Congenital Poisoning by Polychlorinated Biphenyls and Their Contaminants in Taiwan

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In 1979, a mass poisoning occurred in Taiwan from cooking oil contaminated by thermally degraded polychlorinated biphenyls. Because these chemicals persist in human tissue, children born to female patients after the outbreak were exposed in utero. In 1985, 117 children born to affected women and 108 unexposed controls were examined and evaluated. The exposed children were shorter and lighter than controls; they had abnormalities of gingiva, skin, nails, teeth, and lungs more frequently than did controls. The exposed children showed delay of developmental milestones, deficits on formal developmental testing, and abnormalities on behavioral assessment. These findings are most consistent with a generalized disorder of ectodermal tissue. This syndrome is one of very few documented to result from transplacental exposure to pollutant chemicals.

COOKING OIL CONTAMINATED BY polychlorinated biphenyls (PCBs) and dibenzofurans led to an outbreak of illness (called *yucheng* or "oil disease") in Taiwan. The illness consisted of chloracne, hyperpigmentation, and meibomian gland dilatation among other findings (*1, 2*). The epidemic was noted in May 1979, and the oil was removed from the market in October; cases were identified retrospectively from as far back as December 1978. There is a registry of about 2000 persons who were exposed to the oil. A similar outbreak ("*yusho*") had occurred in Japan in 1968.

Because these chemicals persist in human tissue [similar dioxins have half-lives in humans of about 7 years (*3*)], offspring of female patients continue to be born affected, even though maternal exposure has ceased. By 1983, 8 of 39 hyperpigmented children born to exposed mothers had died (*1*). In April 1985 we performed a field survey of all living children who were known to have been in utero during or after the period of oil contamination. These children would have had transplacental exposure and possibly exposure through breast milk, but would not themselves have consumed the contaminated oil.

Seventy-four women in the health department's registry had living children born between June 1978 and March 1985. Use of these dates should identify any child with transplacental exposure, since the latent period during which oil was consumed but mothers were asymptomatic was about 6 months. Chinese-speaking nurses interviewed the mothers in their homes and scheduled the examinations. The women reported 159 pregnancies in this time; 3 were ongoing, 5 miscarried, 8 were aborted, 6 were stillborn, and 5 born live later died, leaving 132 living children. We obtained usable information on 128. One more child died between interview and examination. Twenty-nine families had 1 eligible child, 34 had 2, 9 had 3, and 2 had 4. Controls came from 96 families who lived in the same neighborhoods. These 96 mothers reported 205 pregnancies in this period; 3 were ongoing, 8 miscarried, 4 were aborted, and 190 produced live births; we obtained data on 115. The exposed children averaged 32 months old, range from 1 to 82 months; the controls averaged 31 months, range 3 to 98

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months. The families lived near each other and knew of each other's medical difficulties, and some mothers still had obvious chloracne, so that it was not possible to use a blind study design.

Exposed mothers reported lower birth weight (mean ± SE: 2749 g ± 46 g, n = 128; 3228 g ± 40 g, n = 115), hyperpigmentation, conjunctivitis, nail changes, and natal teeth in the children at birth (Table 1). The largest difference in the medical histories was the higher rate of bronchitis in the exposed children. There was consistent reported developmental delay in the exposed children; of the 33 milestones that we asked about, the exposed children were behind in 32 (the no-effect value would be 16.5).

The physical examinations were carried out during 11 days in April 1985 at four local clinics; 117 exposed children and 108 control children attended. There were neurologic, dysmorphologic, dermatologic, dental, and general examinations. The exposed children were smaller than controls, averaging 93% [95% confidence interval (CI), 90–96] of control weight and 97% (95% CI, 96–99) of control height, adjusted for age and sex. The gum hypertrophy or swelling noted by the mothers at birth was still apparent on examination (Table 2). Neither acne nor conjunctival cysts were much more common in the exposed, but the differences in hyperpigmentation and nail deformities and pigmentation are large. Most of the pulmonary auscultation abnormalities were consistent with bronchitis, and this diagnosis was made clinically in several of the children. The marked differences in eyebrow flare, hypertelorism and clinodactyly were not expected. There were no abnormal reflexes or any localizing findings in the neurologic exam; however, the exposed children were delayed compared to controls in the age at which they performed tasks such as saying phrases and sentences, turning pages, carrying out requests, pointing to body parts, holding pencils, imitating drawn circles, or catching a ball. The neurologists had an overall clinical impression of developmental or psychomotor delay in 12 (10%) of the exposed compared with 3 (3%) of the control children, and of a speech problem in 8 (7%) versus 3 (3%).

We did age-appropriate testing of cognitive development and behavioral assessment in the home after the survey, using new controls matched for neighborhood, sex, age, sib order, and family socioeconomic status. Except for verbal IQ on the Wechsler Intelligence Scale for Children (WISC), the exposed children always scored lower than the controls on the three developmental and cognitive tests (Table 3). On the Rutter scales, the exposed children showed higher (that is, worse) scores on all three scales. There are no Taiwanese norms for the Rutter scales; both exposed and control children scored higher than would be expected based on the norms developed by Rutter *et al.* (*4*).

Thermally degraded PCBs were identifed as human teratogens in the Japanese epidemic in 1968. Children born to *yusho* mothers had low birth weight, hyperpigmentation of gums and nails, conjunctivitis, dysplastic nails, wide fontanels, metastatic scalp calcification, diffuse dark skin pigmentation, and natal teeth; 2 in 13 were stillborn (*5*). Four of these children were reported as normal at ages 8 to 19 months (*6*, *7*), but Harada (*8*) reported that the 13 children he examined up to 7 years after the exposure were apathetic and dull with IQs in the 70s.

