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ACCIDENTAL EXPOSURE TO DIOXINS

HUMAN HEALTH ASPECTS

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CHAPTER 2

AN OVERVIEW ON THE HEALTH EFFECTS OF HALOGENATED DIOXINS AND RELATED COMPOUNDS--THE YUSHO AND TAIWAN EPISODES

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I. INTRODUCTION

There are numerous health effects and symptoms and signs reported in humans following the exposure to halogenated dioxins and related compounds. They are given in the tabulation below and have been adapted after Kimbrough (1).

System or finding	Signs of lesion	Chemical product
General	Weakness, headache, weight loss, impotence, insomnia, loss of appetite, nausea, abdominal pain	Technical PCP, poly- chlorinated naphtha- lenes, -dibenzodioxins, -dibenzofurans, -biphenyls, polybromin- ated biphenyls, diben- zofurans

System or finding	Signs of lesion	Chemical product
Skin	Chlor- or bromacne, hyperpigmentation, hair loss, nail growth, porphyria	Penta- and hexachloro-naphthalenes, tetrachlorodibenzodioxins, tri- and tetrachlorodibenzofuran, hexa- and heptachlorobiphenyls, tetrabromodibenzofuran, polybrominated naphthalene
Hepatic	Liver enlargement, impaired liver function, fatty degeneration, fibrosis, hepatocellular necrosis	Chlorinated naphthalenes, tetrachlorodibenzodioxin, technical pentachlorophenol
Respiratory system	Reduced vital capacity, chronic bronchitis	Technical pentachlorophenol, polychlorinated and polybrominated biphenyls
Central and peripheral nervous system	Muscle and joint pain, numbness and spasm in the limbs, reduced sensory and motor conduction velocity, sensory disturbances (taste, hearing, smell, sight impairment)	Polychlorinated biphenyls, -dibenzofurans, -dibenzodioxin
Endocrine system	Irregular menstrual cycle, retarded growth	Polychlorinated biphenyls and -dibenzofurans
Ocular manifestations	Several degrees of inflammation with burning, discharge, edema of eyelid, cyst formation of tarsal glands and pigmentation of eyelid and conjunctiva	Technical pentachlorophenol, polychlorinated biphenyls, -dibenzofurans and -dibenzodioxin

System of finding

Stomatological alterations

Clinical chemistry laboratory findings

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duct	System of finding	Signs of lesion	Chemical product
achloro- tetra- dioxins, achloro- hexa- robi- abromo- poly- phthalene phthalenes, dibenzo- nical phenol	Stomato- logical alterations Clinical chemistry laboratory findings	Pigmentation of oral mucosa, anomalies in number and growth of teeth Increased serum triglycerides, decreased serum bilirubin	Polychlorinated bi- phenyls and -dibenzo- furans Polychlorinated bi- phenyls, -dibenzo- furans and -dibenzo- dioxins

The clinical features have been observed mainly in cases of occupational exposure where dosage is unknown, route of administration is assumed, latency period to onset of toxic effects is poorly defined, length and intensity of exposure is seldom recorded or available, number of cases entering the study is imposed by circumstances beyond the investigators, baseline data for control are often not adequate, and a comparison with a matching sample is lacking. In addition, the sample consisted mainly of adult males.

The majority of the cases of exposure reported have been cases of serious toxicity, i.e., of unquestionable toxic manifestations which assume exposure and, consequently, absorption of many times the threshold dose level to produce toxic effects. Furthermore, these have been cases of mainly acute exposure following a change in a manufacturing procedure or a lack of safety measures or accidental exposure.

These health effects might somewhat provide indications for long-term exposure to low doses of the same chemicals or for their effects when stored in the body in trace quantities.

Minute amounts of many chemicals can be detected in the human body using very sensitive analytical chemical methods as these methods improve (2) the detection of very low quantities of a chemical in body fluid should provide additional data on adsorption (Table I) and consequently exposure.

II. DETERMINATION OF EXPOSURE

Contact with one or several chemicals assumes an exposure to and consequent absorption of these chemicals. However, the assessment of the level of exposure and of the quantity of the actual absorption are not as easy to ascertain. Terms such as high, medium, and low exposure (dosage exceeding background

TABLE I. Trace Analysis and Its Implications (Tetrachlorodibenzodioxins)^a

Amount	Weight (gm)	Trace contamination level per gm	Number of molecules	Level of analytical expertise required to detect residues
Milligram (mg)	10 ⁻³		10 ¹⁸	Titration
Microgram (μg)	10 ⁻⁶	1 ppm	10 ¹⁵	Spectrophotometry
Nanogram (NG)	10 ⁻⁹	1 ppb	10 ¹²	Gas chromatography
Picogram (pg)	10 ⁻¹²	1 ppt	10 ⁹	Mass spectrometry
Femtogram (fg)	10 ⁻¹⁵	1 ppq	10 ⁶	Mass spectrometry
Attogram (ag)	10 ⁻¹⁸		10 ³	Mass spectrometry
Mologram ?	10 ⁻²¹		(1)	Mass spectrometry

^aAfter Cairns et al., 1980 (2).

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exposure) are all relative and vary quite widely as noted in the literature.

Of the clinical signs and symptoms of toxicity, only chloracne is sufficiently specific for and, therefore, indicative of exposure (3). However, not all chemicals are chloracnegenic and those which are have different levels of acnegenicity. Furthermore, the skin lesions tend to be spontaneous and completely heal. Thus, they may have occurred and disappeared and are not observable at the time of clinical examination. In addition, in its mildest form (a few blackheads on the face around the malar region), it can escape detection by the examining clinician. Finally, the organ susceptibility in man may differ from individual to individual, thus determining whether one develops other toxic effects, irrespective of chloracne.

The detection of the chemical(s) in body fluids and tissues will provide a new dimension in the assessment of exposure i.e., the process of uptake of the chemical from the environment into the systemic circulation. Given the parameters exposure, the detection of the chemical in the blood and urine will provide the evidence that the chemical was not only available but also absorbed. The improved sensitivity of technical analysis will also open the way to the study of the kinetics of the chemical in the human body. Thus, time and level of exposure can be calculated and correlated with the clinical signs and symptoms of toxicity.

