**Chapter 9**

# The Accelerated Excretion of PCBs and PCDFs

## 9.1. Animal Studies

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As described in the previous chapters, it has been revealed that the highly toxic congeners of PCDF and PCB, such as 2,3,4,7,8-PenCDF and 2,3,4,5,3′,4′-HexCB, have been found to still remain in the bodies of the Yusho patients some 20 years after the outbreak of Yusho, although the levels are quite low. In addition to a variety of sustained toxicities, it is alarming to these patients that such polychlorinated aromatic hydrocarbons have been proven to be carcinogenic in animals (Kimura and Baba, 1973; Nagasaki et al., 1972; Kociba et al., 1978). One epidemiologic investigation has also suggested that Yusho might have even caused liver cancer, at least in male patients, however, the evidence is not conclusive (Kuratsune et al., 1987).

These observations led us to the conclusion that, if possible, a method to help accelerate the excretion of these compounds retained in the bodies of the patients should be devised without delay. For this purpose, 2,3,4,7,8-PenCDF was selected as a model compound, since it has been recognized to be the most important causal agent of Yusho among the various congeners of PCB, PCDF and others (Yoshihara et al., 1981; Masuda and Yoshimura, 1984). In this chapter, the metabolic disposition of this PenCDF will first be described in rats and thereafter its potential application in humans will also be discussed.

### *9.1.1. The Metabolic Disposition of 2,3,4,7,8-PenCDF*

When administered orally to rats at a single dose of 1 mg/kg 2,3,4,7,8-PenCDF, about 70% of the dose is absorbed by the intestine and then distributed to all the organs and tissue involving the liver and skin within the first 3 days, but then is redistributed almost solely to the liver from other parts until day 5 (Yoshimura et al., 1984). Thereafter, a high affinity of this compound to the liver is maintained and about 50% of the dose is still retained in the liver 3 weeks after administration. This specific distribution profile seems to be due to the characteristic binding of PenCDF to the specific form of cytochrome P450 (CYP1A2) which is inducible by treatment with the PenCDF (Kuroki et al., 1986). Such a unique property of PenCDF to bind tightly but noncovalently with CYP1A2 was similarly seen with 3,4,5,3′,4′-PenCB which has a strong 3-MC type inducing ability. Thus, PenCDF was found to be quite different from other congeners since they had a tendency to accumulate in the adipose tissue (Yoshimura et al., 1985b).

As shown in Fig. 9.1.1, the remaining 30% of the dose was excreted into the

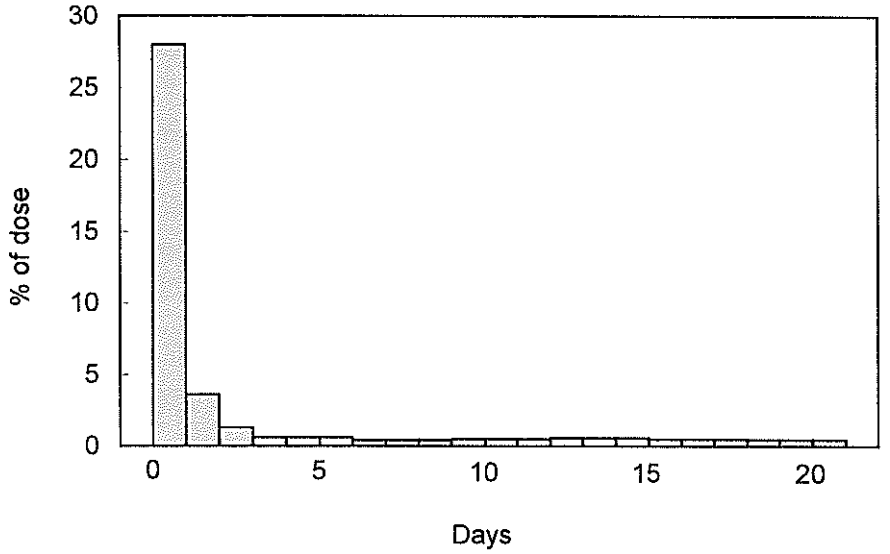


**Fig. 9.1.1.** The Fecal Excretion of Radioactivity in the Rats Given an Oral Dose of 1.0 mg/kg of $^{14}$C-2,3,4,7,8-PenCDF
Each value represents the mean of three rats. Yoshimura et al. (1984).

feces during the first 3 days and this PenCDF was considered to be the portion unabsorbed by the intestine. Thereafter, a small but constant amount of PenCDF was excreted daily throughout the 3-week experiment (Kuroki et al., 1986). This type of excretion over a long period corresponds to exsorption of the PenCDF into the intestinal lumen from the blood (Oguri et al., 1987).

The existence of such an exsorption mechanism of polychlorinated aromatic hydrocarbons in rats was experimentally established for the first time by using 2,4,3′,4′-TCB, one of the major components of KC-400. When this TCB was injected i.v. in rats, a part was metabolized to 5- and 3-hydroxy-2,4,3′,4′-TCB which were then excreted into feces through the biliary system. On the other hand, no unchanged TCB could be detected gas-chromatographically in the bile. Nevertheless, about 0.6% of the injected dose was excreted unchanged daily into the feces of the rats during the 4-day experiment (Yoshimura and Yamamoto, 1975; Yoshimura et al., 1974). This fecal excretion of TCB was later proven to be due to exsorption through the intestinal wall into the lumen by analyzing the unchanged TCB in the contents of the stomach, small intestine, caecum, colon and rectum of the bile duct-ligated rats, every 2 hr after i.v. injection. In this experiment, the unchanged TCB appeared at first in the contents of the small intestine, which indicated the exsorption of TCB from this part of the gastrointestinal tract (Yoshimura and Yamamoto, 1975).

Some other examples of the transport of organochlorine compounds through the extrabiliary pathway have also been reported in the studies of the metabolic fate of dieldrin (Williams et al., 1965), mirex (Pittman et al., 1976) and chlordecone (Boylan et al., 1978; 1979). The PenCDF in the circulating blood of rats is thus transported, though very gradually, into the intestinal lumen. It is thus very likely that this PenCDF in the lumen is eliminated partly into the feces, but is mostly re-absorbed from the lower intestine. If this is the case, then the inhibition of this re-absorption should be a good means of promoting the fecal excretion of the PenCDF.

### *9.1.2. Short-Term Experiments*

Two methods are considered to be suitable for the purpose of inhibiting re-absorption of 2,3,4,7,8-PenCDF transported from the blood into the intestinal lumen. The first method is to use adsorbents such as activated charcoal and cholestyramine. Activated charcoal, a well-known adsorbent, which has been used as an antidote capable of removing other ingested toxic substances, should hasten the fecal excretion of 2,3,4,7,8-PenCDF by disturbing its re-absorption. The effect of activated charcoal was found to be ascribed to its binding not only to the PenCDF, but also to bile salts which are required for the re-absorption of PenCDF (Nakano et al., 1984a). On the other hand, cholestyramine, a drug that lowers the serum cholesterol level, is an inabsorbable anion-exchange resin that binds bile salts in the intestine and may accelerate the elimination of PenCDF into the feces. In addition, cholestyramine is also assumed to have a binding property to PenCDF due to the involvement of phenyl rings in the strutures of both compounds.

Another method is to apply oily substances such as liquid paraffin and squalane that can dissolve PenCDF, but are not highly absorbable themselves by the intestine (Albro and Fishbein, 1970). Liquid paraffin is a mixture consisting of straight-chain hydrocarbons with a carbon number of 15 to 20 while squalane is a saturated derivative of squalene, a branched-chain hydrocarbon with a carbon number of 30.

Based on the above hypothesis, activated charcoal, cholestyramine, liquid paraffin and squalane were all examined to determine which one would be the most effective in accelerating the excretion of PenCDF using rats for 3 weeks (Yoshimura et al., 1986; Kamimura and Yoshimura, 1987; Yoshimura et al., 1985a). Several reports have already been made describing the increased excretion of organochlorine hydrocarbons into the feces of rats after treatment with cholestyramine (Boylan et al., 1978), paraffin (Richter et al., 1979) and squalane (Richter et al., 1983). Concerning the use of activated charcoal, the promotion of the fecal excretion of dieldrin has also been reported using ruminants (Wilson and Cook, 1970).

The methods used are illustrated in Fig. 9.1.2. Briefly, the rats were divided into

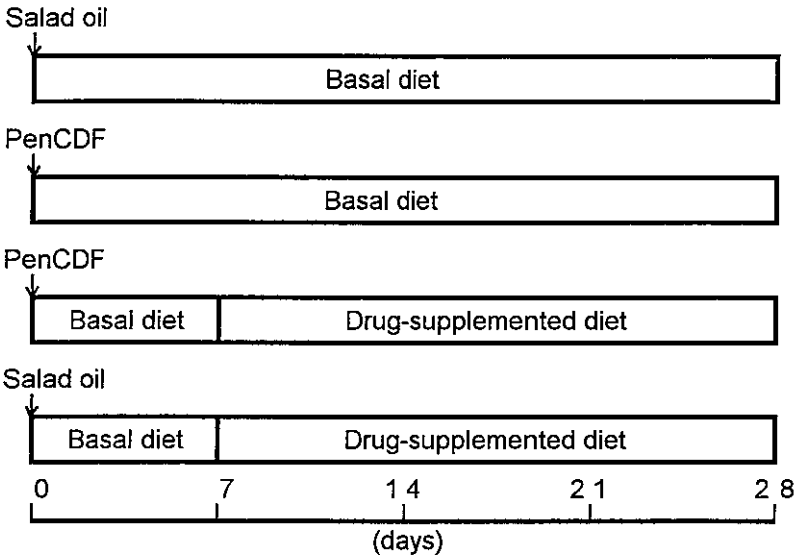


**Fig. 9.1.2.** Treatment with 2,3,4,7,8-PenCDF and the Drug-Supplemented Diet Kamimura and Yoshimura (1987).

4 groups, to which a single dose (1.0 mg/kg) of PenCDF in salad oil or the same amount of salad oil was orally given on day 1. The test groups were then given the antidote-supplemented diets from day 8 to day 28. By day 8, the re-distribution of PenCDF to the liver was completed and its excretion into the feces had greatly slowed and had become constant (Yoshimura et al., 1984). The diet concentration of squalane and liquid paraffin used was 8% while that of cholestyramine and activated charcoal was 5%. Activated charcoal was not used as a powder, but as fine beads of agar in which activated charcoal was enwrapped. Their *in vitro* and *in vivo* adsorption characteristics for various adsorbates have been shown to be equally effective as a powder and easier to handle than a powder to prevent unwanted scattering (Nakano et al., 1984b).

The results are summarized in Table 9.1.1. From 0.1% to 0.15% of the PenCDF dose was excreted daily during the first 3 weeks from day 8 to day 28 in the untreated group (PenCDF-basal diet group). The total amount excreted during this period accounted for 2% to 3% of the dose. This table also shows that all 4 treated groups (the antidote-supplemented diet groups) excreted 2 to 3 times more PenCDF than the untreated group during the 3 weeks of treatment (Yoshimura et al., 1985a; Kamimura and Yoshimura,1987; Yoshimura et al., 1986).

Polychlorinated aromatic hydrocarbons, such as PenCDF, also caused a marked suppression of body weight gain, hypertrophy of the liver with increased lipid content and atrophy of the thymus in rats, which have been used as toxic indices for

**Table 9.1.1.** The Fecal Excretion of 2,3,4,7,8-PenCDF during Treatment with Antidote-supplemented Diets for 3 Weeks in Rats

| Experiments | Dietary treatment | |
|---|---|---|
| | Basal | Supplemented |
| | (% of dose) | |
| 8% Squalane[a] | 3.17 ± 0.32 | 9.07 ± 0.80[d] |
| | (1.0) | (2.9) |
| 8% Paraffin[b] | 2.31 ± 0.39 | 4.98 ± 0.35[d] |
| | (1.0) | (2.2) |
| 5% Cholestyramine[b] | 1.98 ± 0.26 | 3.62 ± 0.53[d] |
| | (1.0) | (1.8) |
| 5% Charcoal[c] | 1.96 ± 0.12 | 5.44 ± 0.25[d] |
| | (1.0) | (2.8) |

Each value represents the mean ± S.E. of 3 or 4 rats and the relative ratio to that of the corresponding basal group in parenthesis.
[a]: Yoshimura et al. (1985a), [b]: Kamimura and Yoshimura (1987), [c]: Yoshimura et al. (1986),
[d]: Significantly different from the value of the corresponding basal group ($p < 0.05$).

these compounds (Yoshimura et al., 1979). The final purpose of this experiment was to establish not only a method to accelerate the fecal excretion of the PenCDF, but also to help induce a cure for Yusho disease. Therefore, the therapeutic effects of the 4 different antidote-supplemented diets were estimated using the above toxic indices.

The body weight gain of the untreated group was remarkably suppressed, and was about 50% less than the control value. This toxic effect of PenCDF could not be improved by administering any one of the antidote-supplemented diets. As described above, treatment with the 4 antidote-supplemented diets accelerated the fecal excretion of the PenCDF. In spite of that, the amounts eliminated during the experiment accounted for only 4 to 9% of the dose (Table 9.1.1), while on the final day of the experiment (day 28) about 40% of the dose still remained in the liver. These findings thus indicated that such a slight increase of PenCDF excretion might not be sufficient to effectively repress the toxic effect.

On the other hand, the changes in the organ weight after the administration of PenCDF definitely improved after treatment with the 4 antidotes. As shown in Fig. 9.1.3, the weight of the liver in the untreated group given PenCDF increased about 1.4-fold, while that of thymus decreased to about one fourth of the control values. Treatment with all the diets supplemented with the 4 antidotes tended to reduce the liver enlargement induced by PenCDF and also the 3 groups, other than the liquid paraffin group, significantly improved the degree of thymus atrophy. These results indicate that all 4 antidotes were able to reduce the toxic effect of PenCDF by accelerating fecal excretion. Among the 4 antidotes, squalane and activated char-

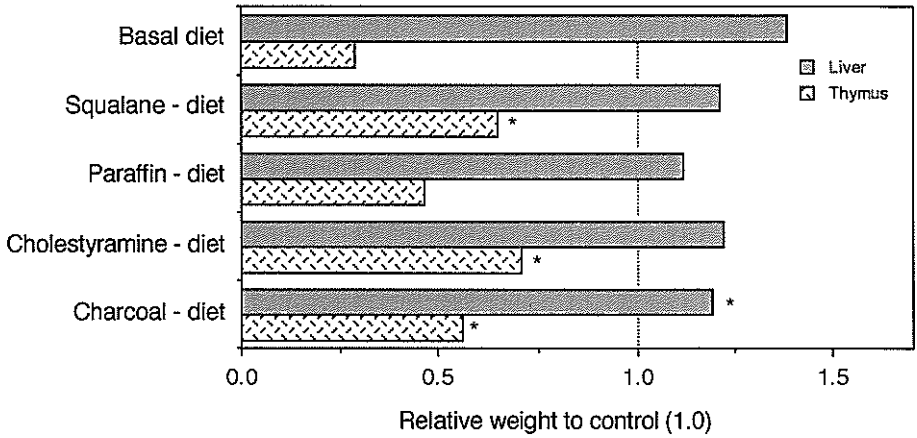


**Fig. 9.1.3.** The Effect of Four Antidotes on the Toxicity of 2,3,4,7,8-PenCDF in Rats
*Significantly different from the basal diet group ($p < 0.05$). Kamimura and Yoshimura (1987).

coal beads were found to be more effective than the other two (Kamimura and Yoshimura, 1987).

### *9.1.3. Long-Term Experiments*

Since the PCBs and PCDFs that are retained in the patients are only being excreted very gradually into feces, it may take quite a long time to recover completely from their poisoning, even if an antidote would be applied. Therefore, long-term experiments (12 weeks) using squalane and activated charcoal beads as antidotes were undertaken to accelerate the fecal excretion of 2,3,4,7,8-PenCDF retained in rats, in the same manner as for the short-term experiments described above (Oguri et al., 1987; Kamimura et al., 1988). In this study, both the reduction of the toxic effect induced by PenCDF as well as the acceleration of its fecal excretion were examined.

The methods used are as follows; a dose of 0.1 mg/kg of 2,3,4,7,8-PenCDF was orally given to the rats twice on the first day and again on day 5. In the test groups given PenCDF, the basal diet was replaced with the diet supplemented with either 1% or 5% of squalane or activated charcoal beads from day 13 to day 97 (12 weeks).

