CHAPTER 9B1

Yusho

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9B1.1. Introduction

'Yusho' is a mass food poisoning caused by ingestion of a commercial brand of rice oil contaminated with polychlorinated biphenyls (PCBs), polychlorinated dibenzofurans (PCDFs) and polychlorinated quaterphenyls (PCQs), as revealed by the latest investigations (Tsukamoto et al., 1969; Nagayama et al., 1975, Miyata et al., 1978; Masuda and Kuratsune, 1979; Yamaryo et al., 1979). The poisoning occurred in Western Japan in 1968, involving more than 1,600 people, the majority of whom were residents of Fukuoka and Nagasaki prefectures (Ibayashi, 1979)

9B1.2. Results of epidemiologic and related studies

9B1.2.1. Descriptive epidemiologic studies

Early in October 1968, a newspaper announced an epidemic of a strange disease characterized by severe acne-like eruptions in Fukuoka prefecture, suggesting the ingestion of a brand of rice oil produced by K company (abbreviated as K rice oil) as its possible cause. We soon started an extensive epidemiologic investigation in order to clarify the cause of the disease which was diagnosed as chloracne by dermatologists (Kuratsune et al., 1969, 1972; Goto and Higuchi, 1969) Early subjective symptoms experienced by Yusho patients are listed in Table 9B1 1

Examination of 325 early patients soon demonstrated very unique characteristics of the distribution of the disease, that is, their distinct familial aggregation and their marked temporal clustering that nearly all of them had been affected between February and October 1968, with a distinguished peak of occurrence in summer

Kimbrough (ed.) Halogenated biphenyls, terphenyls, naphthalenes, dibenzodioxins and related products
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MONS 214307

TABLE 9B1.1
Frequency of early symptoms complained of by Yusho patients (Kuratsune et al. 1969, 1972)

Symptoms	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 palms	50.6	55.0
Acneform skin eruptions	87.6	82.0
Red plaques on the limbs	20.2	16.0
Itching	42.7	52.0
Pigmentation of the skin	75.3	72.0
Swelling of the limbs	20.2	41.0
Stiffened soles of the feet and palms of the hands	24.7	29.0
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

followed by its spontaneous sharp decline. Examination of the geographical distribution of the patients, however, did not indicate any common socioeconomic or environmental features which might be associated with the disease. Both sexes had been equally affected. Age- and sex-specific incidence rates indicated that all age groups were affected, although a considerably lower risk was apparent for both males and females over 60 years of age.

9B1.2.2. Analytical epidemiologic studies

In order to examine the suspicion that K rice oil might be involved in the disease, a thorough investigation was undertaken with regard to the cooking oil that the patients had used. It was discovered that all the patients had used K rice oil either in canned form or in bottled form, and regardless of where they lived, 166 of 170 patients who had used only canned K rice oil had used a very specific one, viz. that produced or shipped by the company on February 5 and 6, 1968. Investigation also revealed that for 143 of 155 patients who had used bottled K rice oil only, their use of the bottled K rice oil shipped between February 5 and 15, 1968 was highly probable. Furthermore, an attack rate as high as 63.9% was calculated for those who

MONS 214308

e et al., 1969, 1972)

	Females (n = 100)
)	
	75.0
	56.0
	55.0
	82.0
	16.0
	52.0
	72.0
	41.0
	29.0
	47.0
	93.0
	71.0
	55.0
	11.0
	74.0
	52.0
	39.0
	19.0
	19.0
	8.0
	39.0
	28.0
	17.0

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had consumed the above specific canned rice oil. It was also shown that 113 persons from 29 households who had regularly used K rice oil, but were not considered to have used the above specifically dated ones, were free of the disease.

In a case-control study, 121 pairs of patients and their randomly selected healthy controls matched individually by age, sex and place of residence to the patients were asked 60 questions concerning their occupation, medical background, health status, habits, custom, diet and other characteristics of their daily lives. Only one of these factors tested, namely the habit of "eating fried foods or tempura almost every day", was significantly commoner among the cases than among the controls. In an additional case-control study, cooking oils used were examined from 68 households with Yusho patients and from 207 control households without such patients being matched by place of residence to each of the case households. A highly significant difference was noted between the two groups only in regard to their regular use of rice oil, as shown in Table 9B1.2.

