a gradient increase with an increasing PCB level; 98.36, 117.78, 117.84, and 127.65 mg/dl (F-value; 2.01, $p = 0.113$), showing a smaller margin between the lowest and highest PCB levels as compared to that in the crude values; 94.77, 117.38, 120.15, and 131.43 mg/dl (3.67, $p = 0.013$). Although the adjusted means indicated no significant difference among the four PCB levels, the difference between the two levels (Fig. 8.1.) was marginally significant when comparing the first with second quartiles ($p = 0.088$), and the first with the third quartiles ($p = 0.066$), and reached significance when the first and fourth quartiles were compared ($p = 0.021$), while dis-

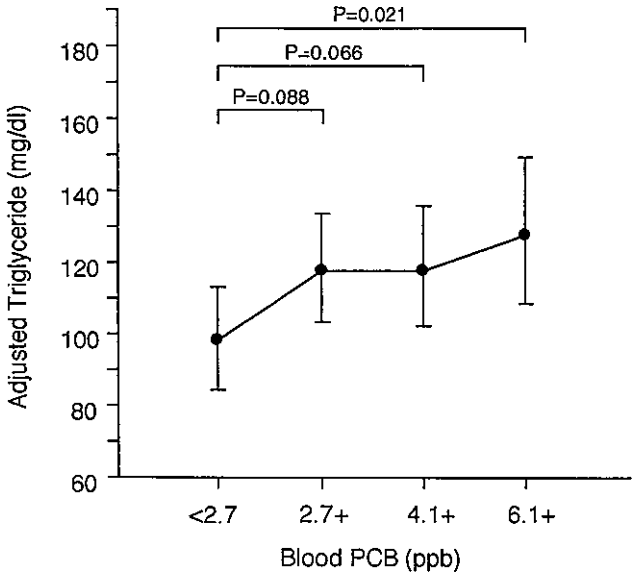

Fig. 8.1. The Association between Blood PCBs and Serum Triglyceride in Chronic "Yusho" Patients, Twenty Years after Exposure

The figure shows the mean value of triglyceride adjusted for age and sex and its 95% confidence interval at each PCB level, and the results of the comparison between two PCB levels by the Fisher's least significant difference method.

playing smaller p-values in comparison to the PCB levels further away from the first quartile.

Thus a weak but statistically significant association between blood PCBs and serum triglyceride was found not only when analyzing triglyceride as a crude value, both in the correlation analysis and in the comparison among the four PCB levels, but also after adjusting triglyceride for age and sex.

8.4. Causal Inference from the Positive Association of Blood PCBs with Symptoms or Signs as well as with the Serum Triglyceride Levels

8.4.1. Blood PCB Concentration as an Index for Exposure

Extensive investigations disclosed, in November 1968, that Yusho was caused by the ingestion of rice bran oil contaminated with PCBs, which had been utilized as a thermic conductor in the oil refining process (Urabe et al., 1979). Afterwards, it became clear that this oil was also contaminated with trace amounts of PCDFs and PCQs (Buser et al., 1978; Miyata et al., 1978). Thereafter, highly toxic PCDFs

were detected in the adipose tissue and liver sampled from the Yusho patients in the early years after the outbreak, as were PCQs in the blood (Miyata et al., 1977; Kuroki and Masuda, 1978; Kashimoto et al., 1981). In addition, animal experiments also demonstrated the manifestation of dermal signs resembling those of Yusho, in cynomolgus monkeys treated with PCDF mixture (Kunita et al., 1984). Therefore, presently, PCDFs are suggested to be the responsible compounds for the development of Yusho (Kunita et al., 1985). It can be outlined that the causal rice oil was contaminated with 150–1,000 ppm of PCBs, 2–7 ppm of PCDFs and 500–1,000 ppm of PCQs (Nagayama et al., 1976; Miyata et al., 1978).

However, blood PCBs are still regarded as a pertinent index for exposure in Yusho patients, since its concentration has shown a gradual decrease after the outbreak but has diminished to only a slight decrease during the recent years (Urabe et al., 1979; Honbo et al., 1989; Ohgami et al., 1989). The concentration of blood PCBs may well reflect the magnitude of the previous acute exposure and current internal exposure to PCBs themselves as well as to other PCB-related compounds involved.