Fig. 9.1.4 illustrates the fecal excretion profiles of PenCDF. In the PenCDF-basal diet group, a small, but constant amount of PenCDF was excreted daily and the excretion was markedly enhanced in the squalane diet groups throughout the experiment, although the absolute amount of the PenCDF excreted gradually decreased in each group over time. Table 9.1.2 indicates that the cumulative fecal

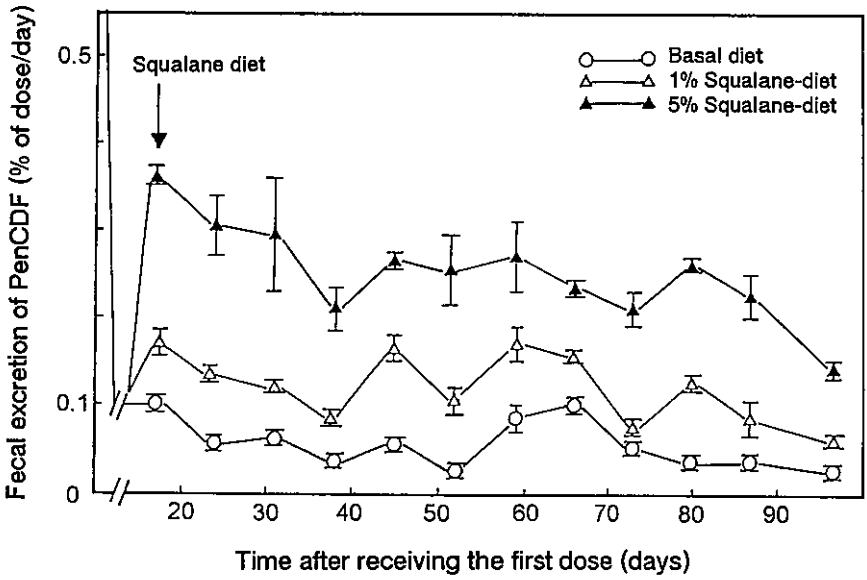


**Fig. 9.1.4.** The Effect of Squalane on Fecal Excretion of 2,3,4,7,8-PenCDF Kamimura and Yoshimura (1987).

excretion of the PenCDF was enhanced approximately 2- and 5-fold in the 1% and 5% squalane diet groups, respectively, compared with that in the basal diet group, during the 12-week-period from day 13 to day 97. About 30% of the dose excreted during the initial 12 days should be mostly ascribed to the PenCDF which was not absorbed by the intestine. The fecal excretion profiles of PenCDF in the 1% and 5% activated charcoal diet groups were almost the same as those of the squalane diet groups shown in Fig. 9.1.4. The cumulative fecal excretion of PenCDF was enhanced dose-dependently and was quite similar in both types of dietary treatments (Table 9.1.2).

The accelerated fecal excretion of the dietary treatments with the two antidotes was reflected in the amount of PenCDF acumulated in the liver as shown in Table 9.1.3. About 66% of the administered PenCDF, which accounted for almost the total amount of absorbed PenCDF, was distributed in the liver at day 12 and this value only decreased to about 49% at day 97 in the basal diet group. In the 1% and 5% squalae or 1% and 5% activated charcoal diet groups, it was further decreased dose-dependently to either 36% and 27%, or 40% and 29%, respectively. The decreased PenCDF concentration in the liver was also in good agreement with the increased fecal excretion of the PenCDF. Furthermore, the PenCDF level in the blood decreased significantly in both dietary treatments.

The accelerated fecal excretion and the decreased level of PenCDF in the liver

**Table 9.1.2.** The Effect of Treatment with Squalane- and Activated Charcoal Bead-supplemented Diets on the Fecal Excretion of 2,3,4,7,8-PenCDF from Day 13 to Day 97 (12 Weeks)[a]

| Dietary treatment | PenCDF in feces (% of dose) |
|---|---|
| Basal | 4.59 ± 0.08 (1.0) |
| 1% Squalane | 10.38 ± 0.30[b] (2.3) |
| 5% Squalane | 21.63 ± 0.53[b,c] (4.7) |
| 1% Charcoal | 9.12 ± 0.45[b] (2.0) |
| 5% Charcoal | 17.41 ± 0.60[b,d] (3.8) |

Each value represents the mean ± S.E. of 3 (basal) or 4 rats, and the relative ratio to that of the basal group in parenthesis.

[a]: Kamimura and Yoshimura (1987), [b]: Significantly different from that of the basal group ($p < 0.05$), [c]: Significantly different from that of the 1% squalane group ($p < 0.05$), [d]: Significantly different from that of the 1% charcoal group ($p < 0.05$).

**Table 9.1.3.** The Effect of 12 week-treatment with Squalane and Activated Charcoal Bead-diets on the Distribution of 2,3,4,7,8-PenCDF in Rats[a]

| Tissue | At day 12 | At day 97 | | | | |
|---|---|---|---|---|---|---|
| | | Basal diet | 1% Squalane | 5% Squalane | 1% Charcoal | 5% Charcoal |
| Liver | 66.06 ± 2.06 | 48.56 ± 1.72 | 36.16 ± 0.96[b] | 27.19 ± 3.67[b,c] | 40.28 ± 1.12[b] | 28.85 ± 1.35[b,d] |
| Blood | 0.44 ± 0.04 | 0.33 ± 0.07 | 0.16 ± 0.01[b] | 0.12 ± 0.01[b,c] | 0.29 ± 0.04 | 0.15 ± 0.01[b,d] |
| | (7.96 ± 0.71) | (2.80 ± 0.57) | (1.33 ± 0.11)[b] | (0.94 ± 0.03)[b,c] | (2.39 ± 0.42) | (1.23 ± 0.09)[b,d] |
| Spleen | N.D. | N.D. | N.D. | N.D. | N.D. | N.D. |
| Thymus | N.D. | 0.01 ± 0.00 | 0.01 ± 0.00 | 0.01 ± 0.00 | 0.01 ± 0.00 | N.D. |
| Lung | N.D. | 0.02 ± 0.01 | 0.01 ± 0.00 | N.D. | N.D. | N.D. |
| Kidney | N.D. | 0.01 ± 0.00 | N.D. | N.D. | 0.01 ± 0.00 | N.D. |
| Adipose tissue | 0.05 ± 0.01 | 0.21 ± 0.05 | 0.11 ± 0.02 | 0.10 ± 0.03 | 0.09 ± 0.01[b] | 0.09 ± 0.01[b] |
| Small intestine | 0.05 ± 0.01 | 0.69 ± 0.22 | 0.27 ± 0.04 | 0.31 ± 0.05 | 0.59 ± 0.16 | 0.43 ± 0.66 |
| Skin | 1.01 ± 0.15 | 2.00 ± 0.53 | 1.35 ± 0.41 | 1.32 ± 0.24 | 1.35 ± 0.33 | 0.77 ± 0.06[b] |

Each value represents the mean of % of the PenCDF dose ± S.E. of 3 or 4 rats, and the parts per billion in parenthesis.

N.D.: not detectable, [a]: Kamimura and Yoshimura (1987), [b]: significantly different from the basal diet group ($p < 0.05$), [c]: Significantly different from the 1% squalane diet group ($p < 0.05$), [d]: Significantly different from the 1% charcoal diet group ($p < 0.05$).

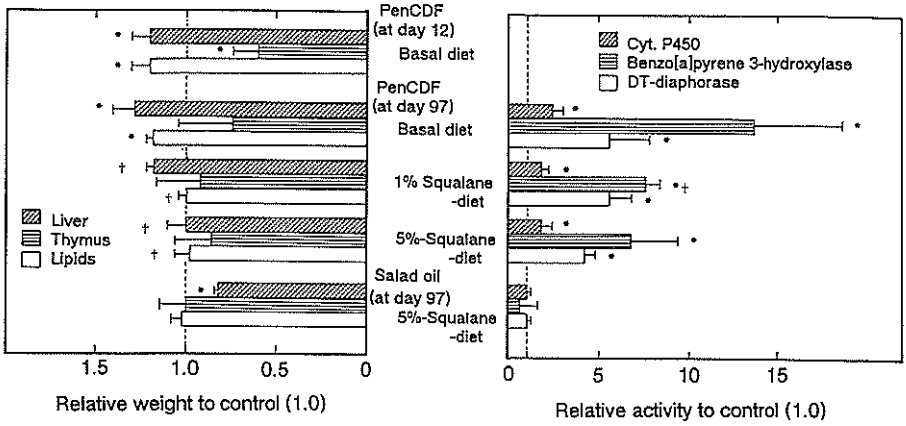


**Fig. 9.1.5.** The Effect of Squalane on the Liver Enzyme Activities (Right), Tissue weight and Liver Lipid Content (Left) in Rats

The activities in the control (mean ± S.D.) were: Cytochrome P-450 (Cyt. P-450) 0.099 ± 0.030 nmole/mg protein, Benzo[a]pyrene 3-hydroxylase 0.035 ± 0.004 nmole metabolite formed/min/mg protein, DT-diaphorase 0.110 ± 0.086 μmole DCPIP formed/min/mg protein.

The weight of the tissue (g/100 g b.w.) and liver lipid (mg/g liver) in the control were: liver 5.107 ± 0.428 (at day 12), 2.957 ± 0.300 (at day 97), thymus 0.272 ± 0.022 (at day 12), 0.126 ± 0.022 (at day 97), liver lipid 45.42 ± 4.61 (at day 12), 46.74 ± 4.30 (at day 97).

*Significantly different from the control ($p < 0.05$). †Significantly different from the PenCDF-basal diet group ($p < 0.05$). Oguri et al. (1987).

resulted in a significant improvement of the toxic signs of PenCDF. As shown in Fig. 9.1.5, for example, the hypertrophy of the liver, atrophy of the thymus and the fatty liver, observed just before the start of the dietary treatment (at day 12) were still present at day 97 in the PenCDF-basal diet group. In the squalane diet groups, however, these toxic changes had significantly improved to the control levels.

In addition, Fig. 9.1.5 indicates a marked increase in the content of cytochrome P450 and activities of microsomal benzo[a]pyrene 3-hydroxylase and cytosolic DT-diaphorase in the PenCDF-basal diet group at day 97. However, these effects of PenCDF were not significantly suppressed by the dietary treatment with squalane. Such a negative result seemed to have been caused by the PenCDF still remaining in the liver at a high level (27% or 36% of the dose for the 5% or 1% squalane diet group, respectively) as indicated in Table 9.1.3.

The therapeutic effect of squalane was also examined by using monkeys given a mixture of PCDF (Kashimoto et al., 1985; Hori et al., 1987). In these studies, a 20 μg dose of PCDFs/monkey/day was administered 3 times a week for 3 weeks to induce "Yusho-like" symptoms and then the monkeys were treated with squalane at a dose of 8 g/monkey/day for 20 weeks. With this treatment, the blood level of

**Table 9.1.4.** The Fecal Excretion of Squalane[a]

| Weeks after treatment | 1% Squalane-diet (% of intake) | 5% Squalane-diet (% of intake) |
|---|---|---|
| 2 | 103.5 ± 2.5 | 100.2 ± 0.9 |
| 6 | 106.1 ± 3.3 | 99.5 ± 0.8 |
| 11 | 97.6 ± 1.0 | 97.3 ± 1.8 |

The feces collected over a one-week period were analyzed for squalane. Each value represents the mean ± S.E. of 4 rats.

[a]: Kamimura and Yoshimura (1987).

PCDFs decreased more quickly and the amounts of PCDFs in the liver, kidney and heart were lowered to 80%, 70% and 62%, respectively, compared with those of the untreated group. Some improvement in the loss of body weight and the increase of serum triglyceride was also observed in the squalane-treated group. The increase in the hepatic microsomal drug metabolizing enzyme activities and the histo-pathological alterations induced by treatment with PCDFs were also slightly suppressed by the squalane treatment.

### *9.1.4. Safety Assessment of Squalane*

Good results similar to those obtained by the squalane treatment were also obtained dose-dependently in rats by dietary treatment with 1% and 5% activated charcoal beads, but the effectiveness was a little weaker than that with squalane treatment. Thus, squalane was selected as the most useful candidate for clinical application and thus was examined first for a safety assessment in rats. As shown in Table 9.1.4, almost all the squalane given during the dietary treatment to accelerate fecal excretion of 2,3,4,7,8-PenCDF in rats was recovered from the feces and only a trace amount of squalane was absorbed and distributed into the liver and other organs. These findings indicate that in rats, squalane was not essentially absorbed from the gastrointestinal tract. It was also found that squalane did not show any appreciable toxic effects including the effect on the growth curve, organ weight and biochemical index of the blood during and after the 12-week treatment in rats (Kamimura and Yoshimura, 1987).

Quite a high degree of safety was thus indicated for rats in the squalane treatment, but further examinations on the distribution, excretion and subacute toxicity of squalane were also conducted in beagle dogs prior to its clinical application (Kamimura et al., 1989; 1991). Although squalane was only slightly absorbable in dogs, about 10% of the dose (1,200 mg/kg) was absorbed from the gut and distributed mostly to the hair and skin. Such concentrations reached a maximum on day 3, accounting for 9.2% and 1.8% of the dose, respectively, and thereafter decreased to 2.3% and 0.09% on day 6. The squalane distributed into the liver was only

**Table 9.1.5.** The Tissue Distribution of Squalane in Beagle Dogs[b]

| Tissue | At day 42 (ppm) | At day 70 (ppm) |
|---|---|---|
| Skin | 120.30 | N.D. |
| Liver | 1,115.92 | 81.66 |
| Lung | N.D. | N.D. |
| Kidney | N.D. | N.D. |
| Adipose tissue | 90.19 | 28.01[a] |
| Small intestine | 20.68 | N.D. |

The dogs were administered squalane at a dose of 1,200 mg/kg/day from day 1 to day 14. Each value represents the mean of 2 dogs.

N.D.: not detected (detection limit 0.1 ppm). [a]: The value is only from one dog since the other dog's value was N.D., [b]: Kamimura et al. (1991).

0.48% of the dose on day 1, but was only slightly eliminated thereafter, with 0.36% of the dose retained on day 6. These findings suggested that a part of squalane given orally was absorbed and eliminated rather quickly through the skin pathway to the hair. In addition, the squalane distributed to the liver was also found to be only slowly eliminated.

The long-term (13 weeks) treatments with squalane at oral doses of 400 mg/kg/day or 1,200 mg/kg/day in male and female dogs, resulted in the accumulation of squalane in the liver at a level of about 3% (400 mg/kg) or 6% (1,200 mg/kg) of the daily dose. This accumulation was the highest in the liver among all the tissues examined and quite a long time was required to eliminate the squalane from the liver (Table 9.1.5). Nevertheless, no appreciable toxic signs were observed in either the serum biochemical tests or the hepatic functional tests for squalane-treated (13 weeks) dogs. Such long-term treatment also suggested that the skin and hair played the most important role in the elimination of squalane. In conclusion, the accumulation of squalane in the liver in place of PenCDF was sufficiently worrisome so that the clinical application of the squalane treatment could not be performed.

### *9.1.5. Additional Experiments*

As described above, squalane treatment afforded satisfactory results for accelerating the fecal excretion of 2,3,4,7,8-PenCDF in rats as well as in monkeys and dogs, but caused an undesirable accumulation of squalane in the liver of dogs during long-term treatment. On the basis of these findings, it is thus considered to be necessary to find a safer method even if it might be less effective.

Dietary fiber was thus taken into consideration to examine its effect in accelerating the fecal excretion of PCB in rats (Takenaka et al., 1991). Since rice bran fiber containing lignin was found to be a strong adsorbent of PCB *in vitro* and is thought

to be generally safe, a combination of this fiber and cholestyramine was tested for the effect described above. The results showed that the fecal excretion of PCB in rats increased 5.7-fold by treatment for 3 weeks with a combination of rice bran fiber (10% of the diet) and cholestyramine (5% of the diet), compared with the control values. Treatment with either substance alone resulted in a much lower effect than that in combination. Based on these studies, Morita et al. (1993) analyzed the increased amount of each congener of PCDF and PCDD in the feces of rats orally administered with the causal rice oil of Yusho disease, by the same treatment as described above. For example, the fecal excretion of the highly toxic 2,3,4,7,8-PenCDF in the group fed the combination diet described above showed a 4.2-fold increase over the control level. This method was thus determined to be the most promising therapeutic approach for Yusho.

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## 9.2. Clinical Experiments on Accelerating the Excretion of PCBs and PCDFs

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### *9.2.1. PCBs, PCDFs and Other Organochlorine Compounds in the Toxic Rice Oil and Tissue of Yusho Patients*

Before any clinical trials were begun in order to find a treatment to accelerate the excretion of PCBs, PCDFs and other compounds, the toxic rice oil ingested by Yusho patients as well as tissue samples of the patients were both extensively examined for these chlorinated compounds in our laboratory.