Thus, all these epidemiological approaches unanimously indicated that Yusho was probably caused by ingestion of the specific K rice oil.

9B1.2.3. Toxic agents in K rice oil

After an investigation for about 2 weeks, the Chemical Study Group on Yusho found that the canned K rice oil produced or shipped on February 5, 1968 and used by some of the patients had been contaminated with a large amount of Kanechlor 400, a brand of PCBs of chlorine content 48%, produced by Kanegafuchi Chemical Industry Company (Tsukamoto et al., 1969). Since no analytical methods specific for PCBs were available at that time, the concentration of Kanechlor 400 in the oil was estimated from its organic chlorine content to be 2,000–3,000 ppm. It was also demonstrated that the oil did not contain any significant amounts of Cu, Ni, Zn, Co, As, Hg, chlorinated naphthalenes, or pentachlorophenol. This contamination of the rice oil with PCBs was limited to the products from February 5, 1968, to the middle of the same month, with the highest contamination on February 5 and 6.

TABLE 9B1.2
Results of case-control study on fat and oils used

Fat or oil	Cases[a]		Controls[b]	
	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
Rapeseed 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

a 69 patient households
b 207 non-patient households

MONS 214309

(Tsukamoto et al., 1969; Kuratsune et al., 1972) Components of Kanechlor 400 were also readily found in various tissues of patients Thus, the results of the chemical analyses were completely consistent with the epidemiological findings

Kanechlor 400 had been used by K company for heating the rice oil over 200°C at a reduced pressure of 3–4 mmHg in a metal container in order to remove odorous matters from it at the final process of the production It is generally believed that Kanechlor must have leaked from the heating pipe and contaminated the processed oil, but the real mechanism of the contamination does not seem to have been solved yet

Three samples of the canned K rice oil used by the patients were recently reanalyzed by us for PCBs by using the government standard analytical method for PCBs, finding approximately 1,000 ppm PCBs in each of them (Nagayama et al., 1975, 1976). This concentration was much lower than was originally estimated from the content of organic chlorine. There must be a fairly large amount of chlorine-containing compounds other than PCBs in the oil. Thus, we analyzed the above samples of the oil for PCDFs and polychlorinated dibenzodioxins.

As shown in Table 9B1.3, the oil contained on average 5 ppm of PCDFs, about 250 times the concentration (0.020 ppm) expected from the concentration of PCDFs in the unused Kanechlor 400 (Nagayama et al., 1975, 1976) This finding was also confirmed by Miyata et al. (1977). This marked increase of PCDFs in the rice oil relative to its PCBs content could be ascribed to the fact that the oil had been contaminated with Kanechlor 400 heated at higher than 200°C to be used as the heat-transferring agent for a prolonged period of time, since PCBs could be converted to PCDFs by heating (Miyata and Kashimoto, 1978). The deodorizing process to which the rice oil was subjected, as already mentioned, is also probably connected with this relative increase of PCDFs.

According to Rappe et al. (1979), the Yusho oil contains more than 40 PCDF isomers, including as their major components highly toxic 2,3,7,8-tetra- and 2,3,4,7,8-pentachlorodibenzofurans. In view of the well known high toxicity of these PCDFs and their strong inducing activity of drug-metabolizing enzymes, the

TABLE 9B1.3
Concentrations of PCBs and PCDFs and their ratios in various materials

Materials	PCBs (ppm[b])	PCDFs (ppm[b])	PCBs/PCDFs
Kanechlor-400 (unused)	1,000,000	ca. 20	50,000
Yusho oils[a]	ca. 1,000	5	200
Yusho patients[c]			
Adipose tissue	1.3	0.009	144
Liver	0.05	0.013	4

a Produced on February 5 or 6, 1968
b On whole base
c Two patients who died in 1969 and one patient who died in 1972 were included

MONS 214310

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PCBs/PCDFs
50,000
200
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above fact seems to be important. Contrary to PCDFs, no polychlorinated dibenzodioxins were detected in the Yusho oil.

