Possible Effect of Neonatal Polybrominated Biphenyl Exposure on the Developmental Abilities of Children

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The preceding two reports,[1,2] offering different conclusions from studies on the same children, should be examined from statistical, clinical pediatric, and toxicologic points of view. The group under study comprised 19 children who were conceived, born, and/or breastfed during the period of maximal polybrominated biphenyl (PBB) exposure in Michigan before the contamination had been identified. Seagull[1] studied these children between the ages of 2 5/12 and 3 11/12 years with five tests of the McCarthy Scales of Children's Abilities[3] and concluded that four of the five tests had significant ($p < 0.05$) correlations with PBB exposure, *i.e.*, the higher the children's PBB levels in adipose tissue, the lower their developmental abilities. Schwartz and Rae[2] later studied these same children between the ages of 4 1/12 and 6 1/12 years ($N = 18$ because one family refused to participate in the follow-up study) with the entire battery of McCarthy Scales of Children's Abilities,[3] plus the Wechsler Preschool and Primary Scale of Intelligence,[4] and concluded that no significant ($p > 0.05$) difference existed. An attempt was made to find a matched control group of 19 children, selected randomly from the same geographic area as that of the PBB cohort, but serum PBB levels did not allow the authors to differentiate between the PBB and control groups.[2]

Statistics

The authors used different approaches to the analysis of the data. Given the small data set, the study should not have been analyzed by multivariate analysis of covariance.[1] The arbitrary division of "low" (<0.1 ppm) and "high" (>0.1 ppm) PBB-exposed groups[1] is not justified, in view of a continuum of PBB levels in adipose tissue over more than three orders of magnitude (from 0.01 ppm to 20.96 ppm). The "low group" thus exhibits less than 8-fold differences between any two individuals, whereas the "high group" exhibits as much as 180-fold differences between two individuals.

Schwartz and Rae[2] have determined rank correlation coefficients between $\log_e$ transformations of PBB levels and developmental scores, which we believe is the method of choice. Several months ago we recommended that both groups of authors compare their data[1,2] to see what had happened to each child's test score over the intervening 2½ years. The authors felt that such a comparison would not be interpretable because of inherent measurement variations in repeat testing at different ages using age-specific tests that would be different the second time.

The *intra*individual variation in gas chromatographic analysis of PBB levels in fat samples should be at least mentioned. Variance of 20 per cent between samples from the same person is not uncommon.[5,6] If subject #10 (0.116 ppm) had had a repeat adipose tissue value of 0.096 ppm of PBB, for example, would he belong in the "high" or "low" group?

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Only five tests from the whole battery of the McCarthy Scales of Children's Abilities were selected by Seagull[1] because of time limitations in the study situation. These tests therefore were given out of context of the entire battery[3] and under circumstances in which the test would not ordinarily be given, *viz* in the midst of an array of physical and medical tests. The results of this screen[1] thus called attention to an aspect of these young children's health that needed confirmation. The confirmatory testing[2] was carried out about two years later with all 18 subtests of the McCarthy Scales of Children's Abilities, under the more ordinary circumstances of the child's school. The five subtests studied by Seagull[1] were placed in the proper context by Schwartz and Rae; the results are listed in Tables 4 and 5 of Reference 2. In addition, the Wechsler Primary Preschool and Primary Scale of Intelligence[4] was used during this follow-up study.[2] It would be important to know whether differences between tests at the two different times are consistent with expected intraindividual variation in the McCarthy Scales of Children's Abilities.

The earlier assertion of a statistically significant effect on childhood development by PBB[1] was not borne out by the more complete follow-up study two years later.[2] It is not possible to determine, however, whether: a) PBB had a specific developmental effect on children exposed *in utero* or early in life and this effect is diminishing, or b) the initial conclusions[1] were related to the conditions under which the original testing was done and to the difficulty of interpreting statistical significance with this small data set. Publication of both papers is therefore important to emphasize the possibility that persistent chemicals might affect child development and should encourage further studies of this kind—both on this cohort, as these children grow older, and other groups with known exposure to environmental pollutants.

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Toxicology

Clinical signs and symptoms attributed to PBB exposure include possible immunologic defects, increased propensity toward respiratory infections,[7] hypothyroidism,[8] and numerous neurological symptoms such as somnolence, ataxia, dizziness, muscle weakness, and memory loss.[9,10] Typically the level of serum or adipose PBB in any one individual has not correlated well with any of these signs and symptoms of toxicity.[7,11–14] This may mean that the effects are not caused by PBBs or that genetic heterogeneity in PBB response by the human population (perhaps at the level of liver metabolism, the central nervous system, or the immune, gastrointestinal and/or endocrine systems) makes the problem of cause-and-effect very complicated. The reported abnormalities in the immune system of PBB-exposed persons[15] emphasizes the need for concern about the appearance of diseases related to such deficiencies in children. Because PBBs have been shown to be weakly teratogenic in mice[16] and to cause liver tumors in rats,[17] it will be clinically important to continue following PBB-exposed individuals indefinitely.