The congeners of PCDDs and PCDFs in the rice oil used by Yusho patients were determined using HR-GC/HR-MS and $^{13}C$ labeled internal standards. As shown in Table 9.2.1, a number of congeners of PCDDs (33 congeners) and PCDFs (58 congeners) were detected in the rice oil, and the total concentrations of PCDDs and PCDFs were found to be 600 ng/g and 10,200 ng/g, respectively.

Since PCDFs are well known to be highly toxic chemicals for both animals and humans, it was considered to be quite important to determine the level of PCDFs still retained in the patients in order to understand the relationship between the concentration of PCDFs and the symptoms of the disease. Therefore, in 1986 the abdominal subcutaneous adipose tissue of 18 Yusho patients and that of 11 normal controls, who were all volunteers, were collected and analyzed for PCDFs (Iida et al., 1989). The results are shown in Tables 9.2.2 and 9.2.3. The principal compounds detected in the adipose tissue of Yusho patients were 2,3,4,7,8-PenCDF, and 1,2,3,4,7,8- and 1,2,3,6,7,8-HxCDFs. The concentrations of the compounds in 7 patients showing typical Yusho symptoms as well as the gas chromatographic pattern A of PCBs ranged from 160 to 3,000 pg/g for 2,3,4,7,8-PenCDF, from 51 to 1,000 pg/g for 1,2,3,4,7,8-HxCDF and from 16 to 220 pg/g for 1,2,3,6,7,8-HxCDF. In the normal controls, 2,3,4,7,8-PenCDF was detected in only five samples of tissue at low levels, ranging from 16 to 39 pg/g. The average level of PCDFs in these seven typical Yusho patients was 1,900 pg/g, which was more than 100 times higher than that observed in the eleven normal controls which was 16 pg/g. We thus considered that the present high levels of PCDFs still remaining in the tissue of these patients probably played an important role in their symptoms and signs. It is also noteworthy that the patients who showed the gas chromatographic pattern of PCBs, BC and C, in their blood had much lower levels of PCDFs

**Table 9.2.1.** The Concentrations of PCDDs and PCDFs Congeners Found in the Rice Bran Oil Which Caused Yusho (ng/g)

| Congener | Concentration | Congener | Concentration | Congener | Concentration |
|---|---|---|---|---|---|
| 1,3,6,8-TCDD | 1.9 | 1,3,6,8-TCDF | 8.3 | 1,2,3,4,6-PenCDF | 153 |
| 1,3,7,9-TCDD | 1.2 | 1,3,7,8-/1,3,7,9-TCDF | 16 | 1,2,3,7,9-PenCDF | 52 |
| 1,3.7,8 -TCDD | 0.7 | 1,3,4,7-TCDF | 37 | 1,2,3,6,7-/1,2,4,6,9-/2,3,4,8,9-PenCDF | 229 |
| 1,2,4,7-/1,2,4,8-/1,3,6,9-TCDD | 0.7 | 1,4,6,8-/1,2,4,7-/1,3,6,7-TCDF | 262 | 1,3,4,8,9-PenCDF | 8.5 |
| 1,2,6,8-TCDD | 0.3 | 1,3,4,8-TCDF | 33 | 1,2,4,8,9-PenCDF | 5.2 |
| 2,3,7,8-TCDD | 0.6 | 1,2,4,8-/1,3,4,6-TCDF | 228 | 1,2,3,6,9-PenCDF | 130 |
| 1,2,3,4-/1,2,3,7-/1,2,3,8-/1,2,4,6-/1,2,4,9-TCDD | 0.2 | 1,2,4,6-/1,2,6,8-/1,4,7,8-/1,3,6,9-/1,2,3,7-TCDF | 192 | 2,3,4,6,8-PenCDF | 12 |
| 1,2,3,6-/1,2,7,9-TCDD | 0.6 | 1,2,3,4-/1,6,7,8-TCDF | 63 | 1,2,3,4,9-PenCDF | 31 |
| 1,2,3,7-8-/1,4,6,9-TCDD | 0.2 | 1,2,3,6-/1,4,6,7-/2,4,6,8-/1,2,3,8-TCDF | 0 | 2,3,4,7,8-PenCDF | 877 |
| 1,2,3,9-TCDD | 0.3 | 1,3,4,9-TCDF | 27 | 2,3,4,6,7-PenCDF | 538 |
| 1,2,6,9-TCDD | 0.3 | 1,2,7,8-TCDF | 56 | 1,2,3,4,6,8-HxCDF | 110 |
| 1,2,6,7-TCDD | 0.2 | 1,2,6,7-/1,2,7,9-TCDF | 28 | 1,3,4,6,7,8-/1,3,4,6,7,9-HxCDF | 117 |
| 1,2,8,9-TCDD | 0.3 | 1,4,6,9-/1,2,4,9-TCDF | 5.0 | 1,2,4,6,7,8-HxCDF | 163 |
| 1,2,3,6,8-/1,2,4,7,9-PenCDD | 25 | 2,3,6,8-TCDF | 191 | 1,2,4,6,7,9-HxCDF | 11 |
| 1,2,3,6,8-PenCDD | 22 | 2,4,6,7-TCDF | 95 | 1,2,3,4,7,8-/1,2,3,4,7,9-HxCDF | 823 |
| 1,2,3,7,8-PenCDD | 3.8 | 2,3,4,7-TCDF | 724 | 1,2,3,6,7,8-HxCDF | 129 |
| 1,2,3,7,9-PenCDD | 13 | 1,2,6,9-TCDF | 17 | 1,2,3,4,6,7-HxCDF | 614 |
| 1,2,3,4,7-/1,2,4,6,9-PenCDD | 2.6 | 2,3,7,8-TCDF | 502 | 1,2,3,6,7,9-HxCDF | 10 |
| 1,2,3,7,8-PenCDD | 7.5 | 2,3,4,8-TCDF | 0 | 1,2,3,4,6,9-/1,2,3,6,8,9-HxCDF | 41 |
| 1,2,3,6,9-PenCDD | 1.2 | 2,3,4,6-TCDF | 80 | 1,2,3,7,8,9-HxCDF | 12 |
| 1,2,4,6,7-/1,2,4,8,9-PenCDD | 2.3 | 2,3,6,7-TCDF | 94 | 1,2,3,4,8,9-HxCDF | 54 |
| 1,2,3,4,6-/1,2,3,6,7-PenCDD | 1.9 | 3,4,6,7-TCDF | 17 | 2,3,4,6,7,8-HxCDF | 224 |
| 1,2,3,8,9-PenCDD | 1.8 | 1,2,8-,9-TCDF | 2.9 | 1,2,3,4,6,7,8-HpCDF | 322 |
| 1,2,3,4,6,8-/1,2,4,6,7,9-/1,2,4,6,8,9-HxCDD | 80 | 1,3,4,6,8-PenCDF | 30 | 1,2,3,4,6,7,9-HpCDF | 29 |
| 1,2,3,6,7,9-/1,2,3,6,8,9-HxCDD | 72 | 1,2,4,6,8-PenCDF | 71 | 1,2,3,4,7,8,9-HpCDF | 26 |
| 1,2,3,4,7,8-HxCDD | 5.6 | 1,3,6,7,8-PenCDF | 84 | 1,2,3,4,7,8,9-HpCDF | 17 |
| 1,2,3,6,7,8-HxCDD | 34 | 1,3,4,7,8-PenCDF | 4.5 | 1,2,3,4,6,7,8,9-OCDF | 38 |
| 1,2,3,4,6,9-HxCDD | 1.2 | 1,3,4,7,9-/1,2,3,6,8-PenCDF | 118 | | |
| 1,2,3,7,8,9-HxCDD | 24 | 1,2,4,7,8-PenCDF | 459 | | |
| 1,2,3,4,6,7-HxCDD | 2.1 | 1,2,4,7,9-/1,3,4,6,7-PenCDF | 65 | | |
| 1,2,3,4,6,7,9-HpCDD | 86 | 1,2,4,6,7-/1,2,3,4,7-/1,4,6,7,8-PenCDF | 1,326 | | |
| 1,2,3,4,6,7,8-HpCDD | 123 | 1,3,4,6,9-PenCDF | 5.7 | | |
| 1,2,3,4,6,7,8,9-OCDD | 81 | 1,2,3,4,8-/1,2,3,7,8-PenCDF | 554 | | |

**Table 9.2.2.** The Concentrations of PCDFs and PCBs in the Subcutaneous Adipose Tissue of Yusho Patients in 1986

| No. | Age | Sex | PCDFs (pg/g) | | | | | PCBs (ng/g) | PCDFs/PCBs (%) | Type of PCB pattern[a] in blood |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | 2,3,7,8-TCDF | 2,3,4,7,8-PenCDF | 1,2,3,4,7,8-HxCDF | 1,2,3,6,7,8-HxCDF | Total PCDFs | | | |
| 1 | 50 | F | 18 | 3,000 | 1,000 | 220 | 4,200 | 5,700 | 0.074 | A |
| 2 | 54 | M | N.D. | 2,400 | 900 | 170 | 3,500 | 2,400 | 0.15 | A |
| 3 | 55 | F | N.D. | 2,000 | 230 | 64 | 2,300 | 1,200 | 0.19 | A |
| 4 | 45 | F | N.D. | 1,400 | 590 | 120 | 1,700 | 2,300 | 0.14 | A |
| 5 | 43 | F | N.D. | 710 | 120 | 37 | 870 | 1,300 | 0.067 | A |
| 6 | 45 | M | N.D. | 240 | 51 | 16 | 310 | 1,200 | 0.025 | A |
| 7 | 50 | M | N.D. | 160 | 54 | 22 | 220 | 1,000 | 0.024 | A |
| 8 | 54 | M | N.D. | 140 | N.D. | N.D. | 140 | 1,300 | 0.011 | BC |
| 9 | 64 | M | N.D. | 100 | N.D. | N.D. | 100 | 1,700 | 0.0059 | C |
| 10 | 59 | F | 11 | 75 | 4 | N.D. | 90 | 980 | 0.0092 | C |
| 11 | 60 | M | 5 | 61 | N.D. | N.D. | 66 | 1,800 | 0.0037 | C |
| 12 | 58 | F | 4 | 55 | 4 | N.D. | 63 | 1,500 | 0.0042 | C |
| 13 | 62 | F | N.D. | 59 | N.D. | N.D. | 59 | 1,100 | 0.0054 | C |
| 14 | 62 | F | 8 | 52 | 3 | N.D. | 63 | 1,400 | 0.0045 | C |
| 15 | 57 | M | N.D. | 55 | N.D. | N.D. | 55 | 900 | 0.0061 | C |
| 16 | 47 | M | N.D. | 15 | N.D. | N.D. | 15 | 820 | 0.0061 | BC |
| 17 | 54 | M | N.D. | 12 | N.D. | N.D. | 12 | 580 | 0.0018 | C |
| 18 | 48 | F | N.D. | N.D. | N.D. | N.D. | N.D. | 1,100 | | C |

[a]: The gas chromatographic pattern of PCBs. N.D.: Not detected.

**Table 9.2.3.** The Concentrations of PCDFs and PCBs in the Subcutaneous Adipose Tissue of Normal Controls

| No. | Age | Sex | PCDFs (pg/g) | | | | | PCBs (ng/g) | PCDFs/PCBs (%) | Type of PCB pattern[a] in blood |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | 2,3,7,8-TCDF | 2,3,4,7,8-PenCDF | 1,2,3,4,7,8-HxCDF | 1,2,3,6,7,8-HxCDF | Total PCDFs | | | |
| 1 | 61 | M | 19 | 39 | N.D. | N.D. | 58 | 1,200 | 0.0048 | C |
| 2 | 45 | M | N.D. | 31 | N.D. | N.D. | 31 | 580 | 0.0053 | C |
| 3 | 45 | M | N.D. | 21 | N.D. | N.D. | 21 | 900 | 0.0023 | C |
| 4 | 56 | M | N.D. | 16 | N.D. | N.D. | 16 | 1,200 | 0.0013 | C |
| 5 | 53 | F | N.D. | 16 | N.D. | N.D. | 16 | 660 | 0.0024 | C |
| 6 | 60 | M | N.D. | N.D. | N.D. | N.D. | N.D. | 1,300 | | BC |
| 7 | 61 | F | N.D. | N.D. | N.D. | N.D. | N.D. | 930 | | C |
| 8 | 47 | M | N.D. | N.D. | N.D. | N.D. | N.D. | 920 | | C |
| 9 | 58 | M | N.D. | N.D. | N.D. | N.D. | N.D. | 970 | | C |
| 10 | 40 | M | N.D. | N.D. | N.D. | N.D. | N.D. | 710 | | C |
| 11 | 29 | M | N.D. | N.D. | N.D. | N.D. | N.D. | 440 | | C |

[a]: The gas chromatographic pattern of PCBs. N.D.: Not detected.

**Table 9.2.4.** PCDDs, PCDFs and Co-PCBs in the Adipose Tissue of Yusho Patients (pg/g)

| No. | 1 | 2 | 3 | 4 | 5 | 6 | 7 | Mean | S.D. |
|---|---|---|---|---|---|---|---|---|---|
| Age | 55 | 50 | 45 | 54 | 50 | 45 | 43 | 49 | 5 |
| Sex | F | M | F | M | F | M | F | | |
| 2,3,7,8-TCDD | N.D. | N.D. | N.D. | N.D. | N.D. | N.D. | N.D. | N.D. | N.D. |
| 1,2,3,7,8-PenCDD | 24 | 38 | 65 | 53 | 56 | 35 | 25 | 42 | 16 |
| 1,2,3,6,7,8-HxCDD | 130 | 60 | 190 | 210 | 400 | 56 | 84 | 161 | 121 |
| OCDD | 120 | 73 | 430 | 140 | 120 | 120 | 120 | 160 | 121 |
| 2,3,7,8-TCDF | N.D. | N.D. | N.D. | N.D. | N.D. | N.D. | N.D. | N.D. | N.D. |
| 2,3,4,7,8-PenCDF | 2,000 | 160 | 1,400 | 2,400 | 3,000 | 240 | 71 | 1,300 | 1,200 |
| 1,2,3,4,7,8-HxCDF | 230 | 54 | 590 | 900 | 1,000 | 51 | 120 | 421 | 407 |
| 1,2,3,6,7,8-HxCDF | 120 | 73 | 430 | 140 | 120 | 120 | 120 | 160 | 121 |
| 1,2,3,4,6,7,8-HpCDF | 29 | 33 | 110 | 0 | 0 | 0 | 72 | 35 | 42 |
| 3,4,3′,4′-TCB | 6 | 13 | 29 | 8 | 8 | 9 | 8 | 12 | 8 |
| 3,4,5,3′,4′-PenCB | 63 | 72 | 130 | 44 | 32 | 75 | 73 | 70 | 31 |
| 3,4,5,3′,4′,5′-HxCB | 300 | 220 | 570 | 190 | 160 | 470 | 1,100 | 440 | 350 |
| Total PCDDs | 270 | 170 | 690 | 400 | 580 | 210 | 230 | 360 | 200 |
| Total PCDFs | 2,400 | 320 | 2,500 | 3,400 | 4,100 | 410 | 380 | 1,900 | 1,600 |
| Total Co-PCBs | 370 | 310 | 730 | 240 | 200 | 550 | 1,200 | 510 | 350 |
| PCDDs TEQ | 25 | 25 | 52 | 48 | 68 | 23 | 21 | 37 | 18 |
| PCDFs TEQ | 1,000 | 93 | 800 | 1,300 | 1,600 | 140 | 60 | 720 | 630 |
| Co-PCBs TEQ | 9 | 9 | 19 | 6 | 5 | 12 | 19 | 11 | 6 |
| Total TEQ | 1,100 | 130 | 870 | 1,400 | 1,700 | 170 | 99 | 770 | 650 |

N.D.: Not detected.

than those who showed pattern A, as shown in Table 9.2.2.

The amounts of PCDDs and Co-PCBs in the subcutaneous adipose tissue of the seven Yusho patients and eight normal controls was determined (Hirakawa et al., 1992). As shown in Table 9.2.4, 1,2,3,7,8-PenCDD, 1,2,3,6,7,8-HxCDD and OCDD were detected in the adipose tissue of the Yusho patients at levels ranging from 24 to 65 pg/g, from 56 to 400 pg/g and from 73 to 430 pg/g, respectively. The TEQ (2,3,7,8-TCDD Equivalent) value calculated by 2,3,7,8-TCDD Toxic Equivalent factors (TEfs) ranged from 21 to 68 pg/g. On the other hand, as shown in Table 9.2.5, 2,3,7,8-TCDD, 1,2,3,7,8-PenCDD, 1,2,3,6,7,8-HxCDD and OCDD were detected in the adipose tissue of the normal controls at levels ranging from 1 to 5 pg/g, from 4 to 18 pg/g, from 21 to 130 pg/g and from 180 to 1,300 pg/g, respectively. The TEQ value of PCDDs calculated by TEfs was from 2 to 10 pg/g.

