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Some Problems on Health Effects of Polychlorinated Biphenyls

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Quantitative and qualitative analyses of polychlorinated biphenyls (PCB) were performed by gas chromatography and the relative peak height method. Samples for the determination of PCB were obtained from Yusho patients and from normal persons and after necropsy. The relative peak height ratio of PCB in the blood of Yusho patients was applied to differentially diagnose the disease, but it was difficult to detect the health effects of PCB taken in through the food chain. The pathological processes of PCB poisoning were not always accompanied by specific signs and developed rather insidiously. The higher chlorinated components of PCB were gradually accumulated into the human organism. It was especially important that PCB crossed the placenta barrier and was accumulated into the fetus. The fetus was the target for the biological concentration of PCB in the human body. The data from necropsy showed that PCB could also cross the blood–brain barrier. From the viewpoint of ontogeny and phylogeny, it is hard to deny the serious influence upon the next generation.

In 1968, there occurred, mainly in southern Japan, the so-called Kanemi Yusho Incident. From 14,000 to 15,000 persons were thought to be affected, with polychlorinated biphenyls (PCB) as the causative agent, but only about 1400 persons have been diagnosed as having Yusho disease.

As the classification of the disease by Umeda (1972a, 1973a) has shown, the development of the disease ranged widely from typical poisoning to latent or vague health effects. Yusho disease was a typical PCB poisoning that had been caused by consuming food cooked in oil contaminated with Kanechlor 400, the main components of which were tetrachlorobiphenyls.

The intoxication was different from the occupational poisoning, which was brought about by exposure to pollutants by inhalation or direct cutaneous contact. Many problems remain which have not yet been resolved practically and theoretically in the medical field, because the Kanemi Yusho Incident was indeed unprecedented in the history of medicine. It was suggested that higher chlorinated biphenyls and their metabolites might still be producing unknown effects in the human organism.

We began to study the Yusho disease in 1969 and discovered several fundamental principles in the pathological processes of PCB poisoning and probable relationship between environmental pollution with PCB and its health effects. The fetus is considered to be the target for PCB concentration in the human body, and, from the standpoint of the health effects of environmental pollutants, we describe in this report the particular problem of fetal contamination with PCB because this problem is the most serious matter for the coming generation.

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MATERIALS AND METHODS

Blood samples were collected by venipuncture from patients and controls, tissue samples were obtained after necropsy or from surgically removed materials, and placentas were supplied by volunteers after spontaneous delivery or stillbirth.

PCB was determined by gas chromatography. The analysis was carried out using a Shimazu GC-5A chromatograph equipped with an electron-capture detector fitted with a 2-m by 3-mm coiled glass column packed with 2% SE-30 on Chromosorb W (AW-DMCS), 100–120 mesh. The nitrogen flow rate was 50 ml/min and the oven was operated at 200°C. The injector and detector temperatures were adjusted at 250 and 210°C, respectively.

Quantitative analysis was made by peak height measurements. Each peak height in the gas chromatogram was compared with that of peak 16 in Fig. 2, and the relative peak height ratio was calculated by the following formula (Nakajima *et al.*, 1974a).

$$R_{Ph_i} = Ph_i/Ph_{16}$$

where R_{Ph_i} is the relative height ratio of peak i to peak 16, Ph_i is the height of peak i, and Ph_{16} is the height of peak 16.

The lipoperoxide in human blood serum was determined by the thiobarbituric acid (TBA) reaction. The TBA reaction was carried out according to the method of Yamasaki (1972). The absorbance at 535 nm obtained by this method was recorded as the TBA value. The analysis was made on 73 samples from Yusho patients and on 19 samples from normal individuals.

RESULTS AND DISCUSSION

The clinical picture of Yusho disease (Umeda, 1972a, 1973a) has become extremely complicated, and this is probably due to the effects of higher chlorinated biphenyls and their metabolites in the organism. Some investigations were made on the relationship of the changes in clinical findings to the quantity and quality of PCB in the blood.

As indicated in Table 1, the concentrations of blood PCB in Yusho patients were higher than those in controls in 1972 ($P < 0.05$) and in 1973 ($P < 0.05$). In 1974, however, there was no significant difference between them. In this way, the

TABLE 1

CONCENTRATIONS OF PCB IN HUMAN BLOOD SAMPLES[a]

	Yusho patients			Controls		
	1972	1973	1974	1972	1973	1974
Mean[b] ± SD	13 ± 11[c]	10 ± 6[c]	5 ± 3	4 ± 2	5 ± 2	4 ± 1
Number of samples	18	23	96	17	8	18

[a] A 3-year comparison of Yusho patients with controls.
[b] Mean value of PCB concentrations in parts per billion on a wet weight basis.
[c] The difference from controls is statistically significant, $P < 0.05$.

concentrations of blood PCB in Yusho patients have gradually decreased year after year.