8.4.2. Validity of Data from Health Examination

Since the present examinees account for only 15% of all officially-identified Yusho cases, the representativeness of the sample should thus be taken into consideration. Possible selection bias, such as the involvement of more health consciousness patients or those with poor health conditions, should also be taken into account. However, the dose-dependent association observed between the blood PCBs and several items in the health examination cannot be fully explained by a such selection bias.

According to the dermatology study (Honbo et al., 1989), comedones and acneiform eruptions were present in half of the patients who were followed for up to twenty years. The observed high prevalence of symptoms was probably because the patients with severe conditions had remained in the study. In the present health examination, however, the proportion of the subjects with comedones or acneiform eruptions were 12% and 6% at most, respectively. Therefore, those who underwent the present health examination are considered to be more representative of the Yusho patients twenty years after exposure.

8.4.3. Association of Blood PCBs with Symptom or Sign

In the diagnostic criteria for Yusho at the chronic stage, three important bases are listed; signs in the skin; and eyes; and the blood PCB concentration. On the other hand, subjective symptoms are listed as only referent items. In fact, it seems unlikely that subjective symptoms are of any crucial importance for diagnosing

individual Yusho cases twenty years after the outbreak. However, when subjective symptoms were collectively investigated in the present study, close associations with blood PCB concentration were observed for general fatigue and numbness in the extremities. For these subjective symptoms, statistically significant elevated risks were indicated at all of three higher PCB levels while a clear dose-response relation was observed. In addition, a distinctive risk increase was also found at the level of 2.7 ppb. For headache, an association with blood PCBs was also suggested, but the dose-response relation was not clearly elucidated. The high frequency of abnormal results in abdominal ultrasonography (No. 13 in Table 8.1.) may be due to the inclusion of findings which bear no pathological meaning.

The diagnostic criteria includes the manifestation of respiratory symptoms similar to chronic bronchitis, characterized by cough and sputum. In the medical examination conducted one year after outbreak, about 40% of smokers with Yusho complained of cough with sputum (Shigematsu et al., 1977). Although respiratory symptoms gradually improved during the subsequent ten years, they have shown little improvement in recent years (Nakanishi et al., 1985). Especially, the patients with high concentrations of blood PCBs or with chronic respiratory infections have been found to suffer from inveterate respiratory symptoms (Shigematsu et al., 1977). A recent study suggested the existence of the target cells in human lungs to which certain PCB-methylsulfones bind specifically (Lund et al., 1986). In the present examination, about 50% of the subjects complained of cough or sputum, but no association was found between cough or sputum and blood PCB concentration. On the other hand, although the number of subjects with abnormal breath sounds was only seven (2.7%), an association with blood PCBs was suggested in the K-S test.

The skin symptoms in Yusho patients demonstrated satisfactory improvement during the first two years after outbreak, although they still persisted in non-exposed area, such as the genital region (Toshitani, 1972). However, those areas have also shown a tendency toward gradual improvement (Toshitani et al., 1987). Altogether, the skin symptoms are the most important features for Yusho, both at the time of outbreak and at present. From among 15 examination items in dermatology (No. 14–28 in Table 8.1.), an association with blood PCB concentration was clearly observed for comedones in the face and trunk, while it was suggested for acneiform eruptions in the genital regions. As for comedones in the face and trunk, a dose-dependent risk increase was indicated among the four levels of blood PCBs, with a distinctive risk increase at the blood PCB level of 6.1 ppb. Among five regions with acneiform eruptions (No. 19–23 in Table 8.1.), an association with blood PCBs was suggested only in the genital regions, although the proportion of subjects with acneiform eruptions in the genital regions was the same as that in the

face. These findings may be related to a previous report which showed persisting acneiform eruptions in non-exposed areas, in contrast with the favorable progress in exposed areas, such as the face (Toshitani, 1972). None of the eye symptoms showed any significant association with the blood PCB level, although they were the most characteristic signs for Yusho at the time of outbreak (Urabe et al., 1979).

