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Congenital PCB Poisoning: A Reevaluation

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A review of the literature reveals a need to clarify the pathologic physiology of congenital polychlorinated biphenyl (PCB) poisoning, which is characterized by intrauterine growth retardation, brown staining of the skin and mucous membranes, as in Addison's disease, natal teeth, widely open fontanelles and sagittal suture and apparent overgrowth of the gingiva. The skull abnormalities may represent irregular calcification, with natal teeth appearing because the bone of the mandible is penetrated more easily than usual. Some fetuses were poisoned at the time the mothers ingested the oil; others were affected in the subsequent years from residual contamination in the mothers' bodies. The misadventure in Japan was repeated in Taiwan in 1979. The seven congenital cases in Taiwan reported thus far seem to differ from those in Japan. In Taiwan the noses were somewhat black, two of the infants did not have low birth weight and the osseous abnormalities of the skull and gingival hyperplasia were not observed. Systematic followup studies should be made in Taiwan of the children born within 2 years of maternal poisoning with PCBs. Special attention should be given to age at first dentition and skull X-rays for spotty calcification, among other measures of physical, neurologic and intellectual development.

The people of Kyushu were in their usual state of health until just before the summer of 1968. On June 8 a 3-year-old girl with chloracne was brought for examination to Kyushu University Hospital in Fukuoka. Her older sister and both parents were similarly affected. One report stated that over the next few months the disease was found in 1291 people (*1*). Another report put the number at more than 3000 (*2*). The cause of the illness was quickly traced to rice-bran oil contaminated during manufacture with polychlorinated biphenyls (PCBs), used as a heat-transfer agent. The PCBs were, in turn, contaminated with polychlorinated dibenzofurans (*3*).

Medical reports of the epidemic were slow to become known outside Japan because the journals in which they were published are not widely circulated. In 1971, Taki et al. (*3*) described the effects on nine infants exposed *in utero*. The following year a report by Yamaguchi et al. (*4*) provided further details and added four more cases. A follow-up study by Funatsu et al. (*5*) of four patients until they were 8 to 19 months old includes one patient not recognizable in the earlier lists of patients. The total with congenital Yusho (oil-poisoning) in the studies by physicians at Kyushu University Hospital is thus 14. Two were stillborn, one of which was premature. The list of the 13 term births published in Japanese by Yamaguchi et al. (*4*) has been reprinted in English by Kuratsune (*6*). Two mothers in the series did not have Yusho. Their children had questionable evidence of congenital Yusho, as did one other infant whose mother ingested only a relatively small of the contaminated oil during the third trimester [case 1 (*6*)].

Yoshimura (*7*) and Harada (*2*) described another series with congenital Yusho in the Goto Islands, which are a remote archipelagic part of Nagasaki Prefecture. Harada reported five cases of congenital Yusho due to the oil before its use was discontinued, and 13 cases born in the next two years, due to residual contaminants in the bodies of the mothers. Harada's report appeared in English in a supplement to the Bulletin of Constitutional Medicine of Kumamoto University, which is virtually unavailable outside Japan.

Cola-Colored Skin

A deep brown pigmentation of the skin was the most constant finding among the affected newborn infants. It was definitely present in ten of the Kyushu series and possibly in the other three. Biopsy of the skin showed an increase in melanin and hyperkeratosis. The melanin concentrated in the groin, axilla, gingiva, palate, nails and limbus of the conjunctivae. It looked to the investigators (*5*) like the pigmentation seen in the skin and mucosa of patients with Addison's disease (failure of adrenal cortical function). The pigmentation cleared in 2 to 5 months (*1*). The Japanese referred to it as cola-colored skin.

In the Kyushu series all of the children with congenital Yusho were said to have been jaundiced at birth, but the documentation for this observation was not given. It would be difficult, of course, to recognize jaundice in an infant with skin and sclera stained brown.

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Table 1. Congenital Yusho: birth weight and gestational age.[a]

Gestational age, weeks	Birth weight, g
40	2700
38	1800
41	2500
40	2800
39	2520
43	2930
42	2500
33	660[b]
41	2600[b]
40	2300

[a]From Taki et al. (*3*) and Funatsu et al. (*5*)
[b]Stillborn.