The relative peak height ratio of PCB isomers in the blood of Yusho patients and controls is shown in Fig. 1. There were differences in the peak height ratio between Yusho patients and controls, that is, the relative height ratio of peak 14 to peak 16 in the patients was lower than that in controls, but the ratio of peak 21 in the patients was

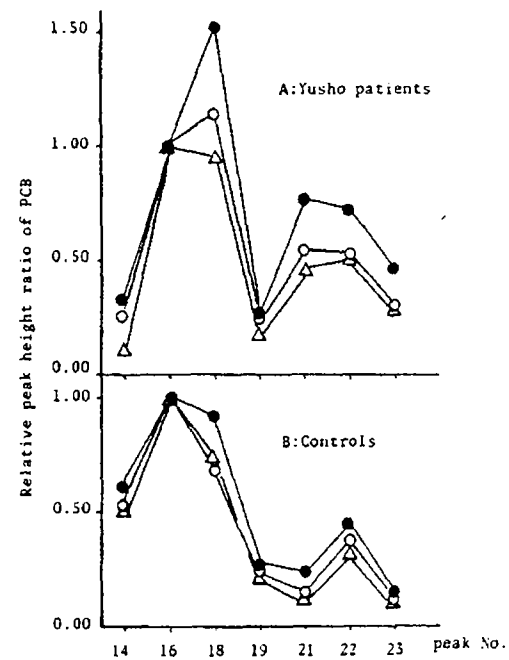

FIG. 1. Relative peak height ratios of PCB in human blood samples. Relative peak height ratio of various peaks is in relation to peak 16 = 1.00. Comparison of Yusho patients with controls for 3 years. ●, 1972; ○, 1973; △, 1974.

higher than that in controls. These differences have contributed to diagnosing Yusho disease.

Epidemiological surveys in the Goto islands were made in 1972 to establish the relationship between environmental pollution with PCB and its effects upon the inhabitants. As indicated in Table 2, the concentrations of PCB in marine organisms were higher than those in human blood. The gas chromatograms of PCB in marine products and human blood are shown in Fig. 2. The relative height ratio of peak 14 to peak 16 in human blood was higher than that in marine organisms (visceral organs of

Sepioteathis lessoniana). As discussed later on the basis of analyzing human visceral organs (Fig. 4), it was suggested that the lower chlorinated biphenyls might be easily carried out of the body. The relative increase in higher chlorinated isomers in marine animals was extremely important in the light of health effects of pollutants through the food chain.

TABLE 2

CONCENTRATIONS OF PCB IN HUMAN BLOOD SAMPLES AND IN MARINE ORGANISMS[a]

Type of sample	Number of samples	PCB
Human blood		
Tamanoura		
Controls	19	5 ± 2
Possible cases[b]	19	7 ± 3
Probable cases[b]	27	8 ± 4
Naru		
Possible cases[b]	20	6 ± 4
Probable cases[b]	4	5 ± 2
Classical cases[b]	19	12 ± 5
Marine organisms		
Caranx equula		
Muscles	1	130
Visceral organs	1	100
Trachurus japonicus		
Muscles	1	110
Visceral organs	1	110
Sphyraena japonica		
Muscles	1	110
Visceral organs	1	420
Sepioteathis lessoniana		
Muscles	1	150
Visceral organs	1	160

[a] Epidemiological surveys were performed in two regions, Tamanoura and Naru, in the Goto Islands in 1972. Values of PCB concentration are means ± SD in parts per billion on a wet weight basis.
[b] Of Yusho disease.

In this regard, a study was done on PCB contamination of the placenta and umbilical cord blood obtained from controls. As shown in Table 3, the concentrations of PCB in the various parts of the placenta were higher than those in the umbilical cord and in the blood. This fact showed that the accumulation of PCB into the placenta of controls could reflect the general condition of environmental pollution in Japan. Simultaneously, we were able to indicate a very important fact, that PCB does concentrate in humans, particularly in the fetus.