III. RISK ASSESSMENT OF LOW DOSES

Experimental data (4-9) have shown that for some chemicals effects are linked with the structure of each isomer. One isomer can induce enzyme production and acnegenic properties at very low doses, while a change in the position of one chlorine atom in the molecule in another may not produce these effects at all. With the exception of 2,3,7,8-TCDD very little is known about the toxicity of these other chemicals. In fact, for the majority of these chemicals, long-term toxicity studies and studies on their effects on reproduction are still lacking.

There is considerable concern in the medical community about the proper methodology to be used for the study of the long-term effect of exposure to low doses of these chemicals. Although the present diagnostic means are adequate for identifying subtle clinical, histologic, and biochemical changes, doubts are raised about the ability to understand the meaning of these findings and their role in predicting the long-term effects on human health. There is uncertainty concerning

whether borderline changes observed in morphologic (liver histology) and blood chemistry tests, immunological tests, cytogenetic tests, nerve conduction velocity tests, and respiratory function tests are the expression of simple physiological adjustment or an unfavorable reaction of an organ which will lead eventually to irreversible damage. In the great majority of cases the chemically induced changes in some functions or structures are probably only an indicator of an exposure to quantities of chemicals which are below the toxic level. The correlation of the level of the chemical(s) in body fluids, may provide a sensitive system that can be used to monitor exposure of humans to the chemicals and the importance of that exposure in the long-term susceptibility to disease. They are not, however, a symptom of disease. Failure to agree on the meaning of these findings masks the definition of "observable adverse health effects."

IV. HUMAN RESPONSE TO EXPOSURE

In the final analysis it is heavy exposure to chemicals that provides an opportunity of measuring human response. Extrapolation from one dose level to another might provide data for estimating the human risk associated with low exposure levels.

There have been a number of episodes of heavy exposure to chemicals. They have involved both sexes of all ages, and a sizable portion of the population. In addition, the dose, route of absorption, and length of exposure could be somewhat defined. A number of these cases are presented below.

In 1973, in Michigan, over 10,000 residents were exposed to polybrominated biphenyls (PBBs). The chemical was absorbed through the consumption of meat, milk, and other dairy products. Of this population, the level of exposure for 4000 residents was determined, although the accuracy of these results were not definitive. The PBB serum levels ranged from 0 to 1900 µg/liter but the daily and total consumption was not established (10,11). Thus far, it has not been shown conclusively that PBBs caused illness in most of the exposed population.

In 1976, in Seveso, Italy, over 5000 residents were exposed to 2,3,7,8-TCDD. For several years, these residents have lived and are still living in a territory contaminated with a known amount of the chemical. The daily and total amount of exposure and the route of absorption of this chemical are not known. However, chloracne was observed in a small subgroup of the population, although this health effect does not provide conclusive information about the route of absorption, the daily intake, the length of exposure, and the total dosage (12).

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At the Love Canal in Niagara Falls, New York, 239 families were exposed to more than 200 organic chemical compounds in a landfill. These 239 families had to be relocated. Of the 22,000 tons of chemical wastes buried in the landfill, there are 200 tons of TCP with approximately 300 ppb of 2,3,7,8-TCDD (about 60 g). The conditions of exposure of this episode are exceedingly complex. The population at risk was exposed to many chemicals and one cannot say if one, several, or an interaction between them, are likely to be responsible for effects observed (13).

Approximately 1600 residents were exposed to a mixture of polychlorinated biphenyls (PCB's), polychlorinated dibenzofurans (PCDF's) and polychlorinated quaterphenyls (PCQ's) in 1968 in South Japan. These residents consumed Yusho contaminated with an edible oil (Yusho poisoning) (14-17).

A similar event occurred in 1978 in central Taiwan, where 2000 residents were exposed to the same mixture of PCB's, PCDF's and PCQ's (18,19).

In the data available, only the last two episodes provide precise information about the daily intake, length of exposure and total dosage, and latency to onset of effects and time of the appearance of the single symptoms and signs of the clinical picture of the poisoning. These episodes are discussed in greater detail in the next section.

V. THE 1968 YUSHO AND THE 1978 TAIWAN EPISODES

A sporadic outbreak of a peculiar skin disease in South Japan between March and October 1968 was the beginning of the so-called "Yusho disease." It was caused by contamination of rice bran oil by Kanechlor, a commercial brand of a polychlorinated biphenyl which leaked from a heating pipe. About 1600 people were identified as having ingested the contaminated rice oil.

On June 7, 1968 a 3-year-old girl was admitted to the Department of Dermatology of the Kyushu University with symptoms of chloracne. Her parents and her elder sister showed the same symptom, leading health authorities to become suspect of the cause of the disease. Similar cases were uncovered in the weeks and months that followed (14-17).

In Taiwan, during the last months of 1978, for reasons which still require explanation, rice cooking oil produced by a local company was contaminated with material containing PCB. In March, 1979, the first cases of unusual ocular and dermatologic manifestations were observed. They occurred mainly in the central region of Taiwan and their number increased rapidly to about 2000. In October, 1979, the Central Health

Authorities in Taiwan issued a statement announcing that the cause of the disease had been the ingestion of edible oil contaminated with PCB (18,19).

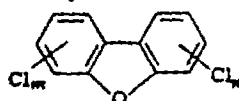
TABLE I
ed Oil

VI. COMPOSITION OF THE TOXIC MATERIAL--QUANTITY AND DURATION OF INGESTION

Japan

Taiwan

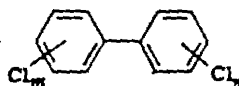
The toxic chemicals involved in the two episodes discussed in the previous sections (20-25) were polychlorinated biphenyls (PCB's), polychlorinated dibenzofurans (PCDF's) and polychlorinated quaterphenyls (PCQ's). Their chemical structures are presented below.