3,3′,4,4′-TCB, 3,3′,4,4′,5-PenCB and 3,3′,4,4′,5,5′-HxCB were also detected in the adipose tissue of the Yusho patients at levels ranging from 6 to 29 pg/g, from 32 to 130 pg/g and from 160 to 1,100 pg/g, respectively. The TEQ value for Co-

**Table 9.2.5.** PCDDs, PCDFs and Co-PCBs in the Adipose Tissue of Normal Controls

| No. | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | Mean | S.D. |
|---|---|---|---|---|---|---|---|---|---|---|
| Age | 19 | 24 | 2 | 41 | 52 | 20 | 20 | 47 | 29 | 17 |
| Sex | M | M | M | M | M | M | F | M | | |
| 2,3,7,8-TCDD | 1 | 2 | 5 | 3 | 3 | 3 | 2 | 1 | 3 | 1 |
| 1,2,3,7,8-PenCDD | 7 | 10 | 15 | 13 | 18 | 17 | 14 | 4 | 12 | 5 |
| 1,2,3,6,7,8-HxCDD | 130 | 120 | 68 | 55 | 72 | 120 | 79 | 21 | 83 | 35 |
| OCDD | 280 | 550 | 790 | 1,300 | 180 | 320 | 520 | 250 | 530 | 400 |
| 2,3,7,8-TCDF | 1 | 2 | 7 | 2 | 2 | 1 | 3 | 1 | 2 | 2 |
| 2,3,4,7,8-PenCDF | 9 | 15 | 29 | 31 | 30 | 19 | 14 | 8 | 19 | 9 |
| 1,2,3,4,7,8-HxCDF | 3 | 6 | 11 | 13 | 7 | 6 | 7 | 7 | 8 | 3 |
| 1,2,3,6,7,8-HxCDF | 5 | 6 | 12 | 20 | 8 | 8 | 7 | 3 | 9 | 5 |
| 1,2,3,4,6,7,8-HpCDF | 3 | 6 | 4 | 8 | 3 | 4 | 5 | 2 | 4 | 2 |
| 3,4,3′,4′-TCB | 5 | 5 | 8 | 9 | 6 | 7 | 6 | 3 | 6 | 2 |
| 3,4,5,3′,4′-PenCB | 59 | 83 | 180 | 160 | 280 | 83 | 190 | 41 | 140 | 82 |
| 3,4,5,3′,4′,5′-HxCB | 58 | 79 | 100 | 100 | 200 | 120 | 82 | 47 | 98 | 47 |
| Total PCDDs | 420 | 680 | 870 | 1,400 | 270 | 460 | 610 | 280 | 620 | 390 |
| Total PCDFs | 21 | 35 | 47 | 46 | 39 | 26 | 24 | 16 | 32 | 12 |
| Total Co-PCBs | 120 | 170 | 290 | 270 | 490 | 210 | 280 | 91 | 240 | 120 |
| PCDDs TEQ | 5 | 7 | 9 | 8 | 10 | 10 | 8 | 2 | 7 | 3 |
| PCDFs TEQ | 5 | 8 | 15 | 16 | 15 | 10 | 7 | 4 | 10 | 5 |
| Co-PCBs TEQ | 6 | 9 | 19 | 17 | 30 | 10 | 20 | 5 | 14 | 9 |
| Total TEQ | 16 | 24 | 43 | 41 | 55 | 29 | 36 | 11 | 32 | 15 |

PCBs ranged from 8 to 30 pg/g. Furthermore, those Co-PCBs were detected in the adipose tissue of normal controls at levels, ranging from 3 to 9 pg/g, 41 to 280 and 47 to 200 pg/g, respectively. In addition, the TEQ value for Co-PCBs ranged from 5 to 30 pg/g.

In summary, the average TEQ values calculated by TEfs of the residual PCDDs, PCDFs and Co-PCBs in Yusho patients were 37, 720 and 19 pg/g, respectively. We therefore, concluded that PCDFs play the most important role in the pathogenesis of Yusho and thus the acceleration of their excretion would be essential in the treatment of such patients.

Araki (1974) suggested that the administration of cholestyramine decreased the intestinal reabsorption of PCBs in mice. Various experimental attempts to eliminate these chlorinated compounds retained in animals have been made with the use of squalane, lipid paraffin, and active charcoal beads. For instance, Yoshimura and Yamamoto (1975) reported that chlorinated aromatic hydrocarbons such as 2,4,3′,4′-TCB, administered to rats, were gradually eliminated into the feces through the intestinal wall, but were not excreted into the bile. Yoshimura et al.

(1985) reported that the fecal excretion of 2,3,4,7,8-PenCDF in rats was promoted by the administration of squalane. They concluded that this effect was due to either the inhibition of the reabsorption of 2,3,4,7,8-PenCDF, or the promotion of the excretion of the compound through the intestinal wall. On the other hand, Boylan et al. (1979) reported that in a case of chronic poisoning caused by chlordecone (Kepone), the residual chlordecone in the blood and fat were excreted into the stool by the oral administration of cholestyramine, an anion exchange resin, which appeared to be a practical method for treating chronic poisoning involving lipophilic toxins. Kamimura and Yoshimura (1985) observed that the fecal excretion of PCDFs was stimulated in rats by the use of cholestyramine, active charcoal beads, liquid paraffin or squalane and they thus concluded that the administration of these drugs stimulated the fecal excretion of PCDFs by from 1.8 to 2.9 fold.

In view of these findings using animal experiments, the study group for the therapy of Yusho in Kyushu University decided to start clinical trials for the stimulation of the fecal excretion of PCDFs in Yusho patients. Before beginning such trials, it was important to determine the relationship between the fecal excretion levels of PCDFs and the levels of the chemicals still retained in the tissue of such patients. We therefore investigated the fecal excretion of PCDFs and their concentrations in the blood and adipose tissue of Yusho patients who were subjected to the clinical trials. The patients were administered either cholestyramine or a combination of rice bran fiber (RBF) and cholestyramine. A similar clinical trial was also carried out on Yucheng patients in Taiwan as a joint research project of the Japanese and Taiwanese study groups.

### 9.2.2. *The Levels of PCDFs and PCBs in the Blood, Subcutaneous Adipose Tissue and Stool of Yusho Patients*

We determined the PCB and PCDF levels in the blood, subcutaneous adipose tissue and stool of Yusho patients 22 years after the exposure and the relationship between the fecal excretion and the concentrations of those compounds that had been retained in the blood and adipose tissue were also investigated (Iida et al., 1992). Subcutaneous adipose tissue specimens were obtained by a surgical operation and the stool samples were kept in an ice-box containing dry ice soon after defecation, by each subject.

#### 9.2.2.1. The PCDF and PCB Levels in the Blood

Table 9.2.6 shows the levels of PCDFs and PCBs in the blood of Yusho patents and normal controls. The concentrations of 2,3,4,7,8-PenCDF and 1,2,3,4,7,8- and 1,2,3,6,7,8-HxCDFs in the patients ranged from 0.2 to 6.6 pg/g, and 0.2 to 6.1 pg/g, respectively. Compared with the highest control values, the concentrations of

**Table 9.2.6.** The Concentrations of PCDFs and PCBs in the Blood of Yusho Patients and Normal Controls (on wet weight)

| Specimen | Sex | Age | Sample weight (g) | PCDFs (pg/g) | | | | PCBs (ng/g) |
|---|---|---|---|---|---|---|---|---|
| | | | | TCDF[a] | PenCDF[b] | HxCDF[c] | HpCDF[d] | |
| OM | M | 58 | 15 | NA[e] | 4.6 | 5.3 | 0.4 | 12 |
| YM | F | 54 | 14 | NA[e] | 6.6 | 6.1 | 0.4 | 22 |
| Patient MK | M | 54 | 13 | NA[e] | 0.3 | 0.3 | 0.2 | 3 |
| TK | F | 49 | 10 | NA[e] | 2.2 | 2.6 | 0.6 | 7 |
| TM | M | 49 | 15 | NA[e] | 0.2 | 0.2 | 0.2 | 3 |
| EM | F | 47 | 14 | NA[e] | 0.9 | 0.4 | 0.3 | 4 |
| YY | F | 57 | 96 | NA[e] | 0.05 | 0.04 | 0.1 | 4 |
| Control KT | M | 65 | 53 | NA[e] | 0.08 | 0.1 | 0.08 | 4 |
| TI | M | 44 | 86 | NA[e] | 0.09 | 0.04 | 0.1 | 2 |

[a]: 2,3,7,8-TCDF, [b]: 2,3,4,7,8-PenCDF, [c]: 1,2,3,4,7,8- and 1,2,3,6,7,8-HxCDFs, [d]: 1,2,3,4,6,7,8-HpCDF, [e]: due to a contamination of the charcoal used for the chromatographic column, an accurate determination was not feasible, and thus reading was not available.

2,3,4,7,8-PenCDF and 1,2,3,4,7,8- and 1,2,3,6,7,8-HxCDFs in the patients ranged from 2 to 73 fold, and from 2 to 61 fold higher than the highest control value, respectively. In patients OM and YM, who had both been seriously affected, the concentrations of the PenCDF and HxCDFs were much higher than those in the other patients. In addition, the concentrations of these PCDFs were also higher in female patients than in male patients. The concentrations of HpCDF in the blood of the patients that were lower than those of PenCDF and HxCDFs, ranged from 0.2 to 0.6 pg/g, which was about 2 to 6 times higher than those of the controls. The levels of PCBs in the blood were 12 ng/g for OM, and 22 ng/g for YM, while those of the other four patients were less than 7 ng/g, which were the same levels as that of the controls.

9.2.2.2. The PCDF and PCB Levels in the Subcutaneous Adipose Tissue

As shown in Table 9.2.7, the concentrations of PenCDF and HxCDFs in the subcutaneous adipose tissue of patients ranged from 100 to 1,700 pg/g, and from 110 to 1,400 pg/g, respectively, and were 4 to 64 times, and 3 to 41 times higher than the highest concentration of the three controls, respectively. 2,3,7,8-TCDF was also detected at concentrations of 18 to 34 pg/g, which was 1.5 to 3 times higher than the highest control concentration. HpCDF was not detected in samples from either OM, TM and EM, whereas from 33 to 110 pg/g of the compound was detected in the tissue specimens of YM, MK and TK. In addition, the concentration of PCBs in the adipose tissue of OM, YM and TK were slightly higher than those of the controls, but the levels of PCBs of patient MK, TM and EM were similar to

**Table 9.2.7.** The Levels of PCDFs and PCBs in the Subcutaneous Adipose Tissue of Yusho Patients and Normal Controls (on wet weight)

| Specimen | Sex | Age | Sample weight (g) | PCDFs (pg/g) | | | | PCBs (ng/g) |
|---|---|---|---|---|---|---|---|---|
| | | | | TCDF[a] | PenCDF[b] | HxCDF[c] | HpCDF[d] | |
| OM | M | 58 | 0.63 | 24 | 1,340 | 1,310 | N.D. | 2,200 |
| YM | F | 54 | 0.50 | 34 | 1,730 | 1,440 | 72 | 5,700 |
| Patient MK | M | 54 | 1.02 | 32 | 100 | 150 | 33 | 1,000 |
| TK | F | 49 | 0.93 | 18 | 850 | 770 | 110 | 2,300 |
| TM | M | 49 | 0.43 | 33 | 170 | 110 | N.D. | 1,200 |
| EM | F | 47 | 0.47 | 28 | 420 | 160 | N.D. | 1,300 |
| YY | F | 57 | 1.00 | 4 | 13 | 10 | N.D. | 1,300 |
| Control KT | M | 65 | 0.61 | 12 | 27 | 35 | 19 | 1,200 |
| TI | M | 44 | 0.78 | 6 | 18 | 9 | 9 | 710 |

[a]: 2,3,7,8-TCDF, [b]: 2,3,4,7,8-PenCDF, [c]: 1,2,3,4,7,8- and 1,2,3,6,7,8-HxCDFs, [d]: 1,2,3,4,6,7,8-HpCDF.

those of the controls.

9.2.2.3. The PCDF and PCB Levels in the Stool

Table 9.2.8 summarizes the fecal excretion of PCDFs and PCBs into the stool of both the patients and normal controls. The stool weights varied from an average from 64 to 213 g per day. The concentrations of PCBs in the stool were higher in the patients than in the controls, and were excreted at rates ranging from 320 to 1,400 ng per day. Similarly, PenCDF and HxCDFs were excreted at rates from 200 to 1,400 pg per day, and from 190 to 1,600 pg per day, respectively. In all cases, the levels of PenCDF and HxCDFs excreted in the stool, were higher than those of HpCDF. The excretion rates of these compounds in the stool were higher among females than males. In addition, no relationship was observed between the concentrations of these compounds in the stool and the total stool weights.

All the above findings clearly indicated that PenCDF and HxCDFs were the major congeners of the PCDFs remaining in the tissue of Yusho patients. Fig. 9.2.1. shows an important fact that the amount of PenCDF and HxCDFs daily excreted in the stool are correlated with the levels of these chemicals in both the blood as well as the subcutaneous adipose tissue ($p < 0.01$). The levels of these chemicals excreted in the stool of the six patients were also considerably higher than those of the three normal controls. Taking into account the observation by Yoshimura et al. (1984) that 2,3,4,7,8-PenCDF was mainly excreted in the feces of animals, we considered that the residual PCDFs were mainly excreted in the stool of Yusho patients as well. As shown in Table 9.2.8, PenCDF and HxCDFs were excreted in the stool of patients at rates ranging from 200 to 1,400 pg per day,

**Table 9.2.8.** The Fecal Excretion Levels of PCDFs and PCBs in the Stool of Yusho Patients and Normal Controls (on wet weight)

| Specimen | | Sex | Age | Sample weight (g/day) | PCDFs (pg/day) | | | | PCBs (ng/day) |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | TCDF[a] | PenCDF[b] | HxCDF[c] | HpCDF[d] | |
| Patient | OM | M | 58 | 112 ± 51 | 91 ± 36 | 1,050 ± 400 | 1,030 ± 740 | 90 ± 50 | 680 ± 290 |
| | YM | F | 54 | 137 ± 64 | 38 ± 15 | 1,380 ± 560 | 1,530 ± 570 | 120 ± 64 | 1,370 ± 600 |
| | MK | M | 54 | 126 ± 36 | 44 ± 14 | 200 ± 49 | 200 ± 61 | 31 ± 10 | 570 ± 180 |
| | TK | F | 49 | 213 ± 28 | 160 ± 160 | 1,160 ± 500 | 1,590 ± 740 | 130 ± 75 | 1,220 ± 600 |
| | TM | M | 49 | 75 ± 18 | 44 ± 14 | 200 ± 52 | 190 ± 50 | 38 ± 12 | 550 ± 90 |
| | EM | F | 47 | 64 ± 21 | 28 ± 6 | 330 ± 130 | 220 ± 69 | 28 ± 8 | 320 ± 110 |
| Control | YY | F | 57 | 157 ± 62 | 50 | 42 | 28 | 28 | 180 |
| | KT | M | 65 | 97 ± 25 | 34 | 54 | 46 | 46 | 92 |
| | TI | M | 44 | 162 ± 19 | 36 | 44 | 32 | 32 | 170 |

[a]: 2,3,7,8-TCDF, [b]: 2,3,4,7,8-PenCDF, [c]: 1,2,3,4,7,8- and 1,2,3,6,7,8-HxCDFs, [d]: 1,2,3,4,6,7,8-HpCDF.

