Hyperlipemia in Infant Monkeys Fed Excess L-Histidine.* (30238)

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The ability to induce hyperlipemia in small laboratory animals by a variety of experimental conditions has advanced the knowledge of lipid metabolism in health and disease. The advantage of utilizing the subhuman primate in such studies is self-evident if the data are to be meaningful in terms of the human. Monkeys have provided valuable information relating lipid metabolism to atherosclerosis(1) and the development and progression of the atheromatous lesion in the monkey closely parallels that observed in man(2). Many investigations have shown that the blood lipid level in the subhuman primate quickly reflects alterations in total cholesterol content of the diet(3). It seemed of importance, therefore, to report that hyperlipemia in the infant monkey could also be produced by feeding excess quantities of L-histidine without modifying the dietary lipid. This was especially interesting because hyperlipemia had not been noted in this laboratory when large numbers of rhesus monkeys were fed other amino acids in excess quantities(4,5).

Materials and methods. Experiments with L-histidine were performed on 4 infant rhesus monkeys *(M. mulatta)* of known genetic background and gestational age, which were removed from their mothers on the date of birth and placed in individually heated cages. The infants weighed between 410-570 g at birth and were considered normal in all respects. These infants were maintained in a metabolic nursery under 24-hour observation and care. They were fed at 4-hour intervals, at first by hand, then *ad libitum,* a commercial milk mixture† which was similar in composition to human and monkey breast milk. Daily dietary intake and growth records were kept and blood and urine collections(4) were obtained at appropriate intervals. The infant monkeys did not receive any lipid, carbohydrate, or protein other than that provided by the milk preparation and by supplements of vitamins and fruits. At 7 days of age L-histidine (NRC grade) was added to the milk preparation and the amount was gradually increased to provide approximately 3 g of L-histidine per kilogram body weight per day by 2 months of age. Blood samples were obtained 4 hours after the last feeding and control data were obtained from animals fed the same volume of unsupplemented milk on a similar time schedule.

Serum L-histidine values were determined by the method described by Baldridge and Greenberg(6). Analysis for total serum lipids was performed by the method of Bragdon (7). After preliminary centrifugation of serum to remove the opalescent layer containing chylomicrons and low density lipoproteins, blood glucose was determined by the methods of Slein *et al*(8), and Kornberg and Horecker(9) combined in a commercial analysis kit.‡

Results and discussion. The serum histidine levels usually ranged from 20-60 mg% although levels as high as 80 mg% were observed. Serum from the hyperhistidinemic animals showed an increased turbidity after several weeks on the L-histidine-supplemented milk. Total serum lipid values of the 4 histidine-fed monkeys were elevated over those found in 10 control animals under one year of age as shown in Fig. 1.

For the past several years groups of infant rhesus monkeys have been fed diets supplemented with 2-5 g per kilogram per day of other amino acids (phenylalanine, isoleucine, leucine, valine, alanine, tryptophan and glycine) for the purpose of simulating inborn errors of human metabolism. Neither these animals nor humans with histidinemia or

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† Similac—Ross Laboratories, Columbus, Ohio.

‡ Calbiochem, Los Angeles, Calif.—Glucose-Test.

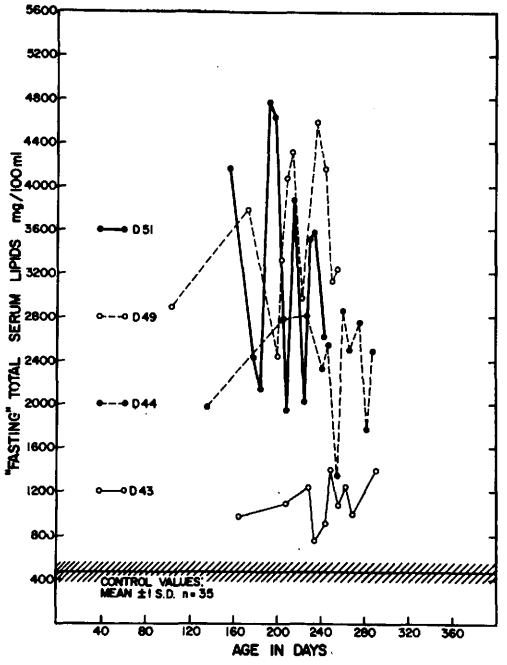

FIG. 1. Serial total serum lipid values demonstrated by each of the 4 animals on the L-histidine-supplemented diet. Cross hatched area indicates mean total serum lipid value ± 1 S.D., demonstrated in 35 determinations from 10 animals of the same age and on the control diet.

other inborn error of amino acid metabolism have shown a comparable degree of hyperlipemia.

Breeding records did not reveal consanguinity among the ancestors of the 4 monkeys used in this experiment. Although the 2 infants with the most marked hyperlipemia grew at a slower rate, growth curves for all 4 monkeys were within the normal range. The total calories, lipid, carbohydrate, and protein intake on a per kilogram body weight basis was within the range observed in control animals. Glucose tolerance curves and the absence of glycosuria eliminated diabetes mellitus as an etiological factor. Ophthalmological examination, blood pressure determinations, and electrocardiograms obtained under anesthesia have not as yet revealed any deviation from normal.

Competition among amino acids for transport across biological membranes has been well documented(10). A deficiency of sulfur amino acids has produced hypercholesterolemia and altered hepatic lipid metabolism in cebus monkeys(11) and Sidransky and Verney(12) found increases in hepatic lipid in rats force fed diets deficient in single amino acids. Therefore, while it is possible that a deficiency of another essential amino acid is responsible for the hyperlipemia found in monkeys fed histidine, preliminary data on serum amino acids do not support this notion. Although the exact mechanism by which amino acids affect both normal and abnormal lipid metabolism are unknown, the data reported here clearly indicate that excess histidine in some way is associated with the marked hyperlipemia. A reappraisal of amino acid and protein metabolism in the etiology of human hyperlipemic syndromes would appear to be of value.

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