Low Birth Weight

Another near-constant finding was low birth weight. In one report, one stillborn and three liveborn infants were judged to be small for date (*4*), but all of the infants were under the mean for their gestational age and sex. Table 1 shows that none of the infants weighed more than 3000 g at birth. The only chemical known previously to cause infants to be small for date is cigarette smoke, i.e., self-pollution by the mother during pregnancy (*8*). This effect represents intrauterine growth retardation.

Eye Secretion and Facial Edema

All but one infant in the Kyushu series of 12 liveborn infants (*4*) had eye secretions of a substance like cream cheese. Cysts of the Meibomian glands were also found. In the special study of four young children with congenital Yusho in the Kyushu series, three were said to have had severe edema of the eyelids in conjunction with marked facial edema (*5*).

"Gingival Hyperplasia" and Natal Teeth

At least two of the newborn infants had "gingival hyperplasia" (*5*), resembling that seen as a side effect of phenylhydantoin therapy in patients with epilepsy. Gingival hyperplasia has not been previously described in a newborn.

Of the 12 liveborn infants in the Kyushu series, two had teeth present at birth—the same two who had "gingival hyperplasia." One had a single tooth and the other had two (*5*). The usual frequency of natal teeth is 1 in 2000 to 3500 births (*9*). The two cases observed in the small series of cases with congenital poisoning with PCBs may well be more than one would expect by chance. In Alaska 1 out of 11 Tlinget Indian infants was born with teeth (*10*), and the Navaho were thought to have higher rates than normal for the U. S. (J. D. Niswander and E. R. Welty, personal communications). The excessive rates among these ethnic groups are apparently on a genetic basis. Natal teeth are commonly seen in infants with certain syndromes with craniofacial abnormalities (*9*).

From the only published photograph (in color), a periodontist at the National Institute for Dental Research, Bethesda, MD, was unable to determine if the prominant gums were due to hyperplasia. The irregular surface led McNulty to suggest that cysts lay beneath the gingival surface, as he has seen in postnatal monkeys poisoned with PCBs (*11*). Others have suggested that the gingiva may look unusual as it covers the first dentition just before it erupts. It would be interesting to know if the deciduous teeth appeared earlier than usual in these children, but the follow-up may not have included this information.

Calcifications in the Skull and Large Fontanelles

The two children with "gingival hyperplasia" and natal teeth, and one other in the special study of four children in the Kyushu series (*5*) also had spotty calcification in the occipital part of the skull, as seen on X-ray. Wide separation of the sagittal suture and large anterior and posterior fontanelles were seen in these and perhaps other infants with congenital Yusho (*5*). At the time, the Japanese investigators thought the array of osseous findings (open fontanelles, natal teeth and unusual calcification of the skull) might have been due to a disturbance in calcium metabolism. They wondered about the relationship between these observations and the thin shells of birds' eggs due to DDT (or, as was later learned, PCBs).

Large fontanelles and a wide sagittal suture are commonly found in newborn infants with intrauterine growth retardation, and with a variety of craniofacial abnormalities, including those in which natal teeth are found. Some of these syndromes have soft areas in the occipital region which, according to a standard textbook of pediatrics (*12*), is suggestive of irregular calcification. Such calcification, if it occurred in other parts of the skull, particularly the mandible, could reduce resistance to the eruption of teeth, and thus explain their presence at birth in these syndromes and in congenital PCB poisoning. This would be an alternate explanation to that suggested by observations in monkeys; namely that squamous pearls in the gingiva lead to bone cysts which alter the path of dental development (*11*).

Follow-up Studies

In the Kyushu series only four children were studied until they were 8 to 19 months old (*5*). At the end of this time, the children were said to be essentially normal mentally and physically.