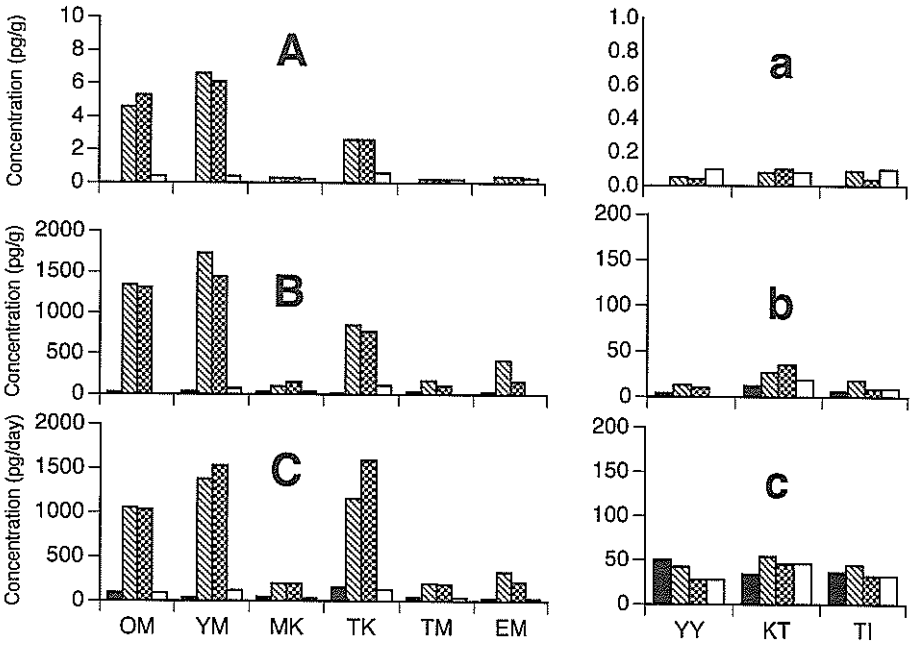


**Fig. 9.2.1.** PCDFs in the Blood, Subcutaneous Adipose Tissue and Stool of Yusho Patients and Normal Controls

Patient blood (A), subcutaneous adipose tissue (B) and stool (C). Control blood (a), subcutaneous adipose tissue (b) and stool (c).

2,3,7,8-TCDF; 2,3,4,7,8-PenCDF; 1,2,3,4,7,8- and 1,2,3,6,7,8-HxCDF; 1,2,3,4,6,7,8-HpCDF

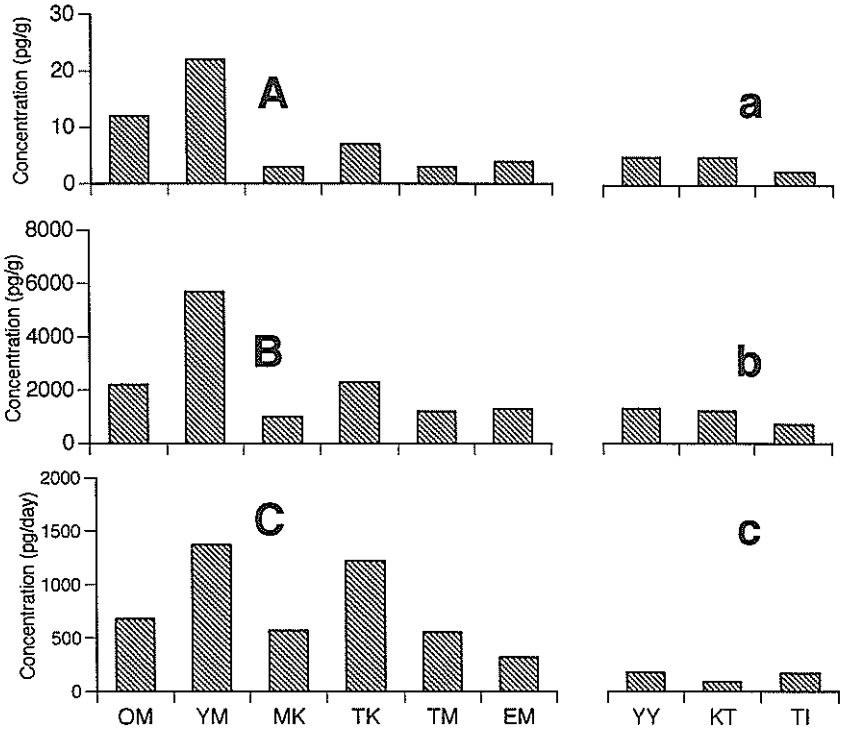


**Fig. 9.2.2.** PCBs in the Blood, Subcutaneous Adipose Tissue and Stool of Yusho Patients and Normal Controls
Patient blood (A), subcutaneous adipose tissue (B) and stool (C). Control blood (a), subcutaneous adipose tissue (b) and stool (c).

respectively, and were equivalent to those compounds contained in one gram of adipose tissue. Assuming that 10 kg of fat is contained in the body of a Yusho patient, over 30 years may thus be required to eliminate all the PCDFs retained in the tissue of the patient.

The PCB levels in the blood, the subcutaneous adipose tissue and the stool of the patients and normal controls, are illustrated in Fig. 9.2.2. The results were similar to those for the PenCDF and HxCDFs, but the correlation among three concentrations was less evident. Since PCBs are much less toxic than PCDFs, they may not be very important in the pathogenesis of the disease.

### 9.2.3. *Clinical Trials of Cholestyramine and a Combination of Rice Bran Fiber and Cholestyramine in Yusho Patients*

Takenaka et al. (1991) observed that, in a group of rats fed a diet containing 10% RBF and cholestyramine, the fecal excretion of PCBs increased 5.4 times that seen in the control group. In the present study we determined whether or not the excre-

**Table 9.2.9.** The Fecal Excretion Levels of PCDFs and PCBs in the Stool from Yusho Patients before and during the Administration of Cholestyramine

| Patient | Age | Sex | Administration | Stool (g/day) | PeCDF[a] (pg/day) | HxCDFs[b] (pg/day) | PCBs (ng/day) |
|---|---|---|---|---|---|---|---|
| A | 60 | M | Before administration | 110 | 1,100 | 1,000 | 680 |
| | | | During administration | 110 | 1,300 | 1,300 | 860 |
| B | 56 | F | Before administration | 140 | 1,400 | 1,500 | 1,400 |
| | | | During administration | 240 | 1,600 | 1,200 | 1,300 |
| C | 53 | M | Before administration | 75 | 200 | 190 | 550 |
| | | | During administration | 76 | 120 | 110 | 370 |
| D | 49 | F | Before administration | 64 | 330 | 220 | 320 |
| | | | During administration | 90 | 330 | 240 | 420 |
| E | 55 | M | Before administration | 130 | 200 | 200 | 570 |
| | | | During administration | 150 | 190 | 200 | 660 |
| F | 53 | F | Before administration | 210 | 1,200 | 1,600 | 1,200 |
| | | | During administration | 230 | 730 | 930 | 850 |

[a]: 2,3,4,7,8-PenCDF, [b]: 1,2,3,4,7,8- and 1,2,3,6,7,8-HxCDFs.

tion of residual PCDFs in Yusho patients is thus enhanced by the administration of RBF and cholestyramine (Iida et al., 1992).

The RBF used was refined using the Prosky method (Prosky et al., 1985) until it contained 85% of dietary fiber (23.5% cellulose, 43.2% hemicellulose and 18.4% lignin).

#### 9.2.3.1. The Influence of Cholestyramine on the Fecal Excretion of PCDFs and Others

Six patients with Yusho took 4 g of cholestyramine suspended in a cup of water three times a day (after each meal) for six months.

They consisted of three married couples who showed the gas chromatographic profile of PCBs which was specific for Yusho. All stool discharged from each patient was collected for 6 consecutive days before the administration of cholestyramine and two, four and six months after the start of continuous administration.

Table 9.2.9. summarizes the results for the fecal excretion of PCDFs by Yusho patients who took cholestyramine. The stool weight increased 1.7 and 1.4 times after the administration as compared with the stool weight before the administration in patients B and D, respectively, while in the other four patients, the stool weight did not change substantially. In patient A, the fecal excretion of 2,3,4,7,8-PenCDF before and during the administration period was 1,100 and 1,300 pg/day, respectively, and that of 1,2,3,4,7,8- and 1,2,3,6,7,8-HxCDFs was 1,000 and 1,300 pg/day, respectively. This was the only patient in whom the excretion of the

**Table 9.2.10.** The Fecal Excretion Levels of PCDFs in the Stool from Yusho Patients before and during the Administration of Rice Bran Fiber and Cholestyramine

| Patient | Age | Sex | Administration | Stool (g/day) | Fecal Excretion | |
|---|---|---|---|---|---|---|
| | | | | | PeCDF[a] (pg/day) | HxCDFs[b] (pg/day) |
| A | 60 | M | Before administration | 68 | 1,100 | 1,400 |
| | | | During administration | 130 | 870 | 1,000 |
| B | 56 | F | Before administration | 210 | 1,130 | 1,170 |
| | | | During administration | 390 | 1,500 | 1,800 |
| G | 53 | M | Before administration | 75 | 420 | 310 |
| | | | During administration | 170 | 630 | 430 |
| H | 49 | F | Before administration | 80 | 2,350 | 2,470 |
| | | | During administration | 150 | 2,300 | 2,200 |

[a]: 2,3,4,7,8-PenCDF, [b]: 1,2,3,4,7,8- and 1,2,3,6,7,8-HxCDFs.

PenCDF and HxCDFs in the stool increased after administration, but the increase was only slight (about 20%). It was thus concluded, therefore, that the fecal excretion of PCDFs is not promoted by the administration of cholestyramine alone.

### 9.2.3.2. The Effect of the Combined Administration of Rice Bran Fiber and Cholestyramine on the Fecal Excretion of PCDFs

For two weeks, two married couples with Yusho took 10 g of RBF and 4 g of cholestyramine suspended in a cup of water three times a day after each meal.

All the stool discharged from each patient was collected for a 7-day period before administration and for a 13-day period during administration.

Table 9.2.10 summarizes the results of the fecal excretion of PCDFs by these patients. The stool weight was increased after administration by 1.9 to 2.3 fold that before administration.

The amount of 2,3,4,7,8-PenCDF in the stool before and after the administration was 1,100 and 1,500 pg/day in patient B, and 420 and 630 pg/day in patient G, respectively. Similarly, the quantity of HxCDFs excreted before and after administration was 1,400 and 1,800 pg/day in patient B and 310 and 430 pg/day in patients G, respectively. In these two patients, the excretion of the PenCDF and HxCDFs was noted to increase by from 30–50% and from 40–50% after administration, respectively, while no such increase was observed in the other two patients. This discrepancy may be related to the fact that the collection of the stool was not 100% complete as indicated by statements made by the patients. The above results only suggest that the administration of cholestyramine together with RBF might be effective for promoting the excretion of PCDFs in stool.

The clinical symptoms and sign shown by the patients during and after the above trials were carefully examined by physicians. No clear beneficial or deleterious effect of the administration was observed (Murai et al., 1991; Tsuji et al., 1993), although some patients stated that they noticed an improvement in their dermal conditions during the trial.

### *9.2.4. The Relationship between the Levels of PCDDs, PCDFs and Co-PCBs in the Blood and Their Fecal Excretion in Yucheng Patients in Taiwan*

The levels of PCDDs, PCDFs and coplanar PCBs were measured in the blood and stool specimens obtained from seventeen patients with Yucheng in Taiwan (Iida, 1995).

The blood samples were collected from seventeen Yucheng patients in January 1993 and in August 1993, while the stool samples were collected for three weeks in August 1993. No Taiwanese controls were examined however.

The analysis of these compounds as well as the method of stool collection were practically the same as those used in the study of Yusho patients.

#### 9.2.4.1. The Levels of PCDDs, PCDFs and Co-PCBs in the Blood in Yucheng Patients

Table 9.2.11 shows that the average concentrations of PCDDs, PCDFs and Co-PCBs in the blood collected in January 1993 and in August 1993 were 590 and 570 pg of TEQ/g lipid, respectively. This clearly indicates that the concentration of the chemicals in the blood did not decrease during a period of about seven months.

It is also notable that the concentrations of PCDDs, PCDFs and Co-PCBs in the blood of these patients were on the average 21, 540 and 10 pg of TEQ/g lipid, respectively.

Among the congeners of PCDFs, the average concentration of HxCDFs was the highest and the next highest was PenCDF.

On the other hand, as shown in Table 9.2.5, the concentrations of those compounds in the normal controls (in Japan) were on average 7, 10 and 14 pg of TEQ/g lipid, respectively. Therefore, the TEQ values of PCDDs and PCDFs in the patients' blood were from 3 and 54 times higher than those in the normal Japanese controls.

#### 9.2.4.2. The Fecal Excretion Levels of PCDDs, PCDFs and Co-PCBs in Yucheng Patients

As shown in Table 9.2.12, the average fecal excretion of OCDD was the highest on average among the congeners of PCDDs. Among the congeners of PCDFs, the average concentration of HxCDFs was the highest while the next highest was

**Table 9.2.11.** The Concentration of PCDDs, PCDFs and Co-PCBs in Blood of Yucheng Patients in Taiwan (pg/g Lipid Basis)

| Congener | Patients | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | A04 | A05 | B01 | B02 | B03 | B04 | B06 | C02 | C04 | D01 | D02 | D03 | D06 | D09 | D10 | D11 | D13 | Mean | SD | Min | Max |
| 2,3,7,8-TCDD | 5 | 4 | ND (< 7) | 6 | ND (< 2) | 7 | 2 | 2 | 7 | 7 | 13 | 4 | 8 | 3 | 3 | 3 | 3 | 5 | 3 | 2 | 13 |
| | 2 | 2 | 2 | 5 | 2 | 2 | 2 | 4 | 17 | 5 | 8 | 2 | 3 | 4 | 3 | 2 | 1 | 4 | 4 | 1 | 17 |
| 1,2,3,7,8-PenCDD | 8 | 11 | 19 | 15 | 10 | 25 | 15 | 16 | 13 | 16 | 14 | 10 | 11 | 14 | 11 | 13 | 10 | 14 | 4 | 8 | 25 |
| | 8 | 7 | 10 | 14 | 14 | 12 | 7 | 15 | 44 | 13 | 18 | 8 | 11 | 9 | 14 | 8 | 9 | 13 | 9 | 7 | 44 |
| 1,2,3,6,7,8-HxCDD | 60 | 81 | 120 | 87 | 92 | 63 | 110 | 120 | 91 | 140 | 56 | 78 | 81 | 110 | 110 | 76 | 100 | 93 | 23 | 56 | 140 |
| | 48 | 73 | 79 | 83 | 82 | 46 | 89 | 100 | 110 | 110 | 68 | 60 | 77 | 110 | 96 | 82 | 92 | 83 | 20 | 46 | 110 |
| 1,2,3,4,6,7,8-HpCDD | 55 | 53 | 72 | 60 | 36 | 170 | 47 | 15 | 45 | 40 | 82 | 45 | 42 | 50 | 42 | 48 | 40 | 56 | 33 | 15 | 170 |
| | 44 | 36 | 27 | 54 | 30 | 110 | 29 | 30 | 110 | 22 | 68 | 42 | 42 | 47 | 38 | 41 | 57 | 49 | 26 | 22 | 110 |
| OCDD | 610 | 320 | 530 | 410 | 280 | 580 | 310 | 130 | 390 | 250 | 530 | 330 | 510 | 310 | 300 | 270 | 330 | 380 | 130 | 130 | 610 |
| | 2,100 | 450 | 420 | 470 | 350 | 800 | 330 | 240 | 700 | 440 | 870 | 470 | 440 | 270 | 320 | 280 | 440 | 550 | 440 | 240 | 2,100 |
| 2,3,7,8-TCDF | 10 | 6 | 14 | 11 | 6 | NA | 9 | 6 | 13 | 15 | 14 | 7 | 14 | 9 | 5 | 9 | 7 | 10 | 3 | 5 | 15 |
| | 4 | 6 | 9 | 11 | 6 | 8 | 6 | 8 | 26 | 9 | 12 | 10 | 63 | 11 | 9 | 18 | 13 | 13 | 14 | 4 | 63 |
| 1,2,3,7,8-PenCDF | 13 | 11 | 15 | 8 | 7 | 92 | 7 | 7 | 11 | 11 | 13 | 10 | 6 | 10 | 9 | 15 | 10 | 15 | 20 | 6 | 92 |
| | 7 | 6 | 8 | 7 | 5 | 7 | 5 | 10 | 31 | 9 | 15 | 8 | 7 | 8 | 8 | 16 | 10 | 10 | 6 | 5 | 31 |
| 2,3,4,7,8-PenCDF | 420 | 810 | 840 | 420 | 650 | 350 | 430 | 1,300 | 870 | 2,100 | 570 | 890 | 460 | 1,300 | 610 | 260 | 520 | 750 | 460 | 260 | 2,100 |
| | 380 | 850 | 720 | 450 | 550 | 200 | 370 | 1,000 | 630 | 2,400 | 550 | 650 | 520 | 1,300 | 640 | 190 | 330 | 690 | 520 | 190 | 2,400 |
| 1,2,3,4,7,8-HxCDF | 580 | 1,300 | 2,200 | 870 | 1,500 | 850 | 1,600 | 2,900 | 1,900 | 3,900 | 1,500 | 1,500 | 1,200 | 2,800 | 1,400 | 1,500 | 1,200 | 1,700 | 840 | 580 | 3,900 |
| | 620 | 1,500 | 2,300 | 960 | 1,600 | 650 | 1,400 | 4,500 | 1,500 | 5,200 | 1,600 | 1,400 | 1,300 | 2,900 | 1,600 | 1,800 | 1,500 | 1,900 | 1,200 | 620 | 5,200 |
| 1,2,3,4,6,7,8-HpCDF | 30 | 46 | 75 | 37 | 36 | 67 | 81 | 36 | 39 | 67 | 56 | 49 | 49 | 60 | 33 | 43 | 35 | 49 | 16 | 30 | 81 |
| | 28 | 42 | 67 | 48 | 39 | 31 | 73 | 54 | 85 | 67 | 72 | 56 | 61 | 58 | 41 | 68 | 65 | 56 | 16 | 28 | 85 |
| 3,3′,4,4′-TeCB | 33 | 20 | 38 | 34 | 15 | 9 | 18 | 7 | 16 | 35 | 27 | 13 | 29 | 19 | 9 | 22 | 44 | 23 | 11 | 7 | 44 |
| | 15 | 12 | 21 | 28 | 10 | 19 | 15 | 23 | 11 | 16 | 24 | 15 | 13 | 30 | 18 | 39 | 30 | 20 | 8 | 10 | 39 |
| 3,3′,4,4′,5-PenCB | 30 | 29 | 62 | 66 | 66 | 115 | 46 | 140 | 70 | 100 | 47 | 88 | 38 | 52 | 91 | 140 | 170 | 79 | 42 | 29 | 170 |
| | 39 | 40 | 62 | 69 | 56 | 67 | 64 | 160 | 53 | 92 | 82 | 64 | 63 | 96 | 100 | 120 | 150 | 81 | 35 | 39 | 160 |
| 3,3′,4,4′,5,5′-HxCB | 24 | 27 | 36 | 49 | 35 | 61 | 30 | 68 | 38 | 45 | 27 | 30 | 24 | 29 | 42 | 37 | 56 | 39 | 13 | 24 | 68 |
| | 33 | 38 | 41 | 65 | 54 | 31 | 49 | 83 | 37 | 57 | 41 | 34 | 41 | 44 | 82 | 34 | 77 | 49 | 17 | 31 | 83 |
| Total-TEQ[a] | 290 | 560 | 670 | 330 | 500 | 300 | 400 | 970 | 670 | 1,500 | 470 | 630 | 380 | 990 | 480 | 320 | 490 | 590 | 320 | 290 | 1,500 |
| | 270 | 590 | 610 | 360 | 460 | 190 | 350 | 1,000 | 530 | 1,800 | 470 | 490 | 420 | 970 | 520 | 310 | 350 | 570 | 380 | 190 | 1,800 |
| Fat (%) | 0.44 | 0.42 | 0.34 | 0.46 | 0.70 | 0.36 | 0.40 | 1.62 | 0.44 | 0.56 | 0.35 | 0.49 | 0.35 | 0.36 | 0.51 | 0.37 | 0.37 | 0.50 | 0.30 | 0.34 | 1.62 |
| | 0.50 | 0.45 | 0.42 | 0.37 | 0.59 | 0.33 | 0.42 | 0.51 | 0.43 | 0.54 | 0.29 | 0.37 | 0.36 | 0.36 | 0.42 | 0.35 | 0.31 | 0.41 | 0.08 | 0.29 | 0.59 |