In Taiwan, Wong and Hwang (*9*) noted skin desquamation, deformed, pigmented nails, hypersecretion of the meibomian glands, hyperpigmentation of the nose, and acne in six offspring of *yucheng* mothers. Four of these children weighed 2500 g or less at birth. Lan *et al.* (*10*) added another case with diffuse skin hyperpigmentation and low birth weight who died at 22 months. Law *et al.* (*11*) reported twins seen at 3 months of age for respiratory distress and pneumonia. They weighed 1800 and 2820 g at birth, and had wide fontanels, hyperpigmentation, and persistent conjunctival swelling.

The effects in the children we saw are most apparent in nails, hair, teeth, gums,

Table 1. Physical signs present at birth and selected medical history items as reported by mothers. Frequencies are those reporting "yes" over those reporting "yes" or "no." "Don't know" and missing values are not included.

Physical sign	Exposed	Control
At birth		
White eye discharge	32/108	5/113
Eyelid swelling	25/106	0/111
Teeth present	11/127	0/113
Irritated or swollen gums	11/ 99	0/114
Hyperpigmentation	54/127	2/114
Deformed or small nails	30/122	1/113
Acne	16/125	0/114
Subsequent history		
Bronchitis or pneumonia in first 6 months	30/124	5/115
Bronchitis bad enough for 2 days in bed	21/126	3/111
Seizure with fever	15/127	5/115
Seizure without fever	1/127	1/113
Chipped or broken teeth	38/107	25/106
Hair loss	14/115	2/105
Acne scars	11/115	0/106
Loss of muscle strength	5/ 89	0/ 85
Joint pain	5/ 91	0/ 84
Generalized itching	32/115	12/102
Skin abscesses or boils	26/116	11/103
Warts	8/114	1/106

Table 2. Selected findings on physical examination. Ratios represent number recorded positive over number examined.

Physical sign	Exposed	Control
Gum hypertrophy	7/116	0/107
Tooth chipping	11/101	0/100
Intraoral hyperpigmentation	43/116	33/107
Caries	68/101	54/100
Acne or acne scars	20/117	10/106
Hyperpigmentation		
Perineal-genital	50/117	29/106
Head or face	13/117	4/106
Pigmented or deformed nails		
Fingers	19/117	1/106
Toes	74/117	22/106
Conjunctivitis or cysts	12/117	9/106
Lymphadenopathy	28/117	11/106
Eyebrow flare	25/117	4/106
Lungs not clear to auscultation	19/116	6/106
Hirsutism	18/117	5/106
Hypertelorism	24/117	10/106
Clinodactyly	47/117	25/106

Table 3. Results of formal developmental testing and behavioral assessment. Entries are mean ± SE; number in parentheses are sample sizes. The Bayley Scales of Infant Development were used until 30 months. The Stanford-Binet yields an intelligence quotient (IQ) and was used from 30 to 72 months. The Wechsler Intelligence Scales for Children (WISC) were used after 72 months. On the Rutter scale higher scores represent more behavior disorders.

Test	Exposed	Control
Bayley		
Mental scale	100 ± 2.5 (45)	106 ± 2.4 (45)
Motor scale	101 ± 2.7 (45)	108 ± 2.1 (45)
Stanford-Binet (IQ)	85 ± 2.7 (52)	89 ± 2.7 (52)
WISC		
Verbal IQ	82 ± 3.1 (21)	82 ± 2.3 (21)
Performance IQ	90 ± 2.7 (21)	97 ± 2.9 (21)
Full IQ	84 ± 2.9 (21)	88 ± 2.4 (21)
Rutter		
Health problems	2.64 ± 0.21 (118)	1.43 ± 0.15 (120)
Habits	1.50 ± 0.13 (117)	0.98 ± 0.11 (120)
Behavior	11.08 ± 0.45 (117)	9.24 ± 0.41 (119)

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skin hyperpigmentation, and growth and development, and are thus generally consistent with an acquired (neuro)ectodermal dysplasia. The acne present at birth and persistent in some children is a specific effect of the class of polycyclic, polyhalogenated hydrocarbons, but may also be a part of the apparent effects on ectodermal structures. The increased frequency of bronchitis may be due to a specific pulmonary lesion, which has been seen in adults (*12*) and children (*11*) exposed to this class of agents, or due to a more generalized immune disorder (*13, 14*). The developmental effects are consistent with those seen in rhesus monkeys exposed transplacentally (*15*), and the behavioral problems may be secondary to the developmental delay or a form of direct toxicity (*16*).

These children have been exposed only by transplacental passage of the chemicals or by breast milk exposure. It is impossible to separate cleanly effects that persist because of structural changes during the fetal period from those that persist because of continued internal exposure. Transplacental passage of the chemicals has been documented in autopsy studies (*10*), and it is reasonable to suspect that the chemicals will persist in the children. There were metabolic changes in the placentae of some of these children (*17*) and a few have mild hepatic porphyria (*18*).

The kinds of toxicities seen are consistent with PCBs, but the exposures are relatively low. The children of workers exposed to PCBs uncontaminated by polychlorinated dibenzofurans (PCDFs) do not show nearly so much toxicity, but the mothers achieve blood PCB levels that are comparable to those seen in the outbreaks (*19*). The most likely reason is the presence of the very toxic PCDFs (*2*) in the cooking oil. Qualitatively, the PCBs and PCDFs are similar in toxicity, but the PCDFs are active at much lower doses. The oil in Taiwan had about 100 ppm PCBs, and about 0.1 ppm PCDFs (*20*). Although there has not been a human exposure to PCDFs in the absence of PCBs, it is reasonable to assume that much of the toxicity seen in both outbreaks is due at least in part to PCDF contamination.

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