

SC-18862: 52 WEEK ORAL TOXICITY STUDY IN THE INFANT MONKEY

K. S. Rao<sup>a</sup>, R. G. McConnell<sup>a</sup> and H. A. Waisman<sup>b</sup>

- a) Department of Biological Research (Pathology-Toxicology)  
Searle Laboratories, Chicago, Illinois
- b) Pediatrics Department, University of Wisconsin Medical Center,  
Madison, Wisconsin (deceased)

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Exhibit D

Relative weight gain (g/kg/day) of all treated animals except monkey P53 was comparable to historical controls.

Rate of growth expressed per unit of diet intake (Figs. 4, 5, 6) was within normal limits despite the falling off of absolute body weight (Figs. 1, 2, 3). This indicates that the dipeptide was utilized efficiently and did not effect the efficiency of food conversion.

There was a marked decrease in total intake of milk formula in all the treated animals (Figs. 4, 5, 6). This could be attributed to the intense sweetness (200 x sucrose) of the dipeptide.

Individual daily body weight and milk formula intake of each experimental monkey may be found in the Appendix.

Body length of all treated animals is essentially within the historical control range; head circumference is likewise within historical control range for 1/2 low level, 1/3 medium level and 2/2 high level monkeys, but is below control level in the remaining animals (Figs. 7, 8, 9). The decrease in head circumference during treatment in low dose monkey P53 (Fig. 7) could be attributed to a proportional decrease in the relative weight gain (g/kg/day) of this monkey. Underdevelopment of this monkey is presumably related to the physical deficiencies observed at birth. An apparent decrease in the head circumference observed during treatment in two medium dose monkeys, M79 and 14 (Fig. 8), is attributed to a relatively lower head circumference at birth.

#### Observations, physical and behavioral signs.

All animals in the medium and high dosage groups exhibited ~~seizure~~ activity. Seizures were observed for the first time following 218 days of

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treatment. Thereafter, sporadic convulsions occurred inconsistently at various times during the treatment period. Seizures occurred most frequently during physical handling of the animal for body weight measurements. The convulsions were of grand mal type similar to those induced by feeding L-phenylalanine to infant monkeys.

All animals in the medium and high dosage groups contracted a Shigella infection at various times during the treatment period. In an effort to treat the Shigella infection, these animals received appropriate antibiotic and intravenous fluid therapy.

One monkey, M38, of the high dose group, died after 300 days of treatment. The cause of death was not determined. All other animals survived the treatment period.

General posture and locomotion, pelage, body orifices and excretions were otherwise unremarkable.

#### Clinical laboratory findings.

Hematology. Individual values of hematology parameters evaluated are presented in Tables 3 and 4. The Primate Research Center, Madison, Wisconsin, supplied mean hematologic values of 16 historical control monkeys of the same age group as the experimental animals; these values are presented in Table 5. In general, hematologic values for individual treated animals were unremarkable; no biologically significant deviation from control ranges was observed. Statistical analysis was not performed due to the lack of individual values for the historical controls.