Polychlorinated
dibenzofuran (PCDF)

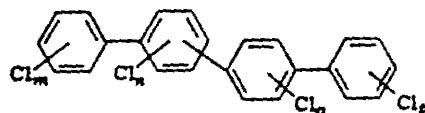
TABLE :

PCB's



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There are 209 possible isomers for the PCB's and 135 for the PCDF's. As can be seen in Table II, the concentration of these chemicals in the rice bran oil differed for Japan and for Taiwan. The toxicity of the oil from Japan was 25 times higher than that from Taiwan. Another difference was the distribution of the isomers. In Taiwan there was a higher concentration of the tetra- and pentachlorobiphenyls whereas in Japan, it was the hexa- and heptachlorobiphenyls. As for the PCDF's, the toxic oil contained isomers with 5 chlorine atoms

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TABLE II. Concentration of PCBs, PCDFs and PCQs in Contaminated Oil in Japan and in Taiwan

	PCBs (ppm)	PCDFs (ppm)	PCQs (ppm)
Japan	920	5	866
Taiwan	40.5	0.26	36.5

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TABLE III. Isomers of Toxic Oil in Japan and Taiwan

	Isomer	Japan	Taiwan
PCB's	Tetrachlor	-	+++
	Pentachlor	+	++++
	Hexachlor	++++	+
	Heptachlor	++++	-
PCDF's	Trichlor	+	+
	Tetrachlor-	++	++
	Pentachlor-	+++	++++
	Hexachlor-	++	++

with smaller amounts of the other congeners (Table III). This was true of the oil from both Japan and Taiwan.

The quantity of the ingested chemicals was calculated by epidemiological surveys (17,19,26), carried out in Japan in 325 cases and in Taiwan (924 cases) (Table IV). The surveys showed that there was a marked difference between the average consumption of rice oil per month in Japan (0.25 kg) as compared to Taiwan (1.42 kg). The ratio of contaminating chemicals ingested per month in Japan as compared to Taiwan was 1:4, respectively. The latency period to the onset of the first clinical symptoms was shorter in Japan (2 months) than in Taiwan (2.7 months). The total length of intake was also shorter in Japan (3.5 months) than in Taiwan (8.7 months). This is probably due to the fact that in Japan only a limited quantity of the rice oil was contaminated and only for a few days at the beginning of February, 1968. As soon as this

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TABLE IV. Quantity of Ingested Toxic Oil and Duration of Ingestion^a

	Quantity in rice oil (ppm=mg/kg)		Quantity rice oil used per month (mg)		Ingested during latency period (mg)		Ingested for total length of intake (mg)		Dose per day (mg)		Dose per kg body weight	
	Japan	Taiwan	Japan	Taiwan	Japan	Taiwan	Japan	Taiwan	Japan	Taiwan	Japan	Taiwan
Chemicals			(0.25 kg)	(1.42 kg)	(2 months)	(2.7 months)	(3.5 months)	(8.7 months)				
PCBs	920	40.5	230	57.5	460	155	805	500	8.4	1.9	0.14 mg	0.03 mg
PCDFs	5	0.26	1.25	0.37	2.5	0.99	4.4	3.2	0.04	0.01	0.06 µg	0.2 µg
PCQs	866	36.5	216.5	57.8	433	140	756	450	7.2	1.7	0.12 mg	0.02 mg

^a Values are calculated for average body weight of 60 kg. 325 cases in Japan, 924 cases in Taiwan.

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quantity had been consumed there was no additional opportunity for poisoning to occur. In Taiwan, it is not known how much of the rice oil had been contaminated and how long it had been available to consumers. The association of the clinical manifestations with the oil contamination was officially announced in October, 1979, i.e., 8 months after the observation of the first cases. The ratio in the total amount of PCB's, PCDF's, and PCQ's ingested in Japan (875 mg, 4.4 mg, and 756 mg, respectively) and Taiwan (500 mg, 3.2 mg, and 450 mg, respectively) is 1:1.6. These last values are probably more instructive with respect to the clinical manifestations observed in both places than the daily dose and the dose per kilogram body weight, where the ratio is roughly 1:4. The route of absorption for all cases was the gastrointestinal tract.

In Japan it was possible to estimate (17) the incidence (rate) of the clinical manifestations in the population in relation to dosage (Table V). It was shown that the toxic dose 100 (eliciting toxic effects in 100% of the cases) could be reached at a dose of 720-1400 mg PCB's, i.e., 3.6-7.2 mg PCDFs and 570-1100 mg PCQ's, and that below that level the incidence of disease decreased.

The clinical severity of the symptoms (27) graded by the dermatologist from 0 to 4 (Grade 0: subjective complaints; Grade 1: pigmentation of skin and mucosae, eye discharge; Grade 2: comedone formation; Grade 3: moderate acne; Grade 4: extensive acne eruptions) correlated closely in Japan with the total amount of oil consumed but not with the amount of oil consumed per kilogram of body weight per day. The acne lesions in the children were generally milder than those of the adults. The daily amount per kilogram body weight calculated for the children was larger than for the adults but the total amount was less. In Taiwan about 1/4 of the cases were severe and clinical severity seemed to be higher in the younger age brackets. There seems to be a direct correlation between total intake of toxic oil and severity of symptoms, but this cannot be confirmed statistically (28-30).

VII. CLINICAL SYMPTOMATOLOGY

Probably the best (31) clinical picture was provided by the examination of a large Taiwanese family of 27 members, comprising three generations. The living conditions were the same and the toxic oil consumption had been identical for all members with respect to daily and total intake (Table VI). Table VI shows the clinical symptoms and signs in order of frequency and time of appearance. Symptoms affecting the eyes were the first to appear after a latency period of 2-3 months (32).

TABLE V. Frequency and Severity of Symptoms in Relation to PCB Concentration in Yusho Oil Japan 1968-1979^a

Total number of users: 146	Not affected (%)	Moderately affected (%)	Severely affected (%)	Attack rate (%)
Light users (80) i.e., <720 ml or less than 662 mg PCB's; 623 PCQ's; 3.6 mg PCDF's	10 12	39 49	31 38.5	87.5
Moderate users (45) i.e., 720-1440 ml or 662-1324 mg PCB's; 623-1247 mg PCQ's; 3.6-7.2 mg PCDF's		14 31	31 69	100
Heavy users (21) i.e., more than 1440 ml			21 100	100

^a Oil contaminated with 920 ppm PCB; 866 ppm PCQ, and 5 ppm PCDF. After Kuratsune et al., 1972 (17).

