AFFIDAVIT OF WILBUR P. McNULTY

Wilbur P. McNulty, having been duly sworn, deposes and says:

My name is Wilbur P. McNulty and I live at 7835 S.W. 136th Avenue, Beaverton, Oregon. I am currently Chairman of the Laboratory of Pathology at the Oregon Regional Primate Research Center, 505 N.W. 185th Avenue, Beaverton, Oregon; I have held this position for 13 years. I received a B.S. from Yale University in 1947 in mathematics and an M.D. degree in 1952, also from Yale University. I was an instructor in physiology for two years at the University of Pennsylvania, and received postdoctoral training in pathology at Yale University and the Armed Forces Institute of Pathology. I became a diplomate of the American Board of Pathology (Anatomy) in 1959.

Except for four years in hospital practice, my activities have been exclusively in research and teaching. For several years, one of my chief interests has been the diseases caused in rhesus monkeys by polychlorinated biphenyls (PCBs) and tetrachlorodibenzo-p-dioxins (TCDD). Attached hereto as Appendix D is my Curriculum Vitae, which includes my list of publications.

Rhesus monkeys are among the most susceptible of all animals which have been tested for the toxic effects of PCBs. Male and female monkeys ranging in age from infancy through adolescence to adulthood were lethally poisoned by PCBs--in this case, probably Aroclor 1260--used in construction of monkey pens in 1967 (Appendix A). Exclusive assignment of the cause of the disease to PCBs was lacking, but the circumstantial evidence of highly characteristic pathology and identifiable PCBs in the livers of the dead animals was persuasive. My subsequent experimental work with PCBs will be summarized in the following paragraphs. In all experiments, the tested monkeys were young (one to three years) males, and the diet was a standard moist cake of ground Purina monkey chow, vitamin and mineral supplements, banana, and water into which was homogenized Aroclor 1242 (one lot only: AD-73) at the designated concentrations.

The purposes of the experiments were (1) to document qualitatively the pathologic changes caused by PCBs and (2) to explore in preliminary fashion the dose range at which deleterious effects could be expected on chronic oral intake. For these reasons, the numbers of animals used were too small for statistical dose-response analysis. Indeed, in view of the decreasing natural resource and escalating expense of monkeys, the destruction of a large number of animals to establish numerically accurate dose-responses relationships would require careful justification.

The dietary concentrations used in different experiments involving 16 monkeys ranged from 3 to 800 ppm. All animals were fully examined postmortem, either after spontaneous death, or electively during development of disease or after a period of recovery on normal diet. The pathologic changes were the same at all dose levels and will be discussed below.

In the first test, two monkeys each were fed diet with Aroclor 1242 at 100, 200, 400, and 800 ppm. It was soon apparent that these levels were far into the toxic range. By the fourth week, all eight monkeys were depressed, eating poorly, and losing weight. Some vomited convulsively. Hair was lost from the head and trunk, the faces were edematous, and the eyelids red and swollen. One monkey at 100 ppm died on the 27th day. Subsequent deaths are recorded in Appendix B. Because of the high toxicity of this range of doses, normal diet was reinstituted on the 40th day. The order of death suggests that the toxicity of diets containing 100 ppm Aroclor 1242 or more was so high that it was independent of dose. In Appendix B are also listed the estimated cumulative doses, based on a normal intake of 50 gm diet per kilogram of body weight per day; these estimates are certainly high, since the monkeys ate poorly after the first two weeks.

The single survivor (100 ppm) was clinically ill for over a year, with failure to gain, depressed activity, and conjunctivitis. Abruptly, he recovered, and 20 months after the PCB exposure of 40 days he was killed for pathological survey.

A second experiment included one animal each at 0, 3, 10, 30, and 100 ppm. For six months, at intervals of one month, biopsies of the wall of the fundus of the stomach were obtained at laparotomy. The order of death correlated inversely with the dietary level in this dose range.

It should be emphasized that death occurred in eight months at only 3 ppm. The contribution of the repeated abdominal surgery to illness and death is difficult to assess; the control, at least, remained in good health for the six months of biopsies and thereafter.

The first recognition of clinical illness, as judged by depressed behavior and appetite, red and swollen eyelids, facial swelling, and rough, ragged appearance of the hair coat was as follows: 100 ppm - 50 days; 30 ppm - 60 days; 10 ppm - 60 days; 3 ppm - indeterminate.

All animals in both experiments showed the same findings at autopsy, independently of the dose. These changes were conversion of all secretory cell types of the stomach to mucous cells, growth of mucous glands into the muscular wall of the stomach, multiple ulcers in the stomach, atrophy of the thymus gland, and either disappearance of sebaceous glands or conversion of these glands to keratin cysts, particularly in the eyelids. The livers were enlarged but showed no consistent changes by light microscopy. In Appendix C is an illustration of the stomach in the 3 ppm monkey.