What is the etiology of PBB-induced toxicity or cancer in laboratory animals? Most likely both toxicity and tumorigenesis occur by way of the *Ah* receptor.[18–20] PBBs and other environmental pollutants probably exert their detrimental effects by occupancy of the *Ah* receptor (Figure 1). Two possible mechanisms are being proposed from animal studies.[18–20] First, the response of the PBB-receptor complex entering the nucleus is to induce new drug-metabolizing enzymes (shown in Figure 1 as "P_1-450"), which in turn might metabolize the PBB inducers to reactive (toxic or carcinogenic) intermediates. Second, the *Ah* receptor binds to an endogenous ligand that might be essential for some critical life function. Occupancy of the receptor by foreign chemicals might prevent the normal interaction of the receptor with the endogenous ligand. No normal body ligand has been identified yet, however, although several dozen candidates have been carefully studied. It is possible that PBB toxicity is associated with reactive metabolites whereas PBB-induced tumorigenesis involves PBB as a more potent promoter[21,22] than initiator of cancer. Possible interactions between the *Ah* receptor and epidermal growth factors and other cell-surface-related phenomena such as tumor promotion and immunosuppression have been discussed.[23] The mechanism of how PBBs are toxic to the human central nervous system—or how PBBs cause any of the other clinical effects described[7–14]—is presently unknown.

Every concern that needs to be expressed about PBB exposure has been already voiced for polychlorinated biphenyl (PCB) exposure. PCB contamination is worldwide,[24,25] including Antarctica.[26] The properties of the PCBs (clinical signs and symptoms, toxicity and carcinogenicity in laboratory animals, enzyme induction patterns, metabolism, and persistence in the environment) parallel very closely those of the PBBs. Halogenated biphenyls having two adjacent nonhalogenated carbon atoms (Figure 2) are metabolized at rates more than 100 times faster, when compared

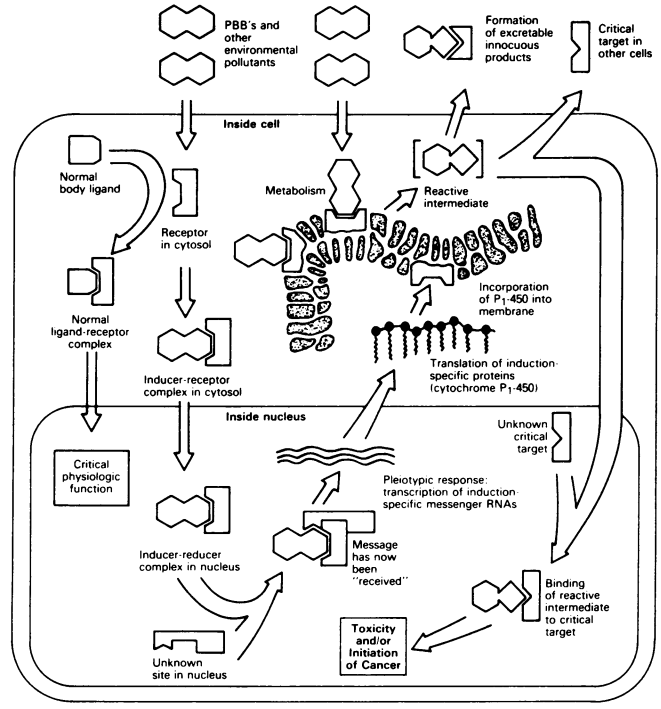

FIGURE 1—Diagram of a cell in which certain halogenated hydrocarbons, combustion products, and other environmental pollutants bind avidly to the cytosolic *Ah* receptor, leading to chemical-induced toxicity or cancer. Whether P_1-450 induction with resultant metabolism to reactive intermediates, or simply occupancy of the receptor, is responsible for the toxicity or tumorigenesis is not yet certain.