2 Health Effects

TABLE VI. Conditions Familial 1979^a

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TABLE VI. Symptoms and Signs of 27 Members of a Three Generations Family 6-7 Months after Beginning of Poisoning, Taiwan, 1979^a

<i>Symptoms and signs</i>	<i>Male (15)</i>	<i>Female (12)</i>
Increased eye discharge	93.5%	91.6%
Swelling of eyelids	86.6	91.6
Acneiform eruptions	86.6	83.3
Pigmentation of nails	86.6	83.3
Pigmentation of conjunctivae	80	83.3
Pigmentation of lips	80	66.6
Black color of nose	66.6	75
Hypoesthesia	66.6	75
Deformity of nails	60	58.3
Pigmentation of gingivae	53.3	66.6
Numbness of limbs	53.3	50
Blurred vision	53.3	50
Keratotic plaques of palms and soles	46.6	66.6
Follicular hyperkeratosis	40	41.6

^aAfter Wei-Min Li et al., 1981 (31).

The same clinical symptoms were observed in groups of cases examined and treated by the Department of Dermatology of the Veteran General Hospital, Taipei, Taiwan (33), as well as by the Departments of Ophthalmology, Neurology, Pediatrics, and Biochemistry of the same Hospital. A comparison of the dermatologic symptoms of two similar groups of cases from Japan shows that there are quantitative differences, which are probably related to differences in the constitutions of the samples, but the quality of the clinical features was the same (Table VII).

Comprehensive neurological examinations have been (34) performed on 39 cases of a group of 122 severe cases which were admitted to the Department of Dermatology of the Veteran General Hospital of Taipei between January and November, 1980.

TABLE VII. Comparison of Dermatologic Signs between 122 Cases in Taiwan (A) and 138 cases in Japan (B)

Sign	Male		Female	
	A (42)	B (72)	A (80)	B (66)
Acneiform skin eruptions (Comedones, follicular hyperkeratosis, yellow cysts, abscesses)	71.4%	86.1%	77.5%	77.3%
Dry Skin	50.0	30.6	56.0	36.4
Deformities of nails	68.5	22.2	67.5	24.2
Nail pigmentation	56.7	75.0	61.5	71.2
Black color of nose	48.7	4.2	57.3	4.5
Hyperkeratosis of palms and soles	19.5	1.4	22.5	4.5

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TABLE VIII. Neurological Signs and Symptoms of 39 Cases Selected in a Group of 122 with Skin Lesions^a

Symptoms and signs	Number
Headache	15 (38.4%)
Dizziness	12 (30.8%)
Paraesthesia, numbness in the distal part of the limbs	25 (64.1%)
Hypoaesthesia, hypoalgesia in the distal part of the limbs	13 (33.3%)
Pain over back, limbs, and orbits	16 (41.0%)
Intermittent blurred vision	11 (33.3%)

^aAll reflexes were normal--no pathological reflexes; no muscle weakness or wasting.

All had been treated unsuccessfully by local district doctors for 6-10 months. All cases had skin lesions of varying degrees of severity. The 39 cases referred to the Department of Neurology had neurologic symptoms upon clinical examination (Table VIII). The cases presented with a mild peripheral neuropathy with involvement of primary sensory neurons without inclusion of the motor neurons. There was also a mild involvement of the central nervous system. The electrographic measurement of nerve conduction velocity provided evidence that in 35 of the 39 cases not only sensory but also motor conduction velocity was slightly reduced. Nerves conduct at velocities ranging from 1 to 100 m/sec. The speed of nerve conduction indicates the functional status of a group of axons. The velocity in the PCB-contaminated cases was slightly longer than in a control group, averaging 63.3 m/sec. for the motor neurons and 52.9 m/sec for the sensory neurons, instead of 58.3 and 46.8 m/sec, respectively.

The neurological signs and symptoms also indicate involvement of the central nervous system, although electroencephalographic analysis did not show abnormalities.

In Japan, many Yusho patients complained of neurological symptoms, such as, numbness of limbs, hypo- and hyperesthesia, feeling of weakness, and muscle spasm. Reduced sensory nerve conduction velocity was observed in 9 out of 23 cases examined soon after poisoning, while reduced motor nerve conduction velocity was seen in only two cases. ✓

Ultrastructural examination of the sciatic nerve of rats treated with PCB's did not show any change. No abnormalities

of the central and peripheral nervous system have been produced in monkeys treated with 0.5 mg PCB's and 2.5 µg PCDF's for 6 weeks (35).

Blood chemistry tests were performed (36, 37) on several of the cases admitted to the Department of Dermatology of Taipei. The level of triglycerides was elevated in all age brackets. The SGOT and SGPT values, as well as those of the alkaline phosphatase, were within or at the upper borderline of the standard values, with the exception of the lowest age brackets (3 months of age). The blood picture and hemoglobin were normal.

Conventional function tests of the liver (bilirubin, SGOT, SGPT, BSP retention, and others) did not show any abnormalities of this organ in the Yusho cases. Although few morphologic changes were detected by light microscopy, the serum triglyceride was abnormal (38). The increase persisted for a few years (Table IX).

In about 20% of the Yusho cases chronic bronchitis was reported 10 years after the poisoning. The PCB concentration in the sputum and blood of these cases seemed to correlate with the severity of the symptoms. This has not thus far been reported in Taiwan.

VIII. PREGNANCY AND CHILD DEVELOPMENT

The course of pregnancy and subsequent child development was studied in 5 pregnant women (39,40) from Taiwan, who had conceived at the time they were using PCB-contaminated oil and who developed the most common dermatological manifestations (mucocutaneous pigmentation, acneiform eruptions, deformity of the nails, ocular manifestations, etc.). Birth was full term in 4 women and 1 month premature in one who gave birth to twins (Table IX).

Of the skin lesions, different degrees of generalized pigmentation, and deformity of the nails was observed in all of the babies. Although bone development was normal during the first year of life, the babies suffered from gastrointestinal and respiratory illnesses. They were not breast fed. Skin lesions and pigmentation disappeared 2-5 months after birth in all but one of the babies (case No. 4), who at the end of the first year of life still had no teeth and was unable to sit and to crawl. Retarded teeth and bone development was also observed in Japanese babies born from mothers who had been poisoned with the Yusho oil (41).