Although the presence of PCDFs cannot be overlooked, they cannot represent the whole of the unidentified organo-chlorine compounds in the oil, because their concentration is small. There must be still other organo-chlorine compounds in the oil. Miyata et al. (1978) and Kamps et al. (1978) found that the toxic rice oil produced or shipped on February 5 and 6, 1968, contained PCQs. Their concentration was as high as that of PCBs, that is, 866 ppm according to the former authors. Thus, it became clear that the major components of the unidentified organo-chlorine compounds in the oil were PCQs. Although the toxicity of PCQs is not clear yet, the possible significance of the above facts should not be dismissed.

9B1 2.4. Consumption of the oil by patients and dose–response relationship

Selecting 146 patients who were known to have used the specific canned K rice oil of February 5 and 6, 1968, we made a rough estimate of their consumption of the oil, disregarding age, sex, amount of food intake and possible losses of oil during and after cooking (Yoshimura, 1971). The average personal oil consumption was calculated to be about 800 ml which should have contained about 2 g of PCBs if the oil was assumed to have contained 2,000–3,000 ppm of Kanechlor 400 according to the original determinations. Furthermore, a dose–response as well as a dose–effect relationship were clearly seen between the intake of the toxic rice oil and the incidence of the poisoning and between the intake and the clinical severity of the poisoning.

As already mentioned, it was later shown that the PCB concentration of the oil was much lower than was originally estimated and the oil contained toxic agents other than PCBs in a significant amount. Consequently, our original data were reanalyzed, using somewhat different assumptions from those used in the former analysis, and taking the age, sex and food intake of the patients into consideration (Hayabuchi et al., 1979). The total amounts of PCBs, PCDFs and PCQs taken by the patients were, on the average, 633, 3.4 and 596 mg, respectively, or 157, 0.9 and 148 μg/kg/day, respectively. The length of latent period of the poisoning was on average 7.1 days, with a range from 2.0 to 19.0 days. The amounts of PCBs, PCDFs and PCQs taken during the latent period were calculated to be, on average, 466, 2.5 and 439 mg, respectively. The smallest amounts of PCBs, PCDFs and PCQs taken by a patient during the latent period were estimated to be 11.1, 0.6 and 10.5 mg, respectively, and the smallest doses 2.9, 0.16 and 2.7 μg/kg/day, respectively.

A highly significant negative correlation was seen between the latent period and the amount of oil consumed per kg per day. Another notable fact was that the clinical severity of the patients showed a close positive correlation with the total amounts of the oil consumed but not with the amount of oil consumed per kg per day in adult males and females aged 20 to 44 years (Hayabuchi et al., 1979). This observation seems important because it may indicate a general rule that exposure to a toxic agent with a strong persistency in the body is better represented by the total dose taken than by the dose per kg per day as commonly practised.

MONS 214311

9B1.2.5 Deaths among Yusho patients

According to Urabe (1974), a total of 22 deaths occurred among 1,200 Yusho patients up to September 13, 1973. Malignant tumors accounted for 41% of the deaths. Among these deaths from malignant neoplasms, two were from liver cancer. One of these cases also had a stomach cancer. The deaths from liver cancer occurred within 3 years after exposure. In 1977, an additional autopsied case of liver cancer was reported. At present, it has not been established what the mortality rate of cancer among Yusho patients is. No reliable analysis of deaths has been made by following the patients' illness for an adequately long period of time.