Table 4 shows the concentrations of PCB in various tissues obtained after necropsy of a stillborn baby born to the Yusho mother. PCB was accumulated specifically into

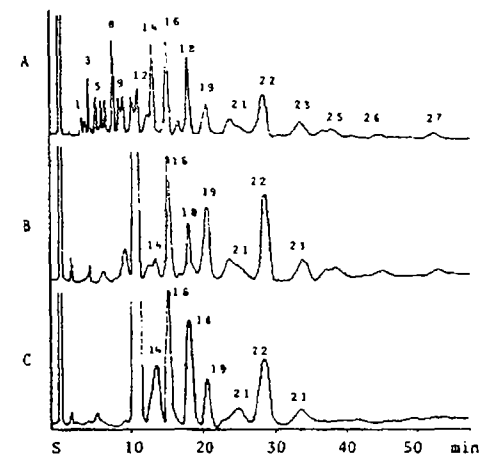

FIG. 2. Gas chromatograms of PCB in marine organisms and human blood samples. A, authentic sample (PCB, 300:400:500:600 = 1:1:1:1); B, marine organism (*Sepioteathis lessoniana*); C, human blood (one of the habitants).

the subcutaneous and adipose tissues of humans. The same results were obtained in normal adults (Nakajima *et al.*, 1974b), and the amount of PCB in them could indicate the environmental contamination as well.

Figure 4A shows a gas chromatogram of PCB in the liver of a control stillborn baby and Fig. 4B shows PCB in the liver of a stillborn baby with typical PCB poisoning born in 1968 to a mother with Yusho disease. Figures 4C and 4D show gas chromatograms of PCB in tissue obtained from a stillborn baby born in 1975 to the mother of the baby in Fig. 4B. This baby had no specific signs of PCB poisoning, such as the characteristic dark brownish skin coloration. Figure 4B shows many lower chlorinated components which resemble the causative material of Yusho disease.

TABLE 3

CONCENTRATIONS OF PCB IN SEVERAL CONTROL PLACENTAL PARTS

Samples	PCB[a]
Placental villi	11 ± 5
Umbilical cord	3 ± 1
Chorion and amnion	10 ± 9
Umbilical cord blood	4 ± 3

[a] Means ± SD of concentrations of five determinations in parts per billion on a wet weight basis.

On the other hand, most of the lower chlorinated components in Fig. 4C decreased, and higher chlorinated components relatively increased. As indicated in Fig. 4, many higher chlorinated components were detected in various parts of the brain of these babies. PCB was detected in the brains of adult Yusho patients as well (Nakajima *et al.*, 1975), and PCB diffusely infiltrated into the brain cortex and subcortical structure. The relationship between the phases of poisoning in mother and newborn baby is shown in Table 5. The physical signs in newborn babies did not always correspond to the phases of the disease in the mothers.

Adult Yusho patients have developed many complicated symptoms such as general tiredness, disturbance of recent memory, and drastic changes in behavior during the

TABLE 4

CONCENTRATIONS OF PCB IN VARIOUS TISSUES OF A STILLBORN BABY[a]

Sample	PCB[b]
Kidney	
Right	30
Left	23
Spleen	15
Liver	49
Bone marrow	3
Bile	13
Blood	8
Brain	
Temporal and occipital lobes	9
Frontal lobe	10
Limbic system	10
Subcutaneous adipose tissues	
Abdominal wall	806
Gluteal region	683

[a] Born in 1975 to a mother with Yusho disease.
[b] Concentrations of PCB in parts per billion on a wet weight basis.

past few years (Umeda, 1973b; Umeda and Takeuchi, 1973; Umeda *et al.*, 1975), all of which are characteristic aspects of the slow phase of the pathological processes of Yusho disease (Umeda, 1973c). To make the process of these general nonspecific reactions clear, we investigated lipoperoxide in blood serum of Yusho patients and controls. As shown in Fig. 5, a significant increase in serum lipoperoxide was obtained as the TBA value in the patients.

Most of the Yusho patients have complained of nervous symptoms, and PCB was detected in the brain. However, we never identified them with any change in the electroencephalograms of Yusho patients (Umeda, 1973d). Furthermore, it was deduced on the basis of the clinical observation and of the examination of transient ischemic attack (Umeda, 1972b) that PCB brought about some change in the central nervous system. To resolve this problem, we administered the Uchida–Kraepelin psychodiagnostic test to the patients and controls. The study was conducted on 45

Yusho patients and 69 normals. The rate of the rest effect was calculated by the following formula.

$$R = (m_2/m_1) \times 100,$$

where R is the rate of the rest effect and m_1 and m_2 are the scores before and after the rest. The distribution of the rate of the rest effect is shown in Fig. 6. The rate of the rest effect in the patients was significantly lower than that in controls. It became