A comparison with findings in Japan has shown a similar general picture. Eleven women with overt symptoms of poisoning and two women married to men who had been exposed to the

TABLE IX. Clinical Findings of Newborn Babies of PCB-Contaminated Mothers, Taiwan, 1979

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TABLE IX. Clinical Findings of Newborn Babies of PCB-Contaminated Mothers, Taiwan, 1979

	Case number					
	1	2	3	4	5	6
Sex	Male	Male	Female	Male	Female twins	
Birth weight (gm)	3600	2500	2400	3600	1800	1800
Pigmentation of skin, nails, and mucosae	+	-	+++	++	++	++
Acneiform eruptions	+	-	+	++	-	-
Dry skin desquamation	+	+	+	++	+	+
Swelling of Meibomean glands	++	-	+++	+++	+	+
Deformity of nails	+ Both 5th fingers	-	+Both 5th fingers	+++	+	+
Black color of nose	+	-	+	+	-	-
Neurologic disorders	-	-	-	-	-	-

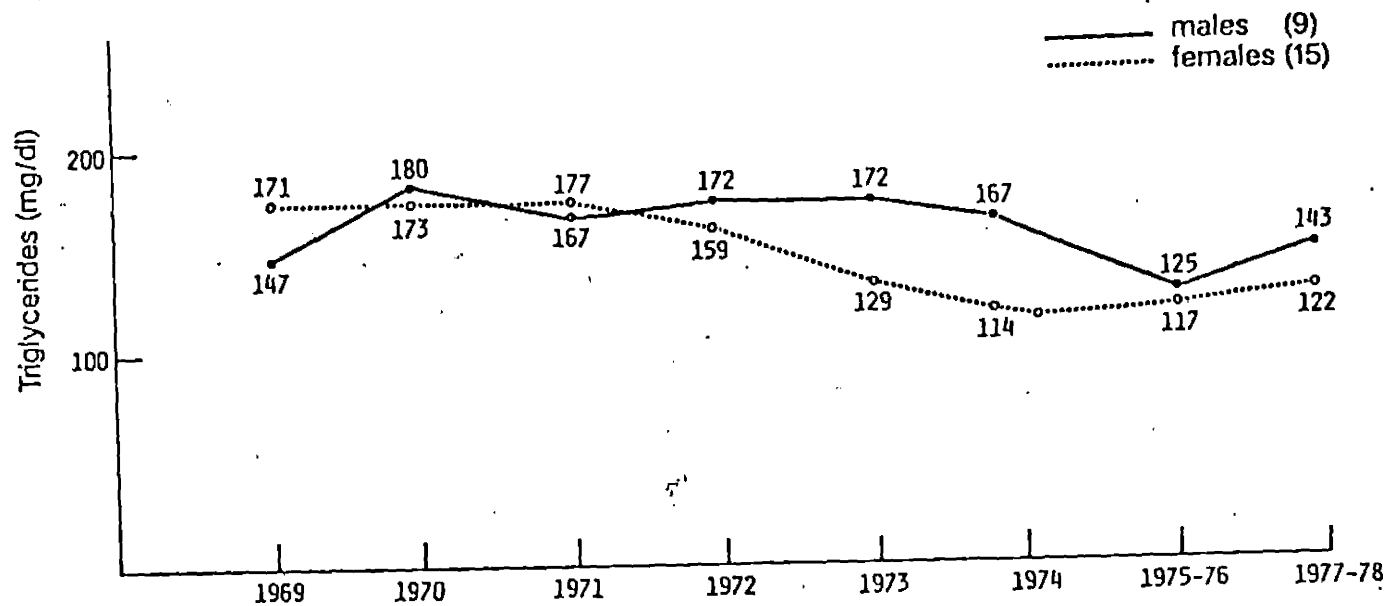


Fig. 1. Ten year follow-up of serum triglyceride levels in 24 Yusho patients (PCB+PCDF)
Standard values: 47-162 mg/dl.

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poison but who did not present overt symptoms of the disease delivered 11 live borns and two stillborn babies. Of these, 10 had dark brown pigmentation of skin mucosae and nails, as well as increased eye discharge. Five were considered to be undersized. A battery of laboratory tests, however, showed no abnormalities. The skin coloration faded within a few months.

Another woman suffering from the disease delivered 3 babies within 4 years after the incident occurred. All showed dark brown skin pigmentation. Pigmentation of the skin also occurred in a baby breast fed by a woman affected by the disease. However, no cases of unusual malformations or increased incidence of spontaneous abortions were reported.

IX. METABOLISM

The rate of absorption, metabolism, distribution, and elimination of these chemicals in humans are practically unknown. However, some data concerning blood levels, storage in adipose tissue and liver, and dissipation from these stores are available (42-44).

The concentration of these chemicals in the blood, liver, and adipose tissue was always higher in cases of poisoning than in the normal population (Table X). Blood PCB levels in normal subjects were below 4 ppb in Taiwan and were about 3 ppb in Japan. Levels in poison cases from Taiwan were ten times higher than normal; they are even higher than the levels found in Japanese cases who showed an average of 6.7 ppb. However the interpretation of these results are difficult because measurement of the blood PCB levels in the Japanese cases was performed 5 years (1973-1974) after the poisoning, whereas the same tests were carried out in Taiwan 1 year after the poisoning.

X. BLOOD AND TISSUE LEVELS AND RELATIONSHIP OF CLINICAL EFFECTS

The correlation between blood levels, severity of clinical symptoms, and blood chemistries has been examined many times, but no close relationship has been found to exist. A high PCB level in blood does not necessarily parallel severity of skin, lesions or rise in the serum triglyceride levels (45,46). On the other hand, blood and tissue concentrations of the chemicals seem to be higher and remain at that level in exposed as compared to the normal population (Table XI).