[a]: Calculated by TCDD equivalent factors decided by the NATO for PCDDs and PCDFs, and WHO for Co-PCBs. NA: Not available. The data on the upper line shows the concentrations in the blood collected in January 1993 (before the clinical trials) while those on the lower lines show the concentrations in the blood collected in August 1993 (after the clinical trials).

**Table 9.2.12.** The Fecal Excretion Levels of PCDDs, PCDFs and Co-PCBs in Yucheng Patients in Taiwan (pg/day)

| Congener | Patients | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | A04 | A05 | B01 | B02 | B03 | B04 | B06 | C02 | C04 | D01 | D02 | D03 | D06 | D09 | D10 | D11 | D13 | Mean | SD | Min | Max |
| 2,3,7,8-TCDD | 3 | 1 | 1 | 4 | 3 | 2 | 4 | 5 | 2 | 1 | 6 | 2 | 3 | 2 | 6 | 4 | 1 | 3 | 2 | 1 | 6 |
| 1,2,3,7,8-PenCDF | 13 | 8 | 6 | 18 | 16 | 13 | 23 | 14 | 25 | 7 | 33 | 10 | 40 | 13 | 57 | 21 | 4 | 19 | 14 | 4 | 57 |
| 1,2,3,6,7,8-HxCDD | 68 | 94 | 65 | 130 | 120 | 57 | 190 | 96 | 67 | 64 | 79 | 140 | 160 | 200 | 240 | 180 | 38 | 120 | 59 | 38 | 240 |
| 1,2,3,4,6,7,8-HpCDD | 150 | 56 | 40 | 110 | 90 | 140 | 88 | 49 | 49 | 41 | 59 | 85 | 87 | 99 | 97 | 73 | 19 | 78 | 35 | 19 | 150 |
| OCDD | 1,800 | 930 | 1,100 | 1,000 | 1,000 | 1,200 | 1,700 | 940 | 560 | 670 | 1,300 | 1,200 | 1,200 | 2,600 | 1,300 | 1,300 | 330 | 1,200 | 520 | 330 | 2,600 |
| 2,3,7,8-TCDF | 7 | 7 | 7 | 13 | 7 | 6 | 18 | 15 | 8 | 6 | 9 | 15 | 13 | 31 | 28 | 23 | 3 | 13 | 8 | 3 | 31 |
| 1,2,3,7,8-PenCDF | 10 | 11 | 15 | 12 | 14 | 9 | 44 | 29 | 9 | 11 | 15 | 28 | 26 | 73 | 51 | 44 | 7 | 24 | 18 | 7 | 73 |
| 2,3,4,7,8-PenCDF | 470 | 930 | 570 | 570 | 690 | 230 | 1,400 | 960 | 660 | 600 | 820 | 1,400 | 980 | 2,400 | 1,900 | 730 | 170 | 910 | 580 | 170 | 2,400 |
| 1,2,3,4,7,8-HxCDF | 900 | 2,000 | 1,700 | 1,300 | 2,200 | 940 | 6,100 | 3,700 | 1,100 | 1,200 | 2,300 | 3,100 | 2,700 | 6,300 | 3,300 | 4,400 | 620 | 2,600 | 1,700 | 620 | 6,300 |
| 1,2,3,4,6,7,8-HpCDF | 52 | 59 | 74 | 67 | 82 | 38 | 200 | 64 | 33 | 30 | 73 | 110 | 79 | 160 | 150 | 140 | 20 | 84 | 51 | 20 | 200 |
| 3,3′,4,4′-TeCB | 33 | 22 | 17 | 57 | 37 | 40 | 81 | 270 | 26 | 37 | 43 | 48 | 39 | 62 | 160 | 340 | 16 | 78 | 92 | 16 | 340 |
| 3,3′,4,4′,5-PenCB | 28 | 35 | 36 | 100 | 46 | 63 | 180 | 110 | 49 | 51 | 68 | 89 | 120 | 92 | 490 | 300 | 54 | 110 | 120 | 28 | 490 |
| 3,3′,4,4′,5,5′-HxCB | 27 | 31 | 24 | 76 | 38 | 42 | 130 | 51 | 41 | 34 | 49 | 60 | 75 | 69 | 220 | 120 | 21 | 65 | 51 | 21 | 220 |
| Total-TEQ[a] | 350 | 690 | 470 | 460 | 600 | 240 | 1,400 | 890 | 470 | 450 | 680 | 1,000 | 820 | 1,900 | 1,400 | 880 | 160 | 760 | 460 | 160 | 1,900 |

[a]: Calculated based on TCDD equivalent factors as determined by the NATO for PCDDs and PCDFs, and as determined by WHO for Co-PCBs.

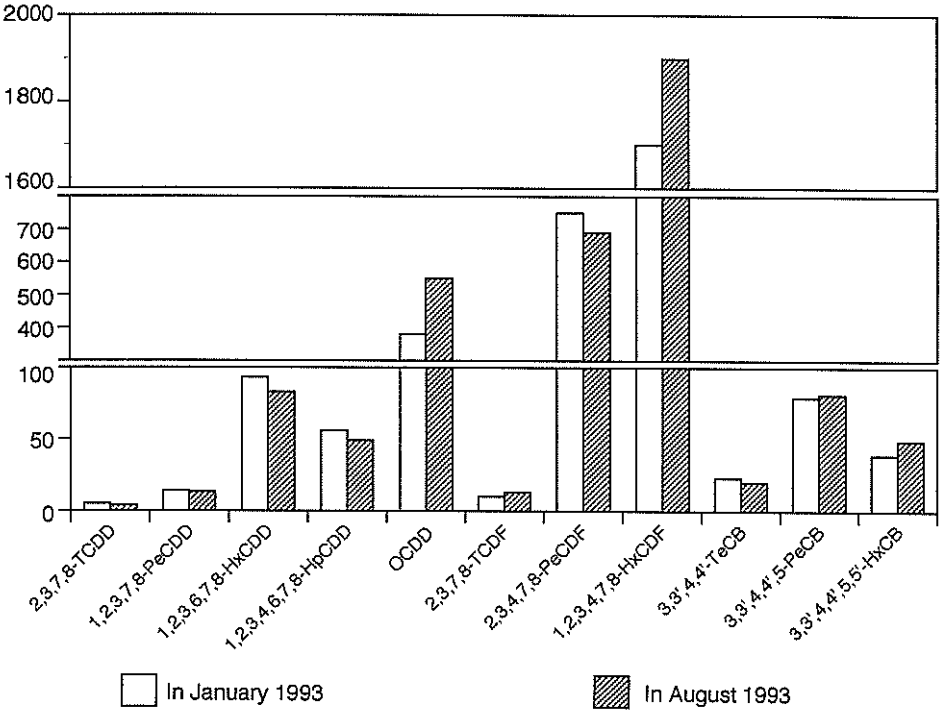


**Fig. 9.2.3.** The Concentration of Congeners of PCDDs, PCDFs and Co-PCBs in the Blood (pg/g lipid) Collected in January 1993 and in August 1993 from the Patients with Yucheng in Taiwan

PenCDF. Fig. 9.2.4 shows the relationship between the concentration of these chemicals and their fecal excretion in Yucheng patients. The fecal excretion closely corresponded to the concentration of each chemical in the blood.

9.2.4.3. The TEQs of PCDDs, PCDFs and Co-PCBs in the Blood and the Fecal Excretion of these Compounds

As shown in Table 9.2.13, the average total TEQ value in the blood was 580 pg/g, and most of which consisted of the TEQ of PCDFs (94%), while those of PCDDs and Co-PCBs were only 4% and 2% of the total TEQ, respectively. The average total TEQ value of these compounds excreted into the feces was 760 pg/day, and most of which was again TEQ of PCDFs (95%) while TEQ of PCDDs and Co-PCBs represented only 3% and 2 % of the total TEQ, respectively.

In view of the above facts, it was thus considered that PCDFs were the most important compounds not only for Yusho but also for Yucheng.

We previously reported that the concentrations of PCDDs, PCDFs and Co-PCBs in the blood lipid closely reflected their concentrations in the adipose tissue

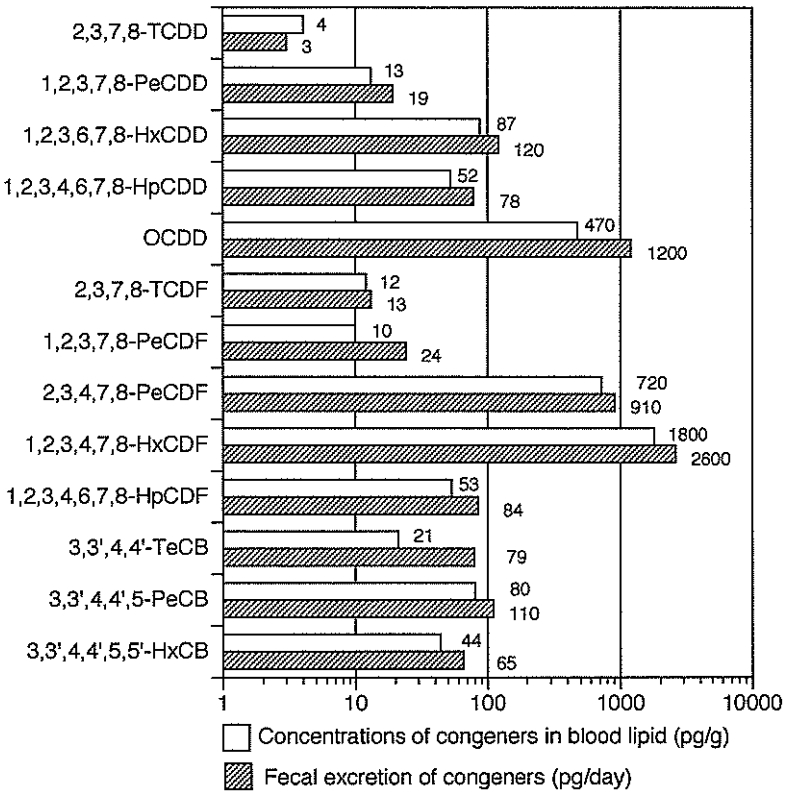


**Fig. 9.2.4.** The Concentration of Congeners of PCDDs, PCDFs and Co-PCBs in the Blood and Fecal Excretion Levels of Those Congeners in the Patients with Yucheng in Taiwan

**Table 9.2.13.** The Concentration of PCDDs, PCDFs and Co-PCBs Congeners in the Blood Lipid and Fecal Excretion of Patients with Yucheng in Taiwan

| | Concentration in blood lipid (pg/g) | | Fecal excretion levell (pg/day) | |
|---|---|---|---|---|
| | Mean ± S.D. | Range | Mean ± S.D. | Range |
| PCDD-TEQ | 21 ± 5 (4 ± 3%)[a] | 15–37 (2–9%)[a] | 26 ± 13 (3 ± 2%)[a] | 7–61 (2–7%)[a] |
| PCDF-TEQ | 550 ± 340 (94 ± 3%)[a] | 210–1,600 (87–98%)[a] | 720 ± 440 (95 ± 2%)[a] | 150–1,800 (89–98%)[a] |
| Co-PCB-TEQ | 10 ± 4 (2 ± 1%)[a] | 5–19 (1–5%)[a] | 15 ± 14 (2 ± 1%)[a] | 4–60 (1–4%)[a] |
| Total TEQ | 580 ± 342 (100%)[a] | 250 ± 1,600 | 760 ± 460 (100%)[a] | 160–1,900 |

[a]: Percentage of the total TEQ.

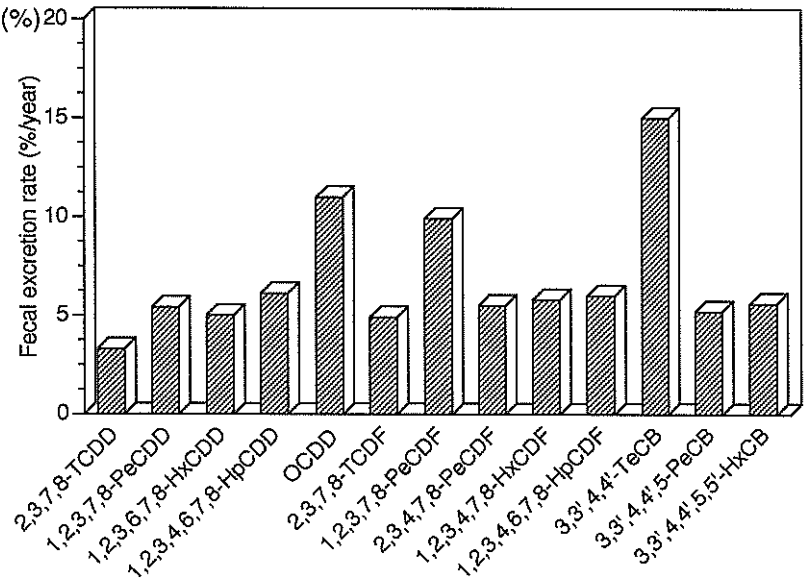


**Fig. 9.2.5.** Estimation of the Fecal Excretion Rate (%/year) in Comparison to the Residual Congeners of PCDDs, PCDFs and Co-PCBs in Yucheng Patients in Taiwan

in normal persons (Hirakawa et al., 1992). Utilizing the data shown in Table 9.2.11 and assuming that the Yucheng patients contain on average 10 kg of body fat, the amounts of these chemicals remaining in their bodies can be readily estimated. On the other hand, the fecal excretion of these compounds per year is calculated based on the daily excretion data shown in Table 9.2.12. Fig. 9.2.5 shows the rate of fecal excretion of specific congeners of PCDDs, PCDFs and the Co-PCBs remaining in the adipose tissue of Yucheng patients, as indicated as a percentage of the amount of these compounds excreted annually to the corresponding total remaining amount. It is thus easily understood that OCDD, 1,2,3,7,8-PenCDF and TCB have higher excretion rates, while 2,3,7,8-TCDD has the lowest rate. The rates of the other compounds are between 5.0% and 6.1% of body burden per year. These compounds are well-known environmental contaminants and their daily intake through foods is known to influence the rate of their fecal excretion. However, in Yucheng patients, the amounts of PenCDF and HxCDFs, remaining in their bodies are very large and the influence of the small daily intake of those compounds from diet could be neglected.