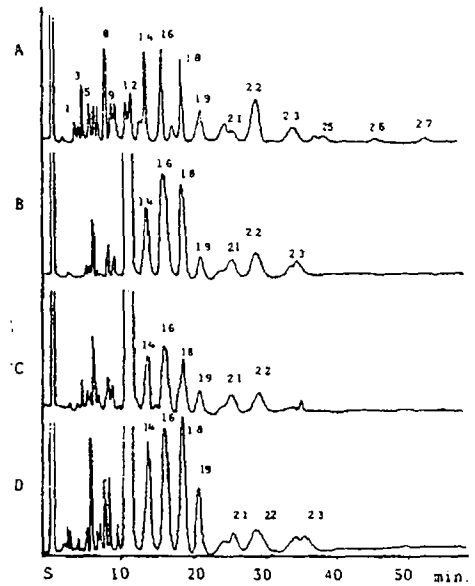

FIG. 3. Gas chromatograms of PCB in several parts of placenta and others obtained from controls. A, authentic sample (PCB, 300:400:500:600 = 1:1:1:1); B, placental villi; C, chorion and amnion; D, umbilical cord blood.

obvious that PCB brought about the functional disorders in the higher parts of the central nervous system, especially the cerebral cortex. From the viewpoint of ontogenesis and phylogenesis, this is a serious matter, because the brain cortex of the fetus is less resistant to harmful materials such as PCB.

SUMMARY

We reported clinical studies on Yusho disease and epidemiological surveys on the contamination with PCB of humans and of the environment:

(1) Yusho disease is caused by the ingestion of contaminated cooking oil with PCB, and the clinical picture changes into a more complicated one after the onset of the disease. On the basis of studies on Yusho disease, it has been shown that it is very

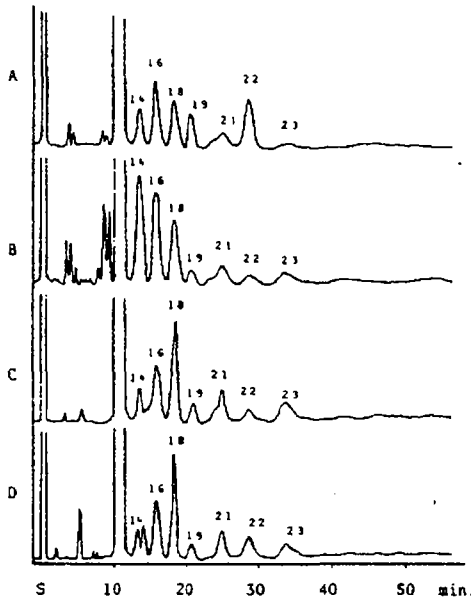

FIG. 4. Gas chromatograms of PCB in a stillborn baby. A, liver (control, 1968); B, liver (born to a manifest-type mother with Yusho disease, 1968); C, liver (born to the same mother as in B, 1975); D, limbic system (the same case as in C, 1975; other parts of the brain showed the same pattern as in D in the gas chromatogram). A and B were provided by Professor M. Kikuchi, Fukuoka University School of Medicine.

TABLE 5

RELATIONSHIP BETWEEN POISONING PHASES IN MOTHER AND NEWBORN BABY

Case[a]	Mother, phase of disease	Newborn baby, resulted in
1	Latent, free of symptoms	Typical manifest[b]
2	Manifest, mild	Atypical, free of symptoms
3	Manifest, moderate	Manifest, mild
4	Manifest, advanced	Typical manifest[b]
5	Manifest, poor in symptoms	Fetuses aborted, the same levels of PCB concentrations
6	Manifest, advanced	

[a] 1, mother was of latent-type poisoning and had no symptoms, but delivered a typical manifest type; 2–4, newborn babies reflected well the seventy of the disease in the mothers, ranging from atypical to typical poisoning; 5 and 6, PCB concentrations in both fetuses (3 and 4 months old) were at the same levels independently of the symptoms and signs in the mothers.

[b] Characteristic dark brownish skin coloration.

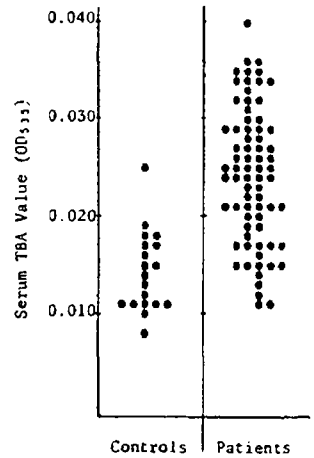

FIG. 5. Lipoperoxide levels as the TBA value of blood serum of Yusho patients and controls. Means ± SD: Yusho patients, 0.025 ± 0.007 (n = 73); controls, 0.014 ± 0.004 (n = 19).

difficult to detect clearly the health effects of PCB taken in through the food chain because PCB intoxication is not always accompanied by specific physical signs, as the classification of Yusho disease by Umeda had indicated.