9B1.3. Clinical features of Yusho

9B1.3.1. PCBs, PCDFs and PCQs in tissues of Yusho patients

As shown in Table 9B1.4 the PCB concentrations in the adipose tissues of 3 Yusho patients who were examined soon after they had become ill were very high as compared to controls. Most of these PCBs retained in the tissues were eliminated relatively rapidly. The concentrations of PCBs in the adipose tissues of 3 other patients who died one year later were much lower than those of the above cases. The

TABLE 9B1.4
Concentration of PCBs in tissues of patients with Yusho or other diseases

Case	Sex	Age	Time of death or surgical operation	PCB concentration (ppm)[b]			
				Adipose tissue		Liver	
				Whole base	Fat base	Whole base	Fat base
1	F	still-born	Oct. 1968	0.02	0.1	0.07	
2	M	high-school student	Nov. 1968	76 (face) 13 (abdomen)			
3,4	M,F	adult	Nov. 1968	32,46 (cheese-like substance from acneform eruptions)			
5	M	17	July 1969	1.3	3.7	0.14	9.5
6	M	25	July 1969	2.8	15.1	0.2	10.4
7	M	73	Nov. 1969	3.8	8.4	0.07	3.1
8	F	48	Dec. 1970	0.7	0.9	0.07	1.3
9	M	46	May 1972	1.3	6.5	0.08	8.4
10	F	33	Sept. 1972	1.9	2.9		
11	M	72	Apr. 1975	0.2	0.4	0.04	3.0
12	M	59	Mar. 1977	1.2	1.4	0.006	
13	M	69	Sept. 1977	0.8	1.1	0.02	
Controls[a]	M,F	0–61	1973	av. 1.0	av. 2.3	av. 0.05	

a 31 patients with diseases other than Yusho

b Calculated as Kanechlor-500 + Kanechlor-600 (1:1)

MONS 214312

d among 1,200 Yusho pa-
counted for 41% of the
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es			
)[b]			
		Liver	
Fat base		Whole base	Fat base
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s)			
3 7		0 14	9 5
15 1		0 2	10 4
8 4		0 07	3 1
0 9		0 07	1 3
6 5		0 08	8 4
2 9			
0 4		0 04	3 0
1 4		0 006	
t 1		0 02	
v 2 3	av	0 05	

concentrations of PCBs in subsequently deceased patients were also low, hardly different from those of the controls A similar trend of PCB concentration was also noted for the liver

Table 9B1 5 shows the concentrations of PCBs in the blood of the Yusho patients, normal persons, and workers of a chemical industry (Masuda et al , 1974b, Hasegawa et al , 1972, Okumura et al , 1979) It is clear that the PCB levels of the patients were still higher than those of normal persons more than 5 years after the poisoning but not remarkably so This is more evident if these figures are compared with those of workers occupationally exposed to PCBs. It is interesting to note that most of these Yusho patients were still suffering frum dermal signs and various symptoms peculiar to Yusho, while the majority of the workers were free of such symptoms in spite of their extremely high blood PCB levels These facts indicate that various signs and symptoms complained of by Yusho patients can hardly be explained by the current levels of PCBs in their bodies alone

Quantitatively speaking, the PCBs retained in the bodies of the Yusho patients are now close to those in normal persons, as already mentioned. We noticed in 1973, however, that they differed qualitatively in a great deal Fig 9B1 1 shows the peculiar gas-chromatographic pattern of the PCBs retained in the tissues and blood of the patients. When 41 patients with Yusho visiting our university hospital were examined, 24 (58 5%) of them showed the so-called type A gas-chromatographic pattern which was characteristic of severe cases of Yusho, while 15 (36 6%) showed the type B pattern, which is an intermediate one between the type A and the normal one, and only 2 (4 9%) showed the normal pattern commonly seen in the general population (Masuda et al., 1974a). These peculiar gas-chromatographic patterns of PCBs persist and can still be seen in most of the Yusho patients even now, greatly facilitating the differential diagnosis of Yusho Table 9B1 6 shows that the composition of PCB isomers present in the blood of Yusho patients is quite different from

TABLE 9B1 5
PCBs in the blood of patients with Yusho and others

Subjects	No of subjects	Year	PCBs (ppb)[a]	
			Mean ± S D	Range
Yusho patients	41	1973	7	2–26[c]
	116	1974	7 0 ± 5 4	1–31
	79	1976	6 2 ± 4 7	1–32[c]
	92	1977	5 3 ± 3 7	1–21[c]
Normal persons	37	1972	3	1–[illegible][d]
Workers[b]	23	1972	364 ± 262	60–920

a Whole base

b Workers engaged in the production of Kanechlor 200–600 inhaling the air containing 0 05–0 2 mg/m³ of PCBs (Kanechlor-300 + Kanechlor-400 (1 1)) Two of them showed dermal signs (Hasegawa et al , 1972)

c Okumura et al (1979)

d Masuda et al (1974b)