TABLE X. PCB Levels in Blood of 66 Cases of Contamination in Taiwan, 1979

Number	Sex	Age	PCB levels (ppb)
26	Male	31.4 (8-60)	47.5 (19-120)
37	Female	25 (12-69)	33.7 (11-71)
2	Female	2 months	18 (15-21)
37	Normal persons (Japan)		2.9 ± 1.7
	Normal persons (Taiwan)		Less than 4

TABLE XI. Concentration of PCB in Tissues of Yusho Patients^a

Case no.	Time of death or operation	Concentration (ppm)	
		Adipose tissue	Liver
1	October, 1969	0.1	0.07
2	July, 1969	3.7	0.14
3	July, 1969	15	0.2
4	November, 1969	8.4	0.7
5	December, 1970	0.9	0.07
6	May, 1972	6.5	0.8
7	September, 1972	2.9	--
8	April, 1977	0.4	0.07
9	March, 1977	1.4	0.06
10	September, 1977	1.1	0.02
Control cases (31)	1973	>1.0	0.05

^aAfter Kikuchi et al., 1979 (46).

Chemical isomerization of the carcinogenic PCBs have been distributed among the population. hexachloro chloro response

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Chemical dissipation time seems to be longer for some cases than for others (Table XII). However, the interpretation of these findings is hampered by the limited number of cases providing this data. Pentachloro isomers apparently longer dissipation times than tetrachloro isomers. The distribution of the PCBs isomers also differs for cases of poisoning than for the normals (Table XIII). In the normal population there is a greater concentration of pentachloro than hexachloro isomers, whereas in the Japanese cases the hexachloro and heptachloro isomers are greater. This finding corresponds to the composition of the ingested oil.

II. CONCLUSIONS

The ingestion of PCBs, PCDFs, and PCQs during several years, at an average daily dose of 1.9-8.4 mg PCBs, 0.01-0.04 mg PCDFs, 1.7-7.2 mg PCQ's, and a total dose of 500-805 mg PCBs, 3.2-4.4 mg PCDF's, and 450-756 mg PCQs resulted in a specific clinical picture, namely, skin manifestations dominated by acneiform lesions, pigmentation of skin, mucosae, and nails, and ophthalmic lesions, pigmentation of skin, mucosae, and ophthalmic lesions. In 20-30% of these cases, neurologic disorders of sensory and motor nerves were also observed. Conventional liver function tests as well as conventional blood analyses were normal. Serum triglycerides were 2-3 fold higher than standard values. Levels returned to normal after 3 to 5 years in the Japanese cases.

There are some general conclusions which can be drawn from the information gained by the two episodes which are possibly applicable for all chemicals. The primary manifestation of the poisoning with these chemicals is skin lesions, which is also characteristic of those chlorinated chemicals which are chlorogenic. Impairment of other physiologic functions, such as the liver and nervous system, and fat and porphyrin metabolism are less frequent and less severe. It can be reasonably argued, further, that if the skin lesion does not appear, the liver functions and organs are not affected. Of course, this does not hold if the contaminated chemicals are not chloroacne (e.g., 2,4-DCP which is specifically neurotoxic and not chloroacne). Skin manifestations heal slowly (47) in about 1 year in about 50% of the cases. In some cases, sequelae remain which can be detected clinically when other symptoms and signs have disappeared. In addition, symptoms such as ocular lesions, peripheral neuropathies, liver function impairment, and increased serum triglycerides return to normal from a few months to 2 years following exposure, depending on the severity of poisoning. As is frequently the case with all these chemicals, there is never a large increase in SGOT (SGPT indicates

TABLE XIII. Concentration of PCB Isomers in Blood of Yusho Patients and Normal Persons^{a,b}

Normal person

TABLE XIII. Concentration of PCB Isomers in Blood of Yusho Patients and Normal Persons^{a,b}

PCB isomers	Yusho patients (N=9) (ppb)	Normal person (N=17) (ppb)
2,4,5, 3', 4'-Pentachloro	0.13 $\pm$ 0.05	0.22 $\pm$ 0.09
2,3,4, 3', 4'-Pentachloro	N.D.	0.05 $\pm$ 0.02
2,4,5, 2', 4', 5'-Hexachloro	0.52 $\pm$ 0.22	0.15 $\pm$ 0.07
2,3,4, 2', 4', 5'-Hexachloro	0.65 $\pm$ 0.21	0.17 $\pm$ 0.07
2,3,4, 5', 3' 4'-Hexachloro	0.28 $\pm$ 0.07	0.04 $\pm$ 0.02
2,3,4,5, 2', 4', 5'-Heptachloro	0.44 $\pm$ 0.15	0.12 $\pm$ 0.07
2,3,4,5, 2', 3', 4'-Heptachloro	0.28 $\pm$ 0.09	0.11 $\pm$ 0.04

^a Detection limit - 0.01 ppb. N.D. = less than 0.01 ppb.

^b After Masuda, 1980.

important hepatocellular lesions). There seems to be a correlation between severity of the clinical symptomatology and the amount of chemicals accumulated in the body.

Inferences about reproductivity are limited by the small number of cases reported. Conception seems to be possible even in cases of overt poisoning. Pregnancy seems to follow a normal course. Early fetal losses (abortions) have not been reported, but some late fetal losses (stillborn) may be related.

The newborn child is extensively exposed to the chemicals through the mother which leads to specific skin manifestations, to decreased birth weight, and retarded development, in some cases. Congenital anomalies have not been reported, with the exception of deranged tooth eruption and growth as a late manifestation.

The immune response of the newborns has not been examined. The rather high frequency of acute infections during the first year of life points to an impairment of immune capability. ✓

In the Japanese episode the toxic oil contained PCB's with mostly 6 and 7 chlorine atoms isomers and only small amounts 5 chlorine isomers. More than 40 isomers of PCDF have been found in the Yusho oil (48), including as their major components the highly toxic 2,3,7,8-tetra- and 2,3,7,8-tetrachlorodibenzofurans. The ratio of PCB's to PCDF's is 200 for Yusho oil (Table XIV), while the ratio is 50,000 for kanachlor. The ratio in adipose tissue is practically the same as in the absorbed product, but it is five times higher in the liver.

The clinical features of the episodes in Japan and Taiwan are probably the result of a concurrent toxicity of the specific isomers of the mixture ingested. The dibenzofurans are probably mainly responsible for the chloracne lesions. Polychlorinated dibenzofurans have a strong chloracnegenic effect, whereas polychlorinated biphenyls are only weakly chloracnegenic.