(2) Quantitative and qualitative analyses of PCB in the blood were done to diagnose Yusho disease, particularly its visceral and latent types of poisoning, which are

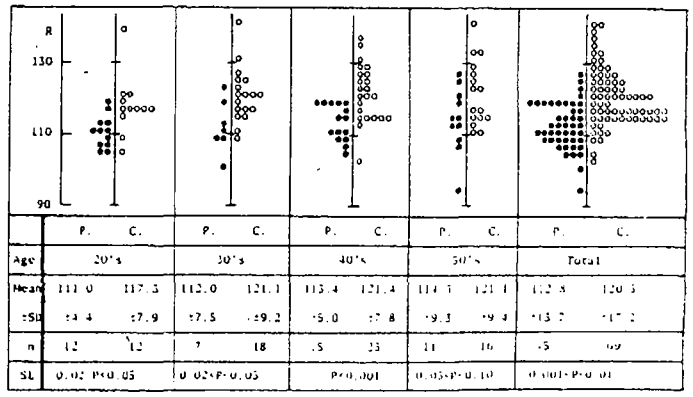

FIG. 6. Distribution of the rate of rest effect. P, patients; C, controls; SL, significant level. $R = (m_2/m_1) \times 100$, where R is the rate of rest effect and m_1 and m_2 are the scores before and after the rest.

composed mainly of nonspecific pathological processes. However, to analyze the pathophysiological changes in the human organism as a whole, further examinations are needed, for example, of lipoperoxide as the TBA value in blood serum and in other organs.

(3) The fetus is considered the target for PCB concentration in humans because PCB induced fetopathy, and the data obtained after necropsy have indicated that PCB crossed the placental barrier and accumulated into the fetus.

(4) Simultaneously, it was very important that PCB was detected in the brains of adults and stillbirth infants, because this makes it clear that PCB could also cross the blood–brain barrier. The cerebral cortex is the youngest part of the central nervous system and, from the standpoint of ontogenesis and phylogenesis, is less resistant to hazardous agents. Therefore, it is hard to deny the serious influence of PCB on the next generation.

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Radionuclide Movement in an Ecological Chain

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Radioactive substances create a considerable hazard, as they move through the environment of man and form an ecological chain. The first link of this chain is atmosphere; the next links are formed by water, soil, plants and animals. At the end of the chain is man. The present paper provides a model of strontium-90 and cesium-137 transfer from the atmosphere to man over Wroclaw (Poland) and its vicinity. It was found that air contamination is responsible for contamination of the remaining media. This correlation is shown in terms of mathematical formulas. Strontium-90 determinations were made in samples by using radiochemical methods, while Cs-137 was determined by spectrometry. The apparatus employed was made in Poland. Our testing methods and apparatus have gained a high mark in the Intercomparison Runs sponsored by IAEA.

Radioactive substances create a special form of contamination. The noxiousness of those substances considered to be a hazard for the natural environment is well known. However, the development of nuclear engineering, as well as nuclear weapons tests, and the search for new and cheap power sources have considerably increased the concentration of radionuclides in particular environment media. Radioactive contamination is known to move through the environment and form an ecological chain. The first link of the chain from which radionuclides begin to move is atmosphere. The subsequent links are formed by fallout, soil, water, plants, and animals, respectively. At the end of the chain is man, constituting the last link in the system.

Of the many radionuclides present in the atmosphere, strontium-90 and cesium-137 require special attention. These radionuclides are characterized by a long half-life period. That is why we have chosen to use these when carrying out investigations intended to give an idea of the movement of radioactive pollution in an ecological chain.

Studies and measurements concerned with this problem were performed at the Environment Protection Engineering Institute of the Technical University of Wroclaw (Poland) during the last 5 years. Measurements were carried out continuously in the city centre of Wroclaw (Głowiak and Pacyna, 1974a). Results obtained from investigating the ^{90}Sr and ^{137}Cs concentrations in the atmosphere during the recent 3 years are shown in Fig. 1.

An analysis of those data indicates the appearance of a maximum concentration in the spring months. This concentration stems from increased coal combustion during the winter heating period when larger amounts of pollutants are emitted into the atmosphere. A similar maximum concentration is observed when investigating fallout and water radioactivities. The results of fallout measurements are shown in Fig. 2.

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