Assuming that the fecal excretion is the only route of excretion, the half lives are also estimated to be 9.1 and 8.6 years for PenCDF and HxCDFs, respectively. In 1982, that is, fourteen years after Yusho broke out, to 1991, using the one compartment model, Masuda et al. (1993) determined the half lives of PenCDF and

HxCDFs in Yusho patients to be 11.7 and 7 years, respectively. These findings are very close to the corresponding half lives in Yucheng patients, as calculated by us.

### 9.2.5. *A Clinical Trial of a Combination of Rice Bran Fiber and Cholestyramine to Promote the Fecal Excretion of PCDFs and PCBs Retained in the Tissue of Yucheng Patients*

Since the levels of PCDFs and PCBs in the tissue of Yusho patients has decreased considerably in the past 20 years, the possible beneficial effect of the oral administration of RBF and cholestyramine to such patients may not clearly be observed as a change which might appear in such lowered levels of the compounds. We therefore considered that the Yucheng patients in Taiwan would be preferable to Yusho patients as subjects for our clinical because they were less chronic sufferers than the Yusho patients and were expected to still maintain a fairly high level of these compounds in their tissue. Fortunately, a joint research project was organized and developed by the Study Group for the Therapy of "Yusho" and the Research Team on Yucheng in Taiwan in order to promote the clinical trial. With the kind cooperation of Yucheng patients and the researchers of Yucheng, it could be determined as to whether or not the administration accelerates the fecal excretion of the compounds (Iida et al., 1995). The cholestyramine and RBF used in this trial were the same materials as those used in the study of Yusho patients.

Eight Yucheng patients were orally administered 6 g of RBF and 4 g of cholestyramine suspended in a cup of water three times a day after meals for two weeks. Before the administration, all the samples of stools excreted by the patients were each collected for a 7-day period. During the administration, all stools samples excreted by the patients were collected for a 14-day period. Twenty milliliters of blood were also obtained from each patient before and after the administration.

#### 9.2.5.1. The PCDF and PCB Levels in the Blood and Stool before and after Administration of Rice Bran Fiber and Cholestyramine

Table 9.2.14. shows the concentrations of PCDDs, PCDFs, Co-PCBs and PCBs in the blood obtained from each patient before and after the clinical trial on a whole base. After the clinical trial, the average concentrations were found to decrease for most of the determined congeners as compared with those before the trial. The decrease seen in the concentration of 1,2,3,6,7,8-HxCDD, PenCDF or Total TEQ was each statistically significant ($p < 0.01$) and the decrease in fat concentration seen was also significant ($p < 0.05$).

Table 9.2.15. shows the fecal excretion levels of PenCDF, HxCDFs and PCBs in six patients during the three specific periods of administration. The average stool weight was $210 \pm 45$ g/day before the administration, $250 \pm 50$ g/day during the

**Table 9.2.14.** The Concentrations of PCDDs, PCDFs, Co-PCBs and PCBs in the Blood of Yucheng Patients (pg/g, whole basis)

| Congener | Patients | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | A01 | A02 | A03 | D04 | D05 | D12 | D14 | D15 | Mean |
| 2,3,7,8-TCDD | N.D. | 0.02 | 0.03 | N.D. | N.D. | 0.01 | 0.03 | N.D. | 0.02 |
| | 0.02 | 0.01 | 0.01 | 0.01 | 0.01 | 0.01 | 0.01 | 0.01 | 0.01 |
| 1,2,3,7,8-PenCDD | 0.05 | 0.07 | 0.13 | 0.02 | 0.04 | 0.04 | 0.04 | 0.03 | 0.05 |
| | 0.04 | 0.03 | 0.08 | 0.03 | 0.03 | 0.03 | 0.03 | 0.04 | 0.04 |
| 1,2,3,6,7,8-HxCDD | 0.31 | 0.42 | 0.92 | 0.18 | 0.33 | 0.36 | 0.36 | 0.44 | 0.41 |
| | 0.28 | 0.33 | 0.72 | 0.17 | 0.22 | 0.18 | 0.26 | 0.39 | 0.32 |
| 1,2,3,4,6,7,8-HpCDD | 0.21 | 0.13 | 0.29 | 0.23 | 0.21 | 0.25 | 0.15 | 0.17 | 0.21 |
| | 0.24 | 0.14 | 0.24 | 0.14 | 0.13 | 0.15 | 0.14 | 0.19 | 0.17 |
| OCDD | 1.7 | 2.9 | 4.6 | 1.3 | 1.1 | 2.0 | 1.8 | 1.6 | 2.1 |
| | 1.8 | 2.4 | 4.0 | 1.0 | 1.7 | 1.4 | 1.4 | 1.5 | 1.9 |
| 2,3,7,8-TCDF | 0.05 | 0.07 | 0.06 | 0.02 | 0.04 | 0.03 | 0.03 | 0.03 | 0.04 |
| | 0.03 | 0.03 | 0.03 | 0.02 | 0.03 | 0.06 | 0.04 | 0.03 | 0.03 |
| 1,2,3,7,8-PenCDF | 0.05 | 0.06 | 0.08 | 0.05 | 0.03 | 0.04 | 0.02 | 0.03 | 0.04 |
| | 0.04 | 0.02 | 0.04 | 0.02 | 0.02 | 0.06 | 0.03 | 0.04 | 0.03 |
| 2,3,4,7,8-PenCDF | 2.6 | 3.5 | 3.8 | 1.3 | 1.9 | 1.0 | 1.9 | 2.7 | 2.3 |
| | 2.0 | 3.0 | 2.8 | 1.0 | 1.3 | 0.5 | 1.2 | 2.3 | 1.8 |
| 1,2,3,4,7,8-HxCDF | 5.4 | 9.7 | 15.8 | 3.8 | 5.2 | 5.3 | 4.7 | 8.7 | 7.3 |
| | 4.9 | 10.8 | 13.1 | 3.1 | 4.0 | 3.3 | 4.2 | 10.1 | 6.7 |
| 1,2,3,4,6,7,8-HpCDF | 0.19 | 0.40 | 0.44 | 0.16 | 0.21 | 0.17 | 0.13 | 0.16 | 0.23 |
| | 0.20 | 0.28 | 0.32 | 0.16 | 0.13 | 0.20 | 0.24 | 0.20 | 0.22 |
| 3,3′,4,4′-TCB | 0.10 | 0.16 | 0.12 | 0.07 | 0.06 | 0.07 | 0.09 | 0.05 | 0.09 |
| | 0.17 | 0.06 | 0.09 | 0.06 | 0.05 | 0.13 | 0.10 | 0.09 | 0.09 |
| 3,3′,4,4′,5-PenCB | 0.21 | 0.21 | 0.53 | 0.21 | 0.22 | 0.34 | 0.34 | 0.96 | 0.38 |
| | 0.31 | 0.14 | 0.50 | 0.19 | 0.17 | 0.29 | 0.26 | 0.65 | 0.31 |
| 3,3′,4,4′,5,5′-HxCB | 0.16 | 0.13 | 0.41 | 0.07 | 0.09 | 0.18 | 0.14 | 0.36 | 0.19 |
| | 0.20 | 0.11 | 0.45 | 0.08 | 0.11 | 0.14 | 0.14 | 0.31 | 0.19 |
| Total TEQ[a] | 2.0 | 2.9 | 3.8 | 1.1 | 1.6 | 1.2 | 1.6 | 2.5 | 2.1 |
| | 1.6 | 2.7 | 2.9 | 0.9 | 1.2 | 0.7 | 1.1 | 2.3 | 1.7 |
| PCBs (ng/g) | 11 | 10 | 45 | 13 | 23 | 18 | 21 | 64 | 26 |
| | 11 | 9 | 32 | 12 | 22 | 19 | 13 | 38 | 20 |
| Fat (%) | 0.46 | 0.43 | 0.80 | 0.34 | 0.37 | 0.54 | 0.44 | 0.48 | 0.48 |
| | 0.38 | 0.40 | 0.56 | 0.33 | 0.33 | 0.41 | 0.39 | 0.40 | 0.40 |

[a]: Calculated based on the TCDD equivalent factors as determined by NATO for PCDDs and PCDFs, and WHO for Co-PCBs.

The data on upper line show the concentrations in the blood collected in January 1993 (before the clinical trials) while those on the lower line show the concentrations in the blood collected in August 1993 (after the clinical trials).

**Table 9.2.15.** Fecal Excretion of PCDFs and PCBs in Yucheng Patients

| Patient | Administration | Stool (g/day) | PenCDF[a] (pg/day) | HxCDFs[b] | PCBs (pg/day) |
|---|---|---|---|---|---|
| A01 | Before administration | 280 | 1,000 | 2,800 | 500 |
| | First week of administration | 300 | 980 | 2,500 | 600 |
| | Second week of administration | 330 | 1,100 | 2,600 | 650 |
| A02 | Before administration | 220 | 1,300 | 3,300 | 420 |
| | First week of administration | 200 | 1,600 | 3,400 | 500 |
| | Second week of administration | 210 | 1,500 | 2,900 | 390 |
| A03 | Before administration | 210 | 900 | 4,100 | 540 |
| | First week of administration | 200 | 840 | 2,900 | 590 |
| | Second week of administration | 230 | 1,200 | 3,500 | 580 |
| D04 | Before administration | 210 | 430 | 1,400 | 380 |
| | First week of administration | 300 | 520 | 1,300 | 470 |
| | Second week of administration | 190 | 470 | 1,300 | 430 |
| D05 | Before administration | 210 | 1,200 | 4,600 | 1,100 |
| | First week of administration | 220 | 1,400 | 4,200 | 1,500 |
| | Second week of administration | 180 | 1,100 | 3,600 | 1,000 |
| D12 | Before administration | 140 | 170 | 1,100 | 460 |
| | First week of administration | 180 | 210 | 1,100 | 630 |
| | Second week of administration | 160 | 290 | 1,300 | 600 |

[a]: 2,3,4,7,8-PenCDF, [b]: 1,2,3,4,7,8- and 1,2,3,6,7,8-HxCDFs.

The data for the fecal excretion of patients D14 and D15 were excluded because the collection of their stool samples was determined to have been imcomplete.

first week of the administration, and 220 ± 61 g/day during the second week of the administration. The fecal corresponding excretion levels of PenCDF were 840 ± 450, 920 ± 520 and 950 ± 460 pg/day, respectively, while those for HxCDFs were 2,900 ± 1,400, 2,600 ± 1,200 and 2,500 ± 1,000 pg/day, respectively. Furthermore, the fecal excretion levels of PCBs were 570 ± 270, 720 ± 390 and 610 ± 220 ng/day, respectively. These findings indicate that due to the administration of RBF and cholestyramine, the quantity of stools and the fecal excretion of PenCDF and PCBs slightly increased. However, the fecal excretion of HxCDFs during administration was less than that before administration.

9.2.5.2. Determination of Cholestyramine Excreted in the Stool

Table 9.2.16 shows the amount of cholestyramine excreted daily in the stool of Yucheng patients during the administration period. Cholestyramine is an anion exchange resin that is neither absorbed nor metabolized. It has been reported that over 96% of cholestyramine administered was excreted into feces within 24 hours in the rat. As 12 g of cholestyramine was daily administered to every patient, it is

**Table 9.2.16.** The determination of Cholestyramine in the Stool of Yucheng Patients (g/day)

| Administration | Patients | | | | | |
|---|---|---|---|---|---|---|
| | A01 | A02 | A03 | D04 | D05 | D12 |
| Before administration | 0.01 | 0.2 | 0.06 | 0.3 | 0.1 | 0.1 |
| First week of administration | 15.4 | 7.9 | 12.3 | 8.7 | 6.5 | 9.8 |
| Second week of administration | 14.6 | 9.2 | 11.7 | 3.9 | 3.6 | 9.3 |

**Table 9.2.17.** The amount of PCDFs and PCBs Excreted into the Feces in Yucheng Patients after the Administration of Rice Bran Fiber and Cholestyramine, and Adjusted Based on the Amounts of Cholestyramine Excreted into the Feces

| Patient | Administration | Stool (g/day) | PenCDF[a] (pg/day) | HxCDFs[b] | PCBs (pg/day) |
|---|---|---|---|---|---|
| A01 | Before administration | 280 | 1,000 | 2,800 | 500 |
| | First week of administration | 300 | 980 | 2,500 | 600 |
| | Second week of administration | 330 | 1,100 | 2,600 | 650 |
| A02 | Before administration | 220 | 1,300 | 3,300 | 420 |
| | First week of administration | 360 | 2,500 | 5,100 | 760 |
| | Second week of administration | 270 | 1,900 | 3,800 | 510 |
| A03 | Before administration | 210 | 900 | 4,100 | 540 |
| | First week of administration | 200 | 840 | 2,900 | 590 |
| | Second week of administration | 230 | 1,200 | 3,500 | 580 |
| D04 | Before administration | 210 | 430 | 1,400 | 380 |
| | First week of administration | 410 | 720 | 1,800 | 640 |
| | Second week of administration | 580 | 1,400 | 4,000 | 1,300 |
| D05 | Before administration | 210 | 1,200 | 4,600 | 1,100 |
| | First week of administration | 410 | 2,500 | 7,700 | 2,800 |
| | Second week of administration | 600 | 3,700 | 12,000 | 3,400 |
| D12 | Before administration | 140 | 170 | 1,100 | 450 |
| | First week of administration | 220 | 260 | 1,300 | 780 |
| | Second week of administration | 200 | 370 | 1,740 | 800 |

[a]: 2,3,4,7,8-PenCDF, [b]: 1,2,3,4,7,8- and 1,2,3,6,7,8-HxCDFs.

thus expected that about the same amounts of the compound should be excreted in the stool. Therefore, the completeness of the stool collection by the patients could be checked by examining the amounts of cholestyramine excreted in the feces by each of them. In Patient A01, the amount of cholestyramine excreted was larger than that administered. At present, no explanation can be made for this discrepancy. Except for A03 whose fecal excretion of cholestyramine was about 12 g, Patients A02, D04, D05 and D12 excreted considerably smaller amounts of

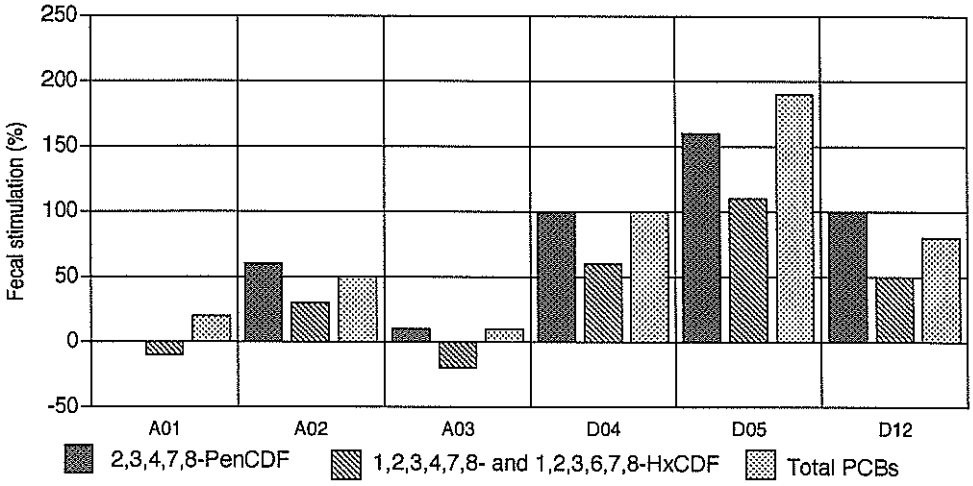


**Fig. 9.2.6.** The Stimulation of PenCDF, HxCDFs and PCBs in the Stool after the Administration of Rice Bran Fiber and Cholestyramine

cholestyramine than expected. This might indicate that these patients had failed to collect all the stools they actually discharged, because of the laboriousness of the collection of feces. Therefore, the data in Table 9.2.15 were adjusted according to the data shown in Table 9.2.16, yielding new data shown in Table 9.2.17.

