## —NOTE—

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# NEOPLASTIC CHANGES IN THE RAT LIVER INDUCED BY POLYCHLORINATED BIPHENYL

**(Phase XII)**

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Polychlorinated biphenyls (PCBs) are now widely dispersed in the global ecosystem. There are many reports that PCBs and such chlorinated insecticides as BHC, Dieldrin, and DDT have extensively polluted the animals in the world, and that high concentrations of PCB have been detected in fish, shell-fish, seals, porpoises, and wildlife in general.[4,5,7,14] PCBs have also been detected in human adipose tissue and mother's milk.[1,2] Not only accumulation of PCBs in human tissue but also their hazard is evident from the unfortunate and miserable accident of "Yusho" (oil disease), a mass food poisoning involving more than 1,000 people who over a long period had ingested rice oil contaminated with PCB that had leaked from a heat exchanger in the course of manufacture, that occurred in 1968 in western Japan.[3,6]

The studies we made this time on the carcinogenic potency of PCB were started by the findings that there were specific morphological alterations in liver cell nucleoli of the animals ingesting PCB as demonstrated by electron microscopy.[16] Similar nucleolar changes caused by several agents known as potent carcinogen have been reported.[9,10,13]

### Materials and Methods

Kanechlor-400, a commercial brand of PCB and the pollutant in the rice oil of the Yusho case, was employed for the present study. Six compounds were recently isolated from Kanechlor-400, and five of them were chemically identified as 2,4,3′,4′-, 2,5,3′,4′-, 2,3,4,4′-, and 3,4,3′,4′-tetrachlorobiphenyls, and 2,3,4,3′,4′-pentachlorobiphenyl.[15] Thirty rats of Donryu strain were used. They were 10 weeks of age at the start of the experiment, and 185~260 g in weight in male group (average, 207 g) and 155~225 g in female group (average, 186 g). They were randomly divided into 2 groups for experiment and control. The experimental group consisted of 10 male and 10 female rats, and the control group had 5 each. The diet for both, experiment and control, were prepared as follows: For the experimental group olive oil containing a certain concentration of Kanechlor-400 was mixed in a concentration of 0.3 ml/g with powdered diet (CE-2, Oriental Co., Tokyo). For the control group, pure olive oil was mixed in the same concentration with the powdered diet. The diet thus prepared and water were given freely. Initial concentration of Kanechlor-400 in the test diet was 38.5 ppm and given for 4 weeks, then referring to the body weight increase of the animals the concentration of Kanechlor-400 was increased by 2 times of the initial one and given for 8 weeks, 4 times for 3 weeks, 8 times for 3 weeks, and 16 times for 8 weeks. The change in body weight of the animals was individually checked every week. Since the body weight decreased remarkably when the diet containing 16 times of the initial concentration (616 ppm) of Kanechlor-400 was given for 8 weeks, its concentration was decreased to 12 times (462 ppm). This dose was maintained for 32 weeks. Total feeding period to the experimental and control animals was 400 days. During the last half of the

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MONS 085685

Table I. *Pathological Findings Induced by Long-term Oral Administration of Kanechlor-400 in Rats*

| Rat No. | Sex | Total exp. period (days) | Approx. amount of KC-400 ingested (mg) | Body weight (g) | | Liver | | | Other pathological findings* |
|---|---|---|---|---|---|---|---|---|---|
| | | | | Initial | Final | Ratio to body wt. (‰) | Fatty degeneration | Multiple adenomatous nodules | |
| 1 | ♂ | 150 | 450 | 199 | 309 | 4.1 | + | − | SA, Pn, LA |
| 2 | ♂ | 256 | 900 | 192 | 273 | 5.4 | + | − | |
| 3 | ♂ | 323 | 1200 | 201 | 192 | 6.8 | + | − | SA, Pn, FDAd |
| 4 | ♂ | 339 | 1300 | 201 | 199 | 6.8 | + | − | Pn, D, FDAd |
| 5 | ♂ | 347 | 1300 | 200 | 328 | 6.2 | + | − | Pn, LA |
| 6 | ♂ | 353 | 1300 | 230 | 210 | 5.4 | + | − | SA, Pn, IA |
| 7 | ♂ | 355 | 1300 | 201 | 296 | 5.2 | + | − | Pn |
| 8 | ♂ | 357 | 1300 | 185 | 226 | 6.3 | + | − | Pn, LA, FDAd |
| 9 | ♂ | 373 | 1300 | 234 | 325 | 6.5 | + | − | LA |
| 10 | ♂ | 530 | 1800 | 228 | 297 | 5.8 | + | − | LA |
| 11 | ♀ | 244 | 700 | 158 | 137 | 5.9 | + | − | LA |
| 12 | ♀ | 357 | 1100 | 161 | 184 | 6.2 | + | − | Pn, D |
| 13 | ♀ | 366 | 1100 | 154 | 177 | 7.1 | + | − | LA, D |
| 14 | ♀ | 396 | 1100 | 165 | 125 | 7.8 | + | − | Pn, LA, D |
| 15 | ♀ | 402 | 1200 | 202 | 212 | 6.7 | + | + | LA, D |
| 16 | ♀ | 461 | 1500 | 168 | 148 | 8.4 | + | + | LA, D, IA, FDAd |
| 17 | ♀ | 477 | 1500 | 178 | 165 | 7.8 | + | + | LA, D, IA, SA, |
| 18 | ♀ | 482 | 1500 | 225 | 145 | 6.3 | + | + | LA, IA, SA |
| 19 | ♀ | 504 | 1500 | 191 | 167 | 6.5 | + | + | LA, D, FN |
| 20 | ♀ | 560 | 1500 | 209 | 253 | 6.4 | + | + | D, AAd |
| 21 | ♂ | 255 | | 257 | 471 | 2.5 | − | − | FDAd |
| 22 | ♂ | 332 | | 149 | 432 | 3.1 | − | − | Pn, FDAd |
| 23 | ♂ | 538 | | 190 | 426 | 2.7 | − | − | FDAd |
| 24 | ♂ | 538 | | 182 | 523 | 2.5 | − | − | |
| 25 | ♂ | 538 | | 256 | 456 | 2.7 | − | − | FDAd |
| 26 | ♀ | 331 | | 192 | 198 | 4.2 | + | − | Pn |
| 27 | ♀ | 448 | | 192 | 495 | 2.6 | + | − | Pn |
| 28 | ♀ | 538 | | 202 | 292 | 2.9 | − | − | |
| 29 | ♀ | 538 | | 201 | 320 | 3.0 | − | − | |
| 30 | ♀ | 538 | | 193 | 314 | 2.6 | − | − | |