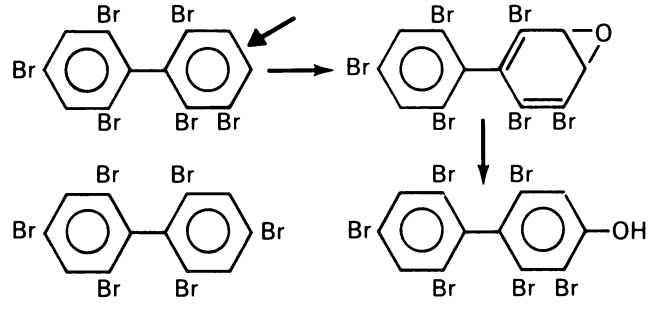

FIGURE 2—Two hexabromobiphenyl isomers (*upper* and *lower left*). Whereas the *lower left* isomer is extremely slowly metabolized, the *upper left* isomer has two adjacent nonhalogenated carbon atoms, rendering the molecule much more easily metabolized by P-450 form(s); metabolism includes formation of the arene oxide (*upper right*), which readily rearranges nonenzymically to the phenol (*lower right*).

with those not having two adjacent nonhalogenated carbon atoms.[27] The two adjacent nonhalogenated carbon atoms provide the easy insertion of an atom of atmospheric oxygen (monooxygenation) by various forms of cytochrome P-450, thereby producing an arene oxide which rapidly rearranges nonenzymically to a phenol. Phenols are readily conjugated with glucuronide or sulfate; the resulting highly polar conjugate can be removed rapidly from the body. Biphenyls having six or more halogens generally remain in the fat and

other tissues of the laboratory animal with half-lives longer than the life of the animal.[27,28]

Since man is at the end of the food chain, persistence of heavily halogenated PCBs and PBBs appears to be with us—at least for the foreseeable future. Heavy contamination of fish with PCBs is well known.[29–31] Consumption of PCB-contaminated fish results in an enhanced total body burden of PCBs. Breastfeeding by PCB-contaminated mothers will lead to an enhanced ingestion of PCBs in these infants from birth.[32–35] This transfer of PCBs from one generation to the next is occurring with PBBs.[36,37] It therefore should be emphasized that one must be on the lookout, at least for the next several decades, for numerous possible clinical effects—including subtle changes in intelligence and long-range effects causing cancer—in PCB-exposed and PBB-exposed individuals.

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Symposium on the Health Aspects of Nuclear Power Plant Incidents

The New York Academy of Medicine announces a symposium on the Health Aspects of Nuclear Power Plant Incidents to be held April 7–8, 1983 at the New York Academy of Medicine, New York, NY.

The program, designed to familiarize physicians with the operations and health aspects of nuclear power plants, will include: 1) presentations on the structure and function of nuclear plants, types of malfunctions and their probabilities, and the biological effects of ionizing radiation; 2) the rationale for government regulations concerning nuclear plants and public safety, and the role of the local health department; 3) the prophylactic value of potassium iodide, the psychological implications of nuclear power plant incidents, and the needs for public information and public relations, and 4) the clinical care of radiation exposed and contaminated individuals.

There is no fee; advance registration is required by March 31, 1983. The optional luncheon fee for the two-day symposium is $25.

For further information, contact Committee on Public Health, New York Academy of Medicine, 2 East 103rd Street, New York, NY 10029.

Symposium on Drinking Water and Human Health

The American Medical Association announces a symposium entitled "Drinking Water and Human Health" to be held April 7–8, 1983 at the Washington Hilton Hotel, Washington, DC. The Symposium, to be cosponsored by the Office of Drinking Water, US Environmental Protection Agency, will identify the human health effects of a broad range of biological and chemical agents in water supplies, review the relationships of organic constituents in water to the frequency of cancer in human populations, and examine the present state of knowledge relating to drinking water and cardiovascular disease.

For further information, contact Jack A. Bell, MPH, American Medical Association, 535 North Dearborn Street, Chicago, IL 60610, telephone 312/751-6529.

Course Announcement

The New England Epidemiology Institute announces a three-day course, "Epidemiology—Methods and Applications," to be held April 6–8, 1983 at the Cathedral Hill Hotel in San Francisco. Drs. Philip Cole and Kenneth Rothman will present modern concepts in epidemiology and their applications to the study of etiology, natural history of disease, and strategies in preventive medicine and public health.

This course, intended for professionals in health and related disciplines who wish to develop a familiarity with epidemiologic research principles, is especially appropriate for persons not actively engaged in epidemiologic research but who are required to evaluate and interpret such research. No previous study of epidemiology or biostatistics is required. Registrants may receive Continuing Medical Education Credits (AMA Category 1) upon application, and/or Certification Maintenance Credits from the American Board of Industrial Hygiene.

For more information, contact: Dr. Nancy Dreyer, New England Epidemiology Institute, Department SC-15, P.O. Box 57, Chestnut Hill, MA 02167; telephone (617) 734-9100.