It was evident that in all of these six patients the fecal excretion of PenCDF and PCBs was increased by the oral administration of RBF and cholestyramine, while such an increase was seen for HxCDFs in only four patients. Fig. 9.2.6 illustrates the change of the amounts of PenCDF, HxCDFs and PCBs excreted in the stool after administration, and is shown as a percentage in comparison with the corresponding amounts before administration.

The above promotion of fecal excretion of 2,3,4,7,8-PenCDF and PCBs could thus be statistically confirmed by the analysis of variance as well as by the t-test. For HxCDFs, a promoted fecal excretion was also noted, but was not statistically significant.

All the above findings indicate that the oral administration of RBF and cholestyramine accelerates the fecal excretion of PCDFs and PCBs retained in the tissue of the patients. Unfortunately, no clinical improvements were seen among these patients either during or after the trials. This might be due to the very limited duration of the administration.

Summarizing all the above findings, we may be able to say that the oral administration of RBF together with cholestyramine in patients with Yusho or Yucheng accelerated the fecal excretion of PCDFs and PCBs retained in their tissue, without any detectable side effects, but the beneficial effect was not so marked but instead

rather moderate. The development of more dramatically effective therapeutic measures is thus still urgently needed.

Nevertheless, our studies are thought to be valuable at least in the following aspects:

1) The concentration of the congeners of PCDFs, PCBs and other compounds that still persist in the blood and adipose tissue of Yusho patients more than 20 years after the initial exposure could be precisely determined. It was thus demonstrated that the persisting PCDFs, in particular, 2,3,4,7,8- PenCDF is overwhelmingly the most important toxic compound for the pathogenesis of Yusho. Similar findings were also seen among Yucheng patients.
2) It was confirmed for the first time that a portion of these PCDFs and other related compounds persisting in the tissue of the patients is steadily excreted into the feces, while the rate of excretion was also determined, thus allowing us to roughly estimate the length of time needed for the complete elimination of the compounds from the patients' bodies.

It is quite probable that PCDFs and related compounds in the tissue of the patients are also excreted into the sebum. We have already started a new research project to investigate this unexplored issue by applying the same analytical techniques used in our present study. After the completion of this new study, the whole picture of the excretion of these persisting compounds from the tissue of such patients can hopefully be better clarified.

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## 9.3. Fasting

*MASANORI* KURATSUNE

### *9.3.1. Clinical Effect*

In view of the fact that Yusho is hardly curable by conventional medical treatments, Dr. Motoo Imamura (Director, Goshiki Clinic, Goshiki-cho, Tsuna-gun, Hyogo Prefecture) who had received a doctoral degree of medical science from Kyushu University by presenting a thesis on a clinical observation of hunger in 1941 and had treated patients by his fasting cure for more than 25 years, proposed application of his cure to patients with Yusho at a meeting of the Study Group for the Therapy of "Yusho" in 1970 (Imamura, 1988). The proposal fell through but Professsor Kentaro Higuchi, chief of the study group, suggested him to try it and to report its outcomes, whatever they might be, to the group.

Since there was no patient with Yusho in the vicinity of his residence 600 km from Kyushu, he soon visited Tagawa City in Fukuoka Prefecture where Yusho raged and explained patients there about his fasting cure. Several months later, 9 patients who had been thrown into despair visited his clinic and applied for the cure. Before fasting, their physical condition was carefully examined by routine clinical tests and examinations, including those by X-ray and electrocardiograms. A fluoroscopic examination was also made on the gastrointestinal tract, if a patient was suspected to have a gastric or duodenal ulcer and only those free from such lesions were allowed to fast. After they were given a small amount of rice gruel (1/3 to 1/2 of daily calories) for two days, they began to fast. On the first and second days of fasting, they were allowed to drink only water but thereafter given, besides water, 200 ml each of a mixed juice of several kinds of fresh vegetables and fruit twice or thrice daily. To those who were weak or showed a marked body weight reduction during fasting, 200 ml each of milk was given twice a day in addition to the juice. After fasting for 10 to 12 days, patients gradually resumed normal diets during the recovery period of 10 to 15 days, taking first liquid diets, then semi-liquid diets, gruels, and finally normal diets which provided approximately 1,800 to 2,000 Cal.

The fasting significantly improved the clinical conditions in most of the nine patients. Thereby, he reported his findings to the Study Group in July 1971 and gained its approval (Tanaka, 1972). Table 9.3.1 summarizes the findings of 20 patients including the above 9 patients, who were subjected to the fasting cure (Imamura, 1972). A dramatically good effect was observed in some patients with stubborn headache, bronchitis or emesis, while some other patients hardly showed

**Table 9.3.1.** Results of Fasting Cure[a]

| Case no. | Age & sex | Clinical severity[b] | Fasting period (days) | Body weight (kg) | | Remedial effect[c] | |
|---|---|---|---|---|---|---|---|
| | | | | Before fast | After fast | Neurological | Dermatological |
| 1 | 32 F | III | 10 | 47.2 | 41.8 | ++ | ++ |
| 2 | 34 F | III | 10 | 52.3 | 47.0 | + | + |
| 3 | 28 F | III | 10 | 58.0 | 52.1 | + | − |
| 4 | 25 F | II | 12 | 50.0 | 44.4 | ++ | + |
| 5 | 23 M | II | 10 | 49.0 | 44.1 | ++ | + |
| 6 | 46 F | III | 12 | 66.8 | 61.0 | ++ | + |
| 7 | 26 F | III | 12 | 52.0 | 46.2 | − | − |
| 8 | 22 F | I | 10 | 50.5 | 46.0 | ++ | + |
| 9 | 25 M | II | 12 | 73.6 | 67.8 | ++ | + |
| 10 | 23 M | II | 10 | 59.0 | 54.2 | ++ | + |
| 11 | 17 M | I | 8 | 44.6 | 41.0 | + | + |
| 12 | 47 F | III | 14 | 62.0 | 56.0 | ++ | + |
| 13 | 22 F | II | 12 | 60.4 | 54.5 | ++ | + |
| 14 | 40 M | III | 12 | 52.0 | 45.9 | ++ | − |
| 15 | 50 F | III | 12 | 52.2 | 46.0 | ++ | + |
| 16 | 21 F | II | 10 | 53.2 | 48.5 | ++ | + |
| 17 | 19 F | II | 10 | 51.0 | 46.2 | + | + |
| 18 | 19 M | II | 10 | 55.2 | 49.0 | + | − |
| 19 | 16 F | I | 12 | 47.0 | 42.2 | ++ | + |
| 20 | 39 F | II | 10 | 42.6 | 37.8 | + | + |

[a]: The clinical trials were made from October 1970 to May 1972. Imamura, 1972.

[b]: Severity was judged by clinical signs. I: light, II: moderate, III: severe.

[c]: Remedial effect, −: no, +: slight, ++: marked.

any improvement at all. It is noteworthy that about one third of these patients wanted to repeat fasting in spite of its harshness (Imamura, 1975). Sixty-two patients with Yusho thus had the fasting cure at his clinic for the 5 ensuing years (Imamura, 1988). In general, it was very effective on the neurological symptoms but not so much on the dermatological symptoms and signs. Neverthless, the guidelines for treatment of Yusho revised in 1972 listed the fasting cure as the effective method for accelerating the excretion of PCB residues remaining in the tissues of patients (see Appendix 1., Table 2).

As well known, a mass food poisoning by PCBs called "Yucheng" very much similar to Yusho in many respects occurred in Taichung, Taiwan in March 1979. The number of patients officially recognized exceeded 2,000. Dr. Imamura was invited by the Department of Health, Republic of China, in December 1980, in order to apply his fasting cure to some of the victims. A group of 8 patients with Yucheng thus had the fasting cure for 7 or 10 days in May 1981, under supervision of Dr. Imamura and his cooperator, Professor Ta-Cheng Tung, Department of Bio-

chemistry, College of Midicine, National Taiwan University (Imamura and Ta-Cheng Tung, 1984). At the second trial carried out in February 1982, all of the above eight patients rejoined the fasting program together with new eight patients. The outcomes of these fasting trials were basically the same as those seen among Japanese patients. They all showed at least some improvements in their sufferings, and some had a dramatic relief. A patient who had been complaining of a sharp stabbing pain in the sole and in the ankle joint for about two years after being poisoned started to feel the pain less on the fourth or fifth day of fasting. It almost disappeared by the seventh day, allowing him to walk on the lawn with bare feet. The dermal lesions were also improved by fasting, but the improvement started very slowly from the seventh or tenth day of fasting and became evident two or three months after fasting. The acneiform eruptions forming cysts or abscesses were hard to cure even by repeating the fast.

There is another report of fasting cure applied to a 33 year old female patient with Yusho for 14 days. Both a marked improvement in acneiform eruptions, pigmentation and itching of the skin and a significant recovery of urinary 17KS to the normal level were observed (Sagami, 1974).

As shown in Table 9.3.2, the concentration of PCBs in the blood of patients with Yusho seems to be elevated during and after fasting as compared with the pre-fasting values. Sagami (1974) for the first time observed such increase in a patient with Yusho 7 days after a fast for 14 days. Imamura et al. (1977) also observed a similar and yet statistically significant elevation of PCB concentration in the blood on the 10th day of fasting and 7 days after fasting. More clearly, all of 8 patients with Yucheng who were subjected to the fasting cure for 7 or 10 days showed an increase of PCB concentration in the blood during and after fasting (Imamura and Ta-Cheng Tang, 1984). The concentration of PCBs in the adipose tissue, however, appeared to decrease by fasting (Sagami, 1974).

Table 9.3.3 shows that the concentration of PCBs in the feces increased in a patient with Yusho during and after fasting and in six of eight patients with Yucheng during fasting. Coinciding with the experimental observations to be described below, these clinical findings indicate that fasting mobilizes PCBs retained in the adipose tissue of patients with Yusho and accelerates their fecal excretion.

### *9.3.2. Mobilization of PCBs by Fasting in Experimental Animals*

It is well known that DDT stored in the adipose tissue of rats is mobilized by fasting with a concurrent decrease of body fat. A marked increase in concentration of DDT as well as DDE in the fat, plasma, brain, liver and kidney was caused, inducing, in certain cases, a typical DDT tremor or even death (Fitzhugh and

**Table 9.3.2.** Concentration[a] of PCBs in the Blood and Adipose Tissue of Patients with Yusho or Yucheng before, during and after Fasting

| Tissue, Patient Sex/age | Year of fast | 1 yr. | 3 m.[b] | Just | 1st day | 3rd day | 5th day | 7th day | 9th day | 10th day | 7 days | 13 days |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | before fast | | | of fast | | | | | | after fast | |
| Blood | | | | | | | | | | | | |
| Yusho[c] | 1975 –1976 | | | | | | | | | | | |
| 1. F/40 | | | | 5 | | | 3 | | | 3 | 6 | |
| 2. M/25 | | | | 10 | | | 9 | | | 9 | 13 | |
| 3. M/52 | | | | 6 | | | 6 | | | — | 8 | |
| 4. F/20 | | | | 9 | | | 19 | | | 24 | 18 | |
| 5. F/16 | | | | 9 | | | 8 | | | 14 | 9 | |
| 6. M/70 | | | | 5 | | | 6 | | | 9 | — | |
| 7. M/23 | | | | 3 | | | 5 | | | 5 | 6 | |
| Mean | | | | 6.7 ± 2.7 | | | 8.0 ± 5.2 | | | 10.7 ± 7.5 | 10.0 ± 4.7 | |
| Yusho[d] | | | | | | | | | | | | |
| 1. F/33 | 1973 | 87.6 | 118.0 | 91.0[f] | | | | | 104.0[f] | | 152.4[f] | |
| | | | | 54.0[g] | | 52.0[g] | | | 55.0[g] | | 63.0[g] | |
| Yucheng[e] | 1981 | | | | | | | | | | | |
| 1. M/31 | | | | | 26 | | | 34 | 39 | | 29 | |
| 2. F/26 | | | | | 18 | | | 29 | 29 | | 31 | |
| 3. F/26 | | | | | 21 | | | 36 | 36 | | 31 | |
| 4. F/31 | | | | | 15 | | | 23 | 21 | | 20 | |
| 5. F/31 | | | | | 10 | | | 19 | 14 | | 18 | |
| 6. F/68 | | | | | 28 | | | 38 | | | 45 | |
| 7. F/27 | | | | | 14 | | | 19 | | | 17 | |
| 8. M/54 | | | | | 27 | | | 33 | | | 37 | |
| Adipose tissue | | | | | | | | | | | | |
| Yusho[d] | | | | | | | | | | | | |
| 1. F/33 | 1973 | | | 42.0[f] | | | | | | | | 34.1[f] |

[a]: ppb for blood and ppm for adipose tissue on whole basis.

[b]: months.

[c]: Imamura et al., 1977.

[d]: Sagami,1974.

[e]: Imamura and Ta-Cheng Tang, 1984.

[f]: Data from the Shiga Prefectural Institute of Public Health.

[g]: Data from the Osaka Prefectural Institute of Public Health.

**Table 9.3.3.** Concentration[a] of PCBs in the Blood and Feces of Patients with Yusho or Yucheng before, during and after Fasting

| Patient sex/age | Year of fast | PCBs in blood | | PCBs in feces | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | 2 yrs. before fast | Just before fast | Just before fast | 1st day of fast | 3rd day of fast | 5th day of fast | 7th day of fast | 9th day of fast | 7 days after fast |
| Yusho[b] | | | | | | | | | | |
| 1. F/33 | 1973 | | 54.0[d] | 34.0[d] | | 82.0[d] | | | 62.0[d] | 114.0[d] |
| Yucheng[c] | 1983 | | | | | | | | | |
| 1. | | 15 | | | 51.49 | | | 59.85 | 68.09 | |
| 2. | | 46 | | | 100.68 | | | — | 82.56 | |
| 3. | | 69 | | | 100.72 | | | 205.33 | 99.87 | |
| 4. | | 113 | | | 216.64 | | | 300.69 | 410.77 | |
| 5. | | 35 | | | 38.64 | | | — | 48.19 | |
| 6. | | 20 | | | 65.50 | | | 76.61 | — | |
| 7. | | | | | — | | | 130.04 | 139.50 | |
| 8. | | 20 | | | 68.50 | | | 237.03 | — | |

[a]: ppb on dry weight basis.
[b]: Sagami, 1974.
[c]: Imamura and Ta-Cheng Tang, 1994.
[d]: Data from the Osaka Prefectural Institute of Public Health.

Nelson, 1946; Dale et al., 1962). However, the concentration of DDT residues in the tissues falls well below the values before starvation only a few days after the resumption of feeding (Lambert and Brodeur, 1976). The above phenomenon may be a general one since mobilization of PCBs persisting in the adipose tissue by fasting has also been reported by several authors. Tanaka and Komatsu (1972), noting a sharp reduction of hexobarbital sleeping time caused by administration of a trace amount of PCBs to rats, observed that such reduction occurs when rats storing PCBs in the adipose tissue were subjected to fasting. According to them, this phenomenon may be due to PCBs released from the adipose tissue by fasting. Demonstrating that fasting enhances the induction of drug-metabolizing enzymes by administration of PCBs to rats, Carlson (1980) also suggested that such effect of fasting is due to mobilization of PCBs from storage sites in the adipose tissue. More clearly, Wyss et al. (1982) observed that 47 percent of 2,2′,4,4′,5,5′-hexachlorobiphenyl (one of the most abundant PCB residues in human tissues) given intravenously is retained in the adipose tissue and 29 percent in the skin, and a prolonged fasting translocates about a half of this PCB congener retained in the adipose tissue to the skin and another half to feces. The concentration of the PCB congener in the skin was maintained high and did not decrease by fasting at all, while the fecal excretion predominantly of the unchanged congener increased ten-

fold by fasting as compared with control animals that were fed *ad lib*. Fasting also translocated the PCB congener in the adipose tissue to the lung, liver, brain, blood and skeletal muscle, causing a marked increase in its concentration in these tissues up to the 4th week of fasting and then a sharp decrease. Thus, the above experiments unanimously indicate the beneficial effect of fasting on the mobilization and fecal excretion of PCBs stored in the adipose tissue. Strictly speaking, however, the major causal agent of Yusho is not PCBs but PCDFs, and neither clinical nor experimental evidence is available for whether PCDFs persisting in the tissues of patients with Yusho can be mobilized and excreted by fasting. The chemical similarity of these two types of chlorinated hydrocarbons suggests that PCDFs would behave like PCBs in pharmacokinetics in fasting. However, further studies are needed to confirm this supposition.

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