* SA = spleen atrophy, Pn = pneumonia, LA = lung abscess, FDAd = fatty degeneration of the adrenal cortex, D = depilation, IA = intracranial abscess, FN = extensive fat necrosis in the abdomen, AAd = adenoma of the adrenal cortex.

Schedule of feeding:

| Concn. of Kanechlor-400 (ppm) | 38.5 | 77 | 154 | 308 | 616 | 462 | —— | 462 | —— | 462 | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Period of feeding (days) | 26 | 57 | 21 | 21 | 56 | 39 | 28 | 98 | 28 | 82 | Total 400 |

A pause (—— ) in PCB feeding was inserted similarly in experimental and control groups, during which and after termination of diet feeding, the rats had free access to the conventional diet (CE-2).

experimental period, a pause in the diet feeding for 4 weeks was inserted twice. Total amount of Kanechlor-400 intake in each rat, the schedule of the feeding, and the results obtained are shown in Table I.

## Results and Discussion

The [illegible] changes induced [illegible] tion of in the liver. Generally, all the rats receiving more than 700 mg of PCB showed hypertrophy of the liver. Pinhead- to pear-sized



MONS 085686

of benzene hexachloride in dd male mice. It must be considered, however, that spontaneous hepatomas have been found frequently in male mice. As to the Yusho case [oil disease] mentioned at the beginning, it was reported that PCB residues were still detected at a high concentration in the adipose tissue of the Yusho patients even 2 years after the onset of the Yusho symptoms.[9]

It is urgent to know beforehand that a lesion would occur in the human body by taking much PCBs on the one hand, and to establish an effective means for therapy against the lesion on the other.

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MONS 085687

## Explanation of Plate XII

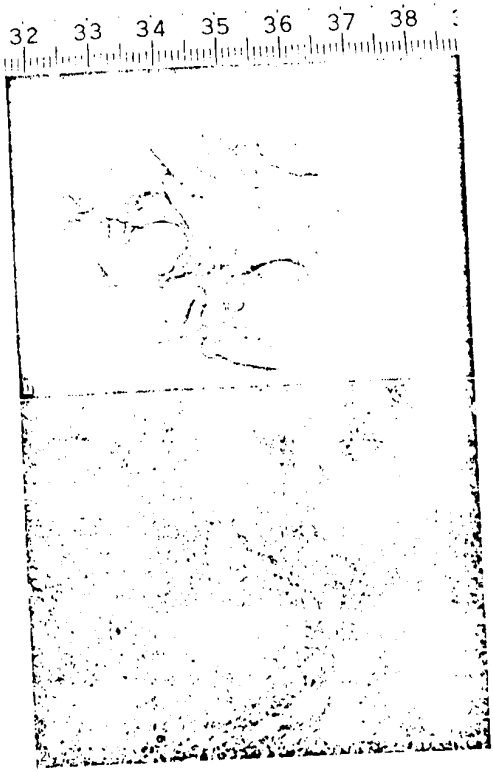
Photo 1. Liver of a female rat (No. 20) ingesting ca. 1,500 mg of Kanechlor-400. Note pinhead- to pea-sized multiple nodules scattering on the surface of the liver.

Photo 2. Photomicrograph of the liver of the rat No. 20. Large and small adenomatous nodules are shown. The nodules consisted of somewhat atypical parenchymal cells with clear and enlarged cytoplasm. Some nuclei are pyknotic but not much atypical. Mitosis is seen infrequently. Liver cells surrounding the nodules are atrophic and seem to be compressed by the nodules. Fatty degeneration is also seen in the parenchymal cells. ×40.





MONS 085688




MONS 085689