as judged by the smallest fall in red cell count after bleeding, oscillation seemed to disappear after bleeding and retransfusion.

These results, therefore, suggest that the steady state of canine erythropoiesis is one of sustained oscillation and that this oscillation is inherent in the nature of the feedback circuit controlling erythropoiesis. There is no direct evidence from our experiments that erythropoietin comprised part of the feedback loop, although this is a reasonable hypothesis. At least for the physiological system of canine erythropoiesis, the term "steady state" appears to be somewhat of a misnomer and might be better replaced with some other term such as "controlled state." Many experimental or therapeutic manipulations of erythropoiesis or other biological systems are based on the assumption that the system being studied does not show time-dependent variation. However, if the system is known to be actively controlled then the possibility of periodicity should be considered and the assumption re-examined. Unsuspected time-dependent variation will merely contribute to the overall variation if the responses of groups are being measured but may seriously confound interpretation if individuals are being studied. On the other hand, the known existence of periodicity in a biological system might suggest the presence of unsuspected feedback control, and consideration of the characteristics of the oscillation might indicate the physical basis for that control. Finally, the periodicity of many periodic diseases may have its origin in an unrecognized physiological rhythm which in turn results from the action of feedback control.

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## Hyperphagia and Polydipsia in Socially Isolated Rhesus Monkeys

Abstract. *Three rhesus monkeys which had been isolated from social contact during their first year of life persistently overate and overdrank during adulthood. These monkeys ingested approximately twice as much fluid and food as the control animals reared normally.*

Evidence regarding the profound effects on social, sexual, and maternal behavior of monkeys removed from their mothers during the first hours of life and raised in total social isolation for the first 6 to 12 months (*1*) indicates that many disturbances persist throughout the animal's adult life.

During an experiment on three isolated monkeys (*2*), it became apparent that they ingested greater quantities of fluid than the controls. To test the limits of this phenomenon we attached 3.8-liter containers of water to their chairs with the intent of measuring consumption under what appeared to be inexhaustible supplies. This procedure was terminated when one of the monkeys (C-2) overdrank and required emergency resuscitation, catheterization of the bladder, and pumping of the stomach. Since the completion of the behavioral experiments and the return of these animals to standard laboratory cage conditions, daily measures of fluid intake and urine output have been obtained.

The three socially isolated monkeys were born in the University of Wisconsin primate laboratories and were separated from their mothers within 24 hours of birth (*3*). They were then kept in total social isolation for 12 months. One of the monkeys, female B-37, was born in July 1961 and the other two, C-2 and C-3, were males born in July 1962. In a series of studies it was determined that these monkeys had suffered severe damage in terms of social relations with other monkeys and that repeated exposure to normal animals in testing situations did not ameliorate their behavior (*4*).

The isolated monkeys were received in our laboratories in May 1966. After a brief period of acclimatization to the new laboratory, they were used, along with three feral males of approximately the same size and age, in an experiment on nonverbal communication (*2*).