MONS 214313

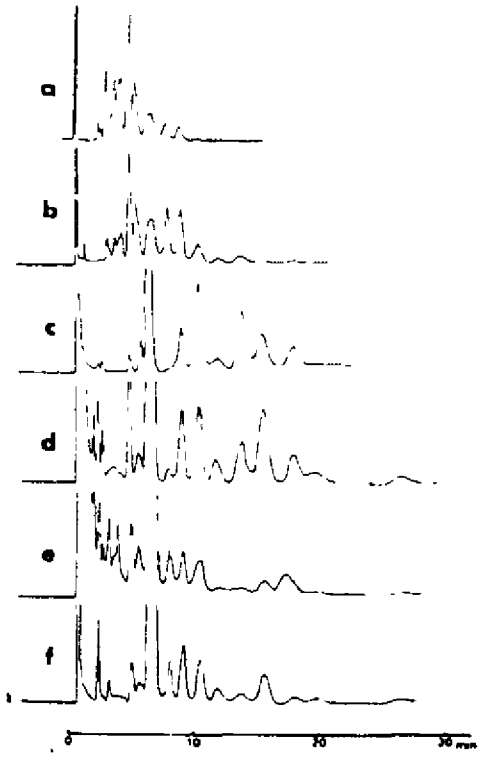

Fig 9B1 1. Gas-chromatograms of PCBs in various specimens a, unused Kanechlor-400, b, PCBs in the toxic K rice oil; c, PCBs from the blood of a Yusho patient, pattern A, d, PCBs from the blood of a Yusho patient, pattern B; e, PCBs from the blood of a Yusho patient, pattern C, f, PCBs from the blood of a normal person

TABLE 9B1 6
Concentrations of PCB isomers in the blood of Yusho patients and normal persons

PCB isomers	Concentration in blood (ppb)[a]	
	Yusho patients (n = 9)	Normal persons (n = 7)
2,4,5,3',4'-Pentachloro-	0 13 ± 0 05	0 22 ± 0 09
2,3,4,3',4'-Pentachloro-	n d [b]	0 05 ± 0 02
2,4,5,2',4',5'-Hexachloro-	0 52 ± 0 22	0 15 ± 0 07
2,3,4,2',4',5'-Hexachloro-	0 65 ± 0 21	0 17 ± 0 07
2,3,4,5,3',4'-Hexachloro-	0 28 ± 0 07	0 04 ± 0 02
2,3,4,5,2',4',5' Heptachloro-	0 44 ± 0 15	0 12 ± 0 07
2,3,4,5,2' 3',4'-Heptachloro-	0 28 ± 0 09	0 11 ± 0 04

a. Mean ± Standard deviation
b n d = less than 0.01 ppb

MONS 214314

normal persons. It may be noteworthy that 2,3,4,5,3',4'-hexachlorobiphenyl, which is known to have a strong inducing activity of drug-metabolizing enzymes, is present in the patients' blood at a much higher level than in the blood of normal persons (Kuroki and Masuda, 1977)

A significant positive association was noted between the gas-chromatographic patterns or concentrations of PCBs in the blood of Yusho patients and their serum triglyceride concentrations, severity of dermal lesions, ocular signs, pigmentation of the oral mucosa, respiratory symptoms, and subjective symptoms such as headache and paresthesia of the limbs (Okumura et al., 1974, Kōda and Masuda, 1975, Ohnishi and Yoshimura, 1977; Fukuyama et al., 1977; Shigematsu et al., 1977, Iwashita et al., 1977).