8.4.4. Association of Blood PCBs with Serum Triglyceride

No laboratory blood test revealed any association with the blood PCB level except for serum triglyceride, although γ-GTP and bilirubin are listed in the diagnostic criteria for the chronic phase patients. The correlation between PCB exposure and serum triglyceride has been a great concern since the outbreak of Yusho. The most prominent finding in the blood tests was the elevated serum triglyceride (mean; 197.2 mg/dl), which was so striking that serum specimens frequently showed lactescence (Okumura and Katsuki, 1969). When the routine measurement on blood PCBs started in 1973, the mean blood PCBs was reported to be 6.7 ppb in Yusho patients compared to 2.8 ppb in normal subjects, and a positive correlation was indicated between blood PCBs and serum triglyceride among patients (Masuda et al., 1974; Okumura et al., 1974).

A study on workers occupationally exposed to PCBs reported a correlation between blood PCBs and serum triglyceride (Takamatsu et al., 1984). In that study, the workers, who were engaged in making marine paints, showed blood PCB concentrations beyond 20 ppb, with the highest value of 252 ppb. In the episode of Taiwan's outbreak of PCB poisoning in May 1979, patients continued to be detected up until March 1981, and they also showed a positive correlation between blood PCBs and serum triglyceride. The blood PCB concentration was reported to be 89.14 ± 6.90 ppb (mean ± SE) ranging 3–1,156 ppb, with no significant difference between sexes nor among age-groups. The serum triglyceride levels were significantly different between the patients and normal subjects (mean; 201 vs. 123 mg/dl), in which 60% of patients showed levels of 150 mg/dl or over (Chang et al., 1980; Ko et al., 1981).

In the present examination, a weak but statistically significant correlation between blood PCBs and serum triglyceride was also observed, with similar values in both Pearson's and Spearman's correlation coefficients, which suggests that the observed correlation was not due to potential outliers. In interpreting this positive association, it might be possible to consider, based on the high affinity of PCBs into fat, that greater serum triglyceride levels brought about a higher blood PCB concentration. However, there have been many studies which advocate the role of PCBs in raising the serum triglyceride levels.

In early studies on Yusho patients with abnormally elevated serum triglyceride

ranging from 200 to 600 mg/dl, agarose gel electrophoresis of serum indicated that the increased triglyceride was of an endogenous origin, and that the remarkable elevation of serum triglyceride was due to an increased pre-β-fraction (Uzawa et al., 1969; Okumura and Katsuki, 1969; Okumura, 1984). The intensive assessment of the serum lipids among patients showed a striking elevation of triglyceride, but not of cholesterol or phospholipids (Nagai et al., 1969). In addition, an animal experiment, in rats treated with chlorobiphenyls (0.1 g p.o./kg/day) for 4 weeks, demonstrated that a ten times greater serum triglyceride levels were detected as compared to the controls (Tanaka et al., 1969). In the episode in Taiwan, it was hypothesized that the extent of abnormal lipid metabolism is paralleled by the increasing enzyme activity of UDP-glucuronyl transferase in the liver (Chang et al., 1980; Ko et al., 1981; Lü and Wong, 1984).

Thus, it is reasonable to consider that the elevation of serum triglyceride was the event following, but not preceding, a high level of blood PCBs, and that the association between serum triglyceride and blood PCBs was not simply attributable to the high affinity of PCBs into fat. In fact, in the present study, the mean serum cholesterol adjusted for age and sex showed no gradient elevation with increasing PCB concentrations; 185.0, 203.1, 215.1 and 201.4 mg/dl at < 2.7, 2.7+, 4.1+, and 6.1+ ppb, respectively.