The earliest changes seen in the mucosa of the stomach in the serial biopsies were as follows: 100 ppm - 6 weeks; 30 ppm - 6 weeks; 10 ppm - 15 weeks; 3 ppm - 15 weeks. The control monkey showed no changes; the repeated surgery alone did not affect the mucosa.

In a third experiment, intended to provide more data on the time of appearance and rate of development of the principal pathologic lesions, three young male monkeys were killed for complete autopsy after eating diet with Aroclor 1242 at 10 ppm for 30, 51, and 65 days. At 30 days, no microscopic lesions were recognizable, and the liver and thymus were normal in size. At

45 days, the stomach was normal, but the liver was somewhat enlarged and sebaceous glands in the eyelids showed early keratinization. At 65 days, mucous change in the stomach was advanced; the sebaceous glands in the eyelids and on the face were markedly keratinized, the thymus was markedly atrophic, and the liver enlarged. There is, however, wide individual variation in response to PCB intake; an animal currently eating Aroclor 1242 at 10 ppm shows only equivocal clinical signs and minimal gastric mucosal change (biopsy) at 77 days.

Natural Etiology ?

The two animals which survived the first high-level short-exposure experiment for a year or more both had a new lesion: multiple cysts in the jaws surrounding the crowns of unerupted permanent teeth. In the monkey which died at 382 days (400 ppm), this condition was so extensive that the face was grossly deformed. The lesions in the stomach, sebaceous glands, and thymus were still severe, and total PCBs were still high in the liver. The clinically recovered monkey (100 ppm) killed at 20 months had a normal stomach and thymus and partial return to normal of sebaceous glands. The cysts in the jaws were small and partly calcified, but permanent teeth which should have erupted at this age were still deep in the jaw, and the permanent third molar had failed to form at all. PCBs in the liver had by this time declined to a low level.

These experiments may be summarized as follows: Oral intake of Aroclor 1242 consistently caused disease with pathological manifestations in the stomach, sebaceous glands of the skin, thymus, and liver--a disease which could be lethal, even at a dietary level of 3 ppm, if sufficiently prolonged. The characteristics of the disease were identical to those Allen ("Response of the nonhuman primate to polychlorinated biphenyl exposure," Federation Proceedings, v. 34, pp. 1675-1679, 1975) has reported in monkeys fed Aroclor 1248, and to those seen in our animals spontaneously poisoned with a more highly chlorinated product, probably Aroclor 1260. The lesions persisted for at least a year after intake of PCB ceased and, in young animals, an interference in the development of teeth became evident months after exposure.

The following conclusions may be drawn:

(1) Rhesus monkeys, at least young males, are seriously poisoned by oral intake of PCBs as low as 3 ppm in food. They appear to be 10 to 100 times more susceptible than laboratory rats.

(2) Some of the pathologic changes caused by PCBs in rhesus monkeys are different from those reported for other animals. In particular, the change in the stomach is unique, and because this lesion involves alterations in the growth and differentiation in the cells of the gastric mucosa, it is ominous with respect to possible late development of cancer.

(3) Because monkeys are closely biologically related to human beings, they can be expected to be better models for toxicity studies than laboratory rodents, with respect to both levels of susceptibility and qualitative features of toxicity. This expectation is in part supported by the published descriptions of clinical illness in Yusho disease, the accidental PCB poisoning of over 1,000 Japanese. The affected eyelids in these people closely resemble those of monkeys. Fortunately, few of the Japanese have come to autopsy, and gastric lesions have not been reported; however, gastrointestinal disturbances were a prominent symptom.

Monkeys are expensive and difficult to handle, and they constitute a highly variable, outbred population. The kind of "clean" experiments with large numbers of animals showing a narrow range of response which can be done with rats will probably never be possible with monkeys. Nevertheless, it is my conviction that the information already available from Dr. Allen's laboratory and on a limited scale from my own indicates that studies with monkeys have the most relevance for assessing the danger to human beings of low level exposure to PCBs.

Many details of PCB toxicity remain to be uncovered: the toxic ranking of the many possible homologs and isomers, the identification and toxicological

evaluation of contaminants in commercial preparations, the identification and evaluation of new compounds formed from PCBs by degradation in the open environment and by metabolism in organsisms--including man--with body burdens of PCBs, and the late effects, if any, of very prolonged, very low level exposure. For these investigations, nonhuman primates will be highly desirable, if not essential.

Wilbur P. McNulty

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Subscribed as sworn to for me this 23 day of August, 1976

Notary Public

My Commission Expires Aug. 6, 1979