As shown in Table 9B1.3 the adipose tissue and the liver of Yusho patients who died in 1969 or 1972 contained on average 0.009 ppm and 0.013 ppm of PCDFs, respectively. According to Miyata et al. (1977), tissue samples of the omentum and the liver of normal subjects contained at most 45 and 17 ppt of PCDFs, respectively. It is clear, therefore, that Yusho patients contained a far larger amount of PCDFs in the tissues than do normal persons. For PCB concentrations, however, there were no such great differences at all. It is also very interesting that in Yusho patients the PCDF concentrations were very close to those of PCBs in the liver and much closer than they were in the adipose tissue. This relative abundance of PCDFs in the liver was also noted in normal persons (Miyata et al., 1977). Rappe et al. (1979) analyzed the liver tissues from 2 Yusho patients, finding 9 isomers of PCDFs with 4–6 chlorine atoms. Most of the PCDFs present in the Yusho oil were not detected in the liver, but highly toxic 2,3,7,8-tetrachloro- and 2,3,4,7,8-pentachlorodibenzofurans that were the major PCDFs in the Yusho oil were also identified in the liver as its major components of PCDFs, together with 1,2,3,4,7,8-hexachlorodibenzofuran. These researchers noted that none of the isomers retained in the liver had two vicinal hydrogenated C atoms in either of the two carbon rings of the dibenzofuran system. Position of hydrogenated C atoms seems to be closely associated with the retention of PCDFs.

Recently, we were informed that Drs. H. Miyata and T. Kashimoto at the Osaka Prefectural Institute of Public Health succeeded in determination of PCQs in the blood and other tissues of Yusho patients at a similar level to that of PCBs. This suggests an urgent necessity to investigate the toxicity of these compounds.

Taking all the above findings into account, we have to realize the complex nature of Yusho which will not be explained by ingestion of PCBs alone. The fact that a considerable number of patients have suffered from severe clinical manifestations without quick improvements for a prolonged period of time even after their PCB levels in the blood and tissues had decreased nearly to background levels may be associated with the highly persistent toxic compounds other than PCBs, still retained in the patients' bodies.

9B1 3.2. Clinical symptoms and manifestations

Clinical features of Yusho are well summarized in the diagnostic criteria for Yusho

used Kanechlor-400, b.
ml, pattern A; d, PCBs
od of a Yusho patient,

rsons

l (ppb)[a]	
	Normal persons (n = 7)
	0.22 ± 0.09
	0.05 ± 0.02
	0.15 ± 0.07
	0.17 ± 0.07
	0.04 ± 0.02
	0.12 ± 0.07
	0.11 ± 0.04

MONS 214315

TABEL 9B1 7
The diagnostic criteria for Yusho (revised in October, 1972, translated by Kuratsune)

Yusho is considered as an acute or subacute poisoning with PCBs The general symptoms currently seen are retarded growth, neuroendocrine disturbances, phenomenon of enzyme induction disorders in the respiratory system, and disturbed lipid metabolism As the local symptoms, acneform eruptions and pigmentation as cutaneomucosal lesions and ocular symptoms are seen

1 Conditions of attack
Fact of ingestion of Kanemi rice oil contaminated with PCBs and familial occurrence seen in most cases

2 General symptoms
a Subjective symptoms
1 general fatigue
2 heavy headedness and headache
3 inconstant abdominal pain
4 feeling of numbness and pain at the limbs
5 swelling and pain at the joints
6 cough and sputum
7 changes in menstruation

b. Objective signs
1 bronchitis-like signs
2 sensory neuropathy
3 bursitis
4 inhibition in growth and abnormal teeth in children
5 Small For-Dates baby and pigmentation of the entire skin of newborns

c. Results from clinical examination
1 unusual patterns and concentration of PCBs in blood
2 increase of neutral lipids in blood
3 anemia, lymphocytosis, hypoalbuminemia
4 reduced conduction velocity of the sensory nerve and adrenocortical hypofunction