8.4.5. Interpretation of the Positive Association of Blood PCBs with the Symptoms or Signs and Serum Triglyceride

Several years after the outbreak, the average concentrations of PCBs in the adipose tissue, liver, and blood of patients were 1.9 ppm, 0.08 ppm, and 6.7 ppb, respectively, which were only about two times higher than those of ordinary persons (Masuda et al., 1974). Therefore, the major portion of the PCBs ingested by the patients had been eliminated from the bodies, while the remaining PCBs showed a peculiar pattern in the components of PCB congeners as compared to that of the normal subjects; higher concentration of 2,3,3′,4,4′,5-hexa-CB, and lower concentration of 2,3′,4,4′,5-penta-CB, in the blood (Kuroki and Masuda, 1977). Among about 40 PCDF congeners detected in the contaminated rice oil (Buser et al., 1978), main components retained in patients were 2,3,6,8-tetra-, 2,3,7,8-tetra-, 1,2,4,7,8-penta-, 2,3,4,7,8-penta-, 1,2,3,4,7,8-hexa-, and 1,2,3,6,7,8-hexa-CDF in the adipose tissue or liver (Kuroki and Masuda, 1978; Masuda and Yoshimura, 1984), whereas no detectable amount of PCDFs was demonstrated in the normal subjects (Nagayama et al., 1977). Thus, certain PCB isomers and PCB-related compounds, such as PCQs and PCDFs, which were determined in the causal oil and are specifically retained in the Yusho patients, have been suggested to be related to the pathogenesis of this persisting illness (Kunita et al., 1985).

The present health examination for Yusho patients at the chronic stage, twenty years after outbreak, revealed close associations with blood PCB concentration, for general fatigue; numbness in the extremities; and comedones in the face and trunk, all with a clear dose-response relation. A distinctive risk increase was observed at the PCB level of 2.7 ppb for these two subjective symptoms, and at the level of 6.1 ppb for skin symptoms. It has been reported that even healthy fishermen who frequently consume fish or shellfish show relatively high concentrations of blood PCBs (mean ± SD; 5.6 ± 3.2 ppb) (Baba T. and Baba H., 1981). Therefore, it is hardly possible that such a low level of blood PCBs correlates directly to the manifestation of such symptoms or signs, if the patients' blood PCBs are comparable in components to those of natural origin. Thus, it might be a more appropriate interpretation that the present blood PCB concentration is the general index for exposure, and that PCBs with a peculiar pattern in components and PCB-related compounds, such as PCQs and PCDFs, may thus have played a role in bringing about these associations. It is also plausible that the increased risk for subjective symptoms reflects the lasting discomforts of Yusho patients due to the previous acute exposure, and that a clear risk increase for skin symptoms at the level of 6.1ppb suggests the persisting effects of the previous acute exposure as well as the effects of the current internal exposure.

The association between blood PCBs and serum triglyceride so far reported has been based on studies of patients who are in either acute or subacute stages. A large part of the patients showed abnormally elevated levels in both PCBs and triglyceride. And in the present examination, a consistent result was shown among the patients twenty years after outbreak, in spite of the fact that their blood PCBs and serum triglyceride levels were relatively close to that of normal subjects. However, the coefficient of determination was at most 0.047 in the correlation analysis, and 0.070 in the multiple regression analysis. This may indicate that the present blood PCB concentrations explain only a small part of the variance in serum triglyceride which can be largely affected by other common factors, such as dietary or drinking habits (Phillips et al., 1981; Sekimoto et al., 1983), and/or that elevation of triglyceride with increasing blood PCBs is a peripheral event through far more meaningful but unknown events in the causal chain of this intoxication. The observation of a weak, positive association can thus be interpreted from two aspects; first, the small amount of PCBs, in which the components differ from those in normal subjects, or their related compounds, PCQs or PCDFs, retained in the patients, is possibly related to the increased levels of serum triglyceride; and second, this association may be a reflection of hypertriglyceridemia at the acute or subacute stages followed by prolonged remission.

Although a number of studies have been carried out since the outbreak of Yusho

in 1968 and the episode in Taiwan in 1979, the mechanism of this poisoning still remains unclear. However, the weak but significant association between blood PCBs and serum triglyceride observed twenty years after exposure might therefore suggest the role of lipid metabolism disturbance in the pathogenesis of this intoxication due to PCBs or their related compounds.

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