It is not possible to assess the risk of the chemicals involved in these episodes. The LD₅₀ for 2,3,7,8-TCDF varies from 5 to 10 µg/kg in the guinea pig to over 6000 µg/kg in the mouse, with rabbit and monkey in between (49). The total amount of PCDF's absorbed by the Yusho and Taiwan cases is 3-4 mg; the daily dose varied between 0.01 and 0.04 mg, i.e., 0.2-0.6 µg/kg.

Tetra and penta isomers of the PCDFs prevailed in the mixture but the actual amount of the 2,3,7,8-TCDF isomer is not known. It is most probably less than the dose which is lethal for the guinea pig.

The acute and chronic experimental toxicity of the mixture of chemicals involved in the Yusho and Taiwan episodes is not available. An extrapolation of some of the data produced by the study of some isomers has only limited value because a

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TABLE XIV. Concentration of PCB's and PCDF's and Their Ratios in Yusho Cases^a

	PCBs (ppm)	PCDFs (ppm)	Ratio (ppm)
Kanechlor (unused)	1,000,000	20	50,000
Yusho oil	~1000	5	200
Yusho patients			
consumption (mg)	875	4.4	198
adipose tissue (ppm)	1.3	0.009	
total (mg)	13	0.09	144
Liver			
concentration (ppm)	0.05	0.0013	
total organ (mg)	0.075	0.0019	39.5

^aAfter Masuda et al., 1980 (22).

change in the number and position of the chlorine atoms in the molecule can modify the clinical picture. Therefore, not only the quantitative but also the qualitative prediction of the toxic effects in humans of PCDFs and PCBs is questionable, if the composition of the mixture varies. The impact of physical factors, i.e., heat on the technical products, will probably produce a constant change in ratio of the chemicals and of their isomers in the mixture and, therefore, their toxicity. The risks and health hazards of each case must be assessed on its own merits.

SUMMARY

Quantitative toxicology in animals has provided accurate and comprehensive data for some of the halogenated dioxins and related compounds. For many others it has only partially been carried out or is still lacking. In humans the information is lagging behind for several reasons. The determination of exposure should be improved, taking advantage of the increased sensitivity of analytical methods for assessing evidence of absorption in man. Clinical symptomatology should be estimated in relation to the kinetics of the chemicals in the body. Signs of physiological adjustments of organs and functions involved in the detoxification process should not be considered an ad-

verse or irreversible health effect. Precise information about daily intake, length of exposure and total dosing, and latency to onset of effects and time of appearance of the symptoms and signs of the clinical picture of the poisoning are available only rarely. Human response to these chemicals is, at best, measured during episodes of heavy exposure.

The PCB's, PCDF's and PCQ's poisonings in Japan (Yusho) in 1968 and in Taiwan in 1979 offer opportunities to correlate clinical features to the dose absorbed and stored in the body. The follow-up studies of the Yusho cases also provide information about the course and evolution of the symptomatology.

The health effects observed in the two episodes can be indicative for the effects to be expected in cases of long-term exposure to the same chemicals at different dose levels.

REFERENCES

1. Kimbrough, R. D. (1980). Occupational exposure. "Halo-genated Biphenyls, Terphenyls, Naphthalenes, Dibenzodioxins and Related Compounds". Elsevier North Holland, Amsterdam.
2. Cairns, T., et al. (1980). Review of the dioxin problem. Mass spectrometric analysis of TCDD in environmental samples. *Biomed. Mass Spectr.* 7, 11-12, 484-492.
3. Crow, K. (1981). The cutaneous and systematic signs of poisoning with chloracnogens in the human subject. *Symp. Chlorinated Dioxins and Related Compounds*, October 25-29, 1981, Arlington, Virginia.
4. Poland, A. and Glover, E. (1977). Chlorinated biphenyl induction of aryl hydrocarbon hydroxylase activity; a study of structure-activity relationship. *Mol. Pharmacol.* 13, 924-938.
5. Poland, A. and Glover, E. (1980). TCDD: studies on the mechanism of action. *Develop. Toxicol. Environ. Sci.* 6, 223-239.
6. Poland, A. et al. (1976). Stereospecific, high affinity binding of TCDD by hepatic cytosol. *J. Biol. Chem.* 251, 16, 4936-4946.
7. Poland, A. et al. (1979). Studies on the mechanism of action of chlorinated dibenzodioxins and related compounds. *Ann. N. Y. Acad. Sci.* 320, 214-230.
8. Baars, A. J. et al. (1980). Induction of rat hepatic glutathione-transferase activities by 2,3,7,8-TCDD. *Proc. Workshop Impact of Chlorinated Dioxins and Related Compounds on the Environment*, Oct. 22-24, 1980, Rome.
9. Leng, M. (1979). Comparative toxicology of various chlorinated dioxins as related to chemical structure. *CIPAC Proc. Symp. Ser.* 1.