3. Cutaneomucosal signs
a Acneform eruptions
Black comedones and acneform eruptions which are seen at the face, buttocks and other inter triginous sites and their suppurative tendency

b Pigmentation
Pigmentation of the face, palpebral conjunctiva gingiva and nails of the fingers and toes

c Ocular signs
Swelling and hypersecretion of the Meibomian gland and palpebral edema

as revised in 1972 (Urabe, 1974) (Table 9B1 7) The criteria were further revised in 1977 but were essentially the same as the former ones (Sugiyama, 1977)

9B1 3 2.1. Dermal signs. The most notable manifestations of Yusho are dermal lesions such as marked enlargement and elevation of the follicular orifice, comedo formation, acneform eruptions, hyperpigmentation and hyperkeratosis (Goto and Higuchi, 1969, Urabe and Koda, 1976, Asahi et al , 1979) The acneform eruptions

MONS 214316

develop in the face, ear lobe, retroauricular region, external ear canal, axillae, trunk and external genitalia Marked enlargement and elevation of the follicular orifice with hyperkeratosis and formation of keratotic plugs occurs in the axillae, groin, glenoid regions, trunk, thigh, and outer aspect of the forearm Dark colored pigmentation of the gingivae, lips, oral mucosa and nails is frequently seen among Yusho patients The above dermal lesions improved fairly well in light cases in a few years after the intoxication but in severe cases there was a strong tendency for cyst formation which prevented their cure for many years

9B1.3.2 2 Ocular signs In the acute phase of Yusho, most patients showed severe ocular signs. The most prominent ones were hypersecretion of the meibomian glands and abnormal pigmentation of the conjunctiva The meibomian glands swelled like cysts and were filled with yellow infarct-like contents. The pigmentation of the conjunctiva was examined by electron microscopy and considered to be due to melanin deposits. No particular lesion was noted in the intraocular tissues (Iku: et al., 1969). The above signs have well subsided during the past 10 years but 84% of the 75 patients examined recently still showed abnormal changes of the meibomian glands, such as their irregular arrangements, atrophy, secretion of cheese-like material, infarction and lithiasis, and 43% showed pigmentation of the conjunctivae and eyelids. Sixty-four percent of the patients also complained of eye discharge (Kohno and Yamana, 1979)

9B1.3.2 3. Neurological signs. Most Yusho patients complained of various neurological symptoms such as headache, numbness at the limbs, hypoesthesia and neuralgic limbs Electroencephalographic examinations did not show any significant changes which might indicate some central nervous damage (Nagainatsu and Kuroiwa, 1971). However, a reduced sensory nerve conduction velocity of the radial and/or sural nerve was observed in 9 out of 23 cases examined soon after the poisoning, while a reduced motor nerve conduction velocity of the ulnar and tibial nerves was seen only in two cases (Kuroiwa et al., 1969) Thus, it seemed certain that the sensory fibers were preferentially affected in Yusho These findings were well in accord with the fact that the motor functions were intact in all the cases examined No follow-up study has been made for the above disturbed function of the sensory nerves by re-examining the conduction velocity, but according to the authors, the lesions seem to have disappeared relatively soon after exposure as indicated by the sequence of related symptoms and manifestations.

9B1.3.2.4 Endocrine signs One or two years after the onset of the poisoning, laboratory tests for endocrine functions were made for the patients. Rapid ACTH test performed in 86 patients gave no evidence of marked abnormalities of the adrenocortical function (Watanabe et al , 1971) Determination of 17-ketosteroids and 17-hydroxycorticosteroids in urine was made in 95 Yusho patients by Nagai et al (1971) About 40% of the patients showed an elevated excretion of these

MONS 214317

steroids, as possibly caused by the poisoning. Kusuda (1971) observed irregular menstrual cycles in about 60% of the female patients and abnormal patterns of the basal body temperature (mainly inadequate luteal phase and prolonged low phase) in 85% of them, which suggested the existence of corpus luteum insufficiency and retarded follicular maturation Urinary excretion of estrogens and pregnanediol was also found to be low in the patients. All the above facts indicate that endocrine disorders were present in some patients although not extremely severe