Follow-up studies of infants with congenital Yusho who lived on the Goto Islands were described by Yoshimura in 1974 (*7*) and Harada in 1976 (*2*). Twenty-two cases were available for Yoshimura's study, "by direct interview of the mother and child." He identified two

infants who developed congenital Yusho from exposure before use of the oil was discontinued, and one infant who was affected subsequently from intrauterine exposure after use of the oil was stopped. One mother gave birth to a child annually for 3 years, each with less staining of the skin than the previous one.

Harada apparently studied the same group 2 years later (*2*). His report lacks details, and the numbers in the text, figures and tables differ somewhat from one another. He presented data to show (a) that before the oil was contaminated, birth weights were above 3000 as often as they were below this weight, but from late 1968 through 1971 only one of seven birth weights was (barely) above 3000 g.; (b) that 13 infants developed congenital Yusho (until 1971) from residual PCBs in the mother's body after use of the oil was stopped; (c) that some slight brown staining of the skin of several newborns was seen until 1973; and (d) that mental and neurological disturbances were more frequent than usual, as shown in a table, with no information given about the methods or details of the observation made.

History Repeats in Taiwan

We can learn from experiments of nature, but who could ever have guessed that the Yusho experience of Japan would be replicated. The experience in Taiwan in 1979, eleven years after the Japanese epidemic, had the same source of contamination (cooking oil during its manufacture) and about the same number of people were affected with Yusho. Wong and Hwang (*13*) described six newborn infants whose mothers had PCB poisoning. One of the six was delivered at about the time the cooking oil was contaminated and had no real evidence of congenital Yusho. The other five had ample evidence of the disease. It differed in its manifestations from the Japanese experience in that four of the children had "black color of the nose," as did some older affected persons. Two of the infants had acneform eruptions (not described in Japan). No mention was made of neonatal teeth, gingival hyperplasia, or spotty calcification of the skull. Two of the children were not small for date; each weighed 3600 g at birth (*13*). Another report, of twins with PCB poisoning, mentions widening of the anterior fontanelle (*14*). Through February 1983, 39 children with congenital PCB poisoning were observed in Taiwan (*15*). The contamination was only about one-tenth as great in Taiwan as in Japan, but the Taiwanese ingested ten times more oil than the Japanese did. The total amount of contaminants ingested by both groups is believed to have been about the same (*16*). The dissimilar findings at birth, however, suggest differences with regard to the composition of the contaminants.

PCB contamination of food occurred in the same way in 1971 when eggs of chickens in North Carolina exhibited reduced hatchability (*17*). As in the human experiences, PCBs used as heat-transfer agents had leaked through pinhole erosions in the pipes that contained them to contaminate chickenfeed during its manufacture.

Other Human Prenatal Exposures to PCBs

Intrauterine exposures to PCBs are occurring widely due especially to pollution of the food chain from injudicious disposal of PCBs used commercially (*18*). No ailments have been traced to these exposures, and there appears to be little reason to seek them, given the known effects and better opportunities for study in Japan and Taiwan.

Congenital Yusho in Perspective

Early in their studies, Japanese investigators con cluded that the findings in congenital Yusho were due to enzyme–endocrine disorders produced by the contami nation (*5*). Understanding seems not to have advanced much since then. Some of the findings are unique or rare in the human: the congenital transient melanin deposition in the skin and mucous membranes, gingival hyperplasia and spotty calcification in the occipital region of the skull. Intrauterine growth retardation and natal teeth are well known to pediatricians, but not in connection with environmental exposures.

The pathologic physiology for these findings is as much a mystery as it ever was. In part this lack of movement may be due to a tendency to pass over the congenital findings, while concentrating on the effects among the large number of exposed children and adults. A notable new lead from this conference concerns dental problems (a) at birth (*5*), (b) subsequently (*2*, Kim brough, personal communication), and (*c*) in nonhuman primates (*11*). Prospective studies in Taiwan should include careful dental examinations.

None of the reports available in the literature are comprehensive. Ideally follow-up studies should be made, if feasible, of all infants born of Japanese or Taiwanese women who had evidence of rice-oil poisoning in the past. The abnormalities at birth were so pronounced that one would really like to have firm information on the growth, development and health of these individuals over as long an interval as possible. In this way important information about human biology, normal as well as abnormal, would be gained.

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