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10. Landrigan, P. J. et al. (1979). Cohort study of Michigan residents exposed to PBBs. *Epidemiologic and immunologic findings. Ann. N. Y. Acad. Sci.* 320, 284-294.
11. Billiant, L. B. et al. (1978). Breast milk monitoring to measure Michigan's contamination with PBB. *Lancet*, 643-646 (23 Sept.).
12. Caramaschi, F. et al. (1981). Chloracne following environmental contamination by TCDD in Seveso, Italy. *Intern. J. Epidemiol.* 10, 2, 135-143.
13. Kimbrough, R. D. (1981). Studies of human populations exposed to environmental chemicals. *Workshop Assessment of Multichemical Contamination*, April 28-30, 1981, Milan, Italy.
14. Harakuni, U. et al. (1979). Present state of Yusho patients. *Ann. N. Y. Acad. Sci.* 320, 273-283.
15. Kuratsune, M. (1980). Yusho. "Halogenated Biphenyls, Terphenyls, Naphthalenes, Dibenzodioxins and Related Compound." Elsevier North Holland, Amsterdam.
16. Kuratsune, M. et al. (1971). Yusho, a poisoning caused by rice oil contaminated with PCBs. *HSMHA Health Rep.* 86, 12, 1083-1091.
17. Kuratsune, M. et al. (1972). Epidemiologic study on Yusho, a poisoning caused by ingestion of rice oil contaminated with a commercial brand of polychlorinated biphenyls. *Environ. Health Perspect.* 1, 119-128.
18. Hsi-Sung Chen, P. (1981). Polychlorinated biphenyls. Environmental occurrence, biological and toxicological effects. *Clin. Med. (Taipei)* 7, 4-8.
19. Chung-Fu Lan et al. (1981). An epidemiological study on PCB poisoning in Taichung area. *Clin. Med. (Taipei)* 7, 96-100.
20. Hsi-Sung Chen, P. et al. (1981). Toxic compounds in the cooking oil which caused PCB poisoning in Taiwan. I. Levels of PCBs and PCDFs. *Clin. Med. (Taipei)* 7, 71-76.
21. Hsi-Sung Chen, P. et al. (1981). Toxic compounds in the cooking oil which caused PCB poisoning in Taiwan. II. The presence of polychlorinated quaterphenyls and polychlorinated terphenyls. *Clin. Med. (Taipei)* 7, 77-82.
22. Masuda, Y. et al. (1980). Polychlorinated dibenzofurans and related compounds in patients with Yusho. *Proc. Workshop on Impact of Chlorinated Dioxins and Related Compounds on the Environment*, Oct. 22-24, 1980, Rome.
23. Kamps, L. R. et al. (1978). Polychlorinated quaterphenyls identified in rice oil associated with Japanese "Yusho" poisoning. *Bull. Environ. Cont. Toxicol.* 20, 589-591.
24. Yamaryo, T. et al. (1979). Formation of polychlorinated quaterphenyls by heating PCBs. *Fukuoka Med. Acta* 70(4), 88-92.

25. Masuda, Y. and Kuratsune, M. (1979). Toxic compounds in the rice oil which caused Yusho. *Fukuoka Med. Acta* 70 (4), 229-237. 42
26. Hayabuchi, H. et al. (1979). Consumption of toxic rice oil by "Yusho" patients and its relation to the clinical response and latent period. *Food Cosmet. Toxicol.* 17, 455-461. 43
27. Po-Chak Cheng and King-Yin Liu (1981). Dermatopathological findings of PCB poisoning patients. *Clin. Med. (Taipei)* 7, 41-44. 44
28. Hsi-Sung Chen, P. (1981). Dermatological survey of 122 PCP poisoning patients in comparison with blood PCB levels. *Clin. Med. (Taipei)* 7, 15-22. 45
29. Asahi, M. et al. (1979). Dermatological symptoms of Yusho alterations in this decade. *Fukuoka Med. Acta* 70(4), 172-180. 46
30. Masakazu Asahi et al. (1981). Dermatological findings and their analysis in the general examination of Yusho in 1976-1980. *Fukuoka Med. Acta* 72(4), 223-229. 47
31. Wei-Min Li et al. (1981). PCB poisoning of 27 cases in three generations of a large family. *Clin. Med. (Taipei)* 7, 23-27. 48
32. Yao-An Fu (1981). Ocular manifestations of PCB poisoning and its relationships between blood levels and ocular findings. *Clin. Med. (Taipei)* 7, 28-34. 49
33. Wen-Jen Wang et al. (1981). Investigations on severe PCB poisoning in-patients. *Clin. Med. (Taipei)* 7, 62-65.
34. Lie-Gan Chia et al. (1981). Neurological manifestations in PCB poisoning. *Clin. Med. (Taipei)* 7, 45-61.
35. Yoshihara, S. et al. (1979). Preliminary studies on the experimental PCB poisoning in rhesus monkeys. *Fukuoka Med. Acta* 70, 4, 135-171.
36. Okumura, M. et al. (1979). Laboratory examination of the patients with PCB poisoning. *Fukuoka Med. Acta* 70, 4, 199-207.
37. Hirayama, C. (1979). Hepatocellular dysfunction in patients with PCB poisoning. *Fukuoka Med. Acta* 70, 4, 238-245.
38. Okumura, M. et al. (1979). Ten year follow-up study of serum triglycerides levels in 24 patients with PCB poisoning. *Fukuoka Med. Acta* 70, 4, 208-210.
39. Kit-Ching Wong and May-Yae Hwang (1981). Children born to PCB poisoning mothers. *Clin. Med. (Taipei)* 7, 83-87.
40. King-Lee Law et al. (1981). PCB poisoning in newborn twins. *Clin. Med. (Taipei)* 7, 88-91.
41. Miller, R. W. (1971). Cola-colored babies. Chlorobiphenyl poisoning in Japan. *Teratology* 4, 211-212.

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42. Hsi-Sung Chen, P. et al. (1981). Levels and gas chromatographic patterns of PCB in the blood of intoxicated patients after ingestion of toxic cooking oil. *Clin. Med. (Taipei)* 7, 35-40.
43. Chen, P. H. et al. (1980). Levels and gas chromatographic patterns of polychlorinated biphenyls in the blood of patients after PCB poisoning in Taiwan. *Bull. Environ. Cont. Toxicol.* 25, 325-329.
44. Shigematsu, N. et al. (1979). Tissue distribution and biological effects of PCBs components, especially to the respiratory tract. *Fukuoka Med. Acta* 70, 4, 246-251.
45. Chiou-Jye Chen and Rey-Long Shen (1981). Blood PCB level and serum triglyceride in PCB poisoning. *Clin. Med. (Taipei)* 7, 66-70.
46. Kikuchi, M. et al. (1979). Autopsy report of two Yusho patients who died nine years after onset. *Fukuoka Med. Acta* 70, 4, 215-222.
47. Masakazu, A. et al. (1981). Dermatological findings and their analysis in the general examination of Yusho in 1976-1980. *Fukuoka Med. Acta* 72, 4, 223-229.
48. Rappe, C. et al. (1979). Identification of polychlorinated dibenzofurans retained in Yusho patients. *Chemosphere* 4, 259-266.
49. Moore, J. A. et al. (1979). Comparative toxicity of three halogenated dibenzofurans in guinea pig, monkey and mice. *Ann. N. Y. Acad. Sci.* 320, 151-163.