9B1.3.2 5. Respiratory signs. Shigematsu et al. (1971) reported that about 40% of the patients complained of persistent cough with sputum production, suffering from chronic bronchitis. Most of such patients were afebrile, with little change in leucocyte count or erythrocyte sedimentation rate, but secondary respiratory infections were often observed. Their serum IgA and IgM, especially the former, were lower PCBs were proved to be present in the sputa from these patients with respiratory troubles (Kojima, 1971, Shigematsu et al., 1977). The respiratory symptoms seem in general to be improving, but extremely slowly as shown by a follow-up study of 79 cases for about 5 years by Shigematsu et al. (1977) which indicated that 26, 21, 38 and 15% of the cases were free of the symptoms with aggravated, unchanged or improved symptoms in 1972–73, respectively, while the corresponding proportions were 15, 16, 49 and 19% in 1974–75.

9B1.3.2.6. Changes of the liver. Contrary to our expectation, Yusho patients have hardly shown any abnormalities of the liver in gross appearance or in routine function tests such as bilirubinemia, SGOT, SGPT, BSP retention and some others However, a marked proliferation of the smooth endoplasmic reticulum and a distinct reduction of the rough endoplasmic reticulum were noted by electron-microscopy of liver biopsy specimens from a patient (Hirayama et al., 1969). These phenomena were considered to indicate a stimulated induction of drug-metabolizing enzymes occurring in the liver of Yusho patients, as expected from the observations of animals administered PCBs (Nishihara and Yamamoto, 1972) Alterations of the mitochondria such as morphological heterogeneity, and frequent appearance of giant mitochondria and inclusion bodies which are probably connected with the disturbed metabolism of fatty acids were also observed in the liver (Yamamoto et al., 1971). Thus, morphologically speaking, the liver of Yusho patients cannot be said to be intact, although hardly any notable changes were detected by light microscopy.

9B1.3 2.7. Hyperglyceridemia In the early stage of the poisoning, markedly elevated serum triglyceride was one of the few abnormal laboratory findings peculiar to the disease Uzawa et al (1969) observed serum triglyceride ranging from 200 to 600 mg/dl in 12 out of 24 cases, while the serum total cholesterol remained unchanged and phospholipids tended to be somewhat lowered This hyperglyceridemia persisted for several years in most of the patients. According to Okumura et

MONS 214318

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al. (1979), 24 Yusho patients who have regularly been examined every year during the past ten years have showed their serum triglyceride levels lowered to the normal range, approximately since 1973 in females and since 1975 in males

9B1 3 2.8. Babies born to patients and to non-affected wives of patients and babies breast-fed by patients. Eleven wives with Yusho and two unaffected wives of patients delivered 11 live and two stillborn babies in 1968, 10 of whom had unusually dark-brown colored skin with a marked increase in melanin pigment in the basal cells of the epidermis (Taki et al., 1969; Yamaguchi et al., 1971, Funatsu et al., 1971) A similar pigmentation of the gingivae and nails and increased discharge of eyes were also noted in most of these cases A chemical analysis of tissue specimens from one of the stillborn babies showed, however, that the concentration of PCBs in the skin, mesenteric fatty tissue and liver were not high at all, being 0 11, 0 02 and 0.07 ppm on a wet-weight basis, respectively (Table 9B1 4). As the babies grew older, the skin pigmentation gradually faded. Yoshimura (1974) reported a mother with Yusho who delivered 3 babies with dark-brown colored skin within 3 years after exposure. The last baby's skin was only slightly colored He also reported a particular case of a Yusho baby affected by the ingestion exclusively of the milk from his mother with Yusho.

Yusho is one of the most typical man-made health hazards Unfortunately, no effective treatments have yet been developed for it, except for the fasting therapy which seems to be fairly effective according to Imamura's observations (Imamura, 1975). Such a drastic treatment, however, requires great caution in application Not many of the patients can readily be subjected to it Although a general tendency of spontaneous recovery can be seen in most of the patients, it is often too slow and too vague, leaving a considerable number of patients still far from complete recovery even after more than ten years after the onset of the poisoning Further efforts on a world-wide basis to accelerate the recovery of these patients are highly desirable

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MONS 214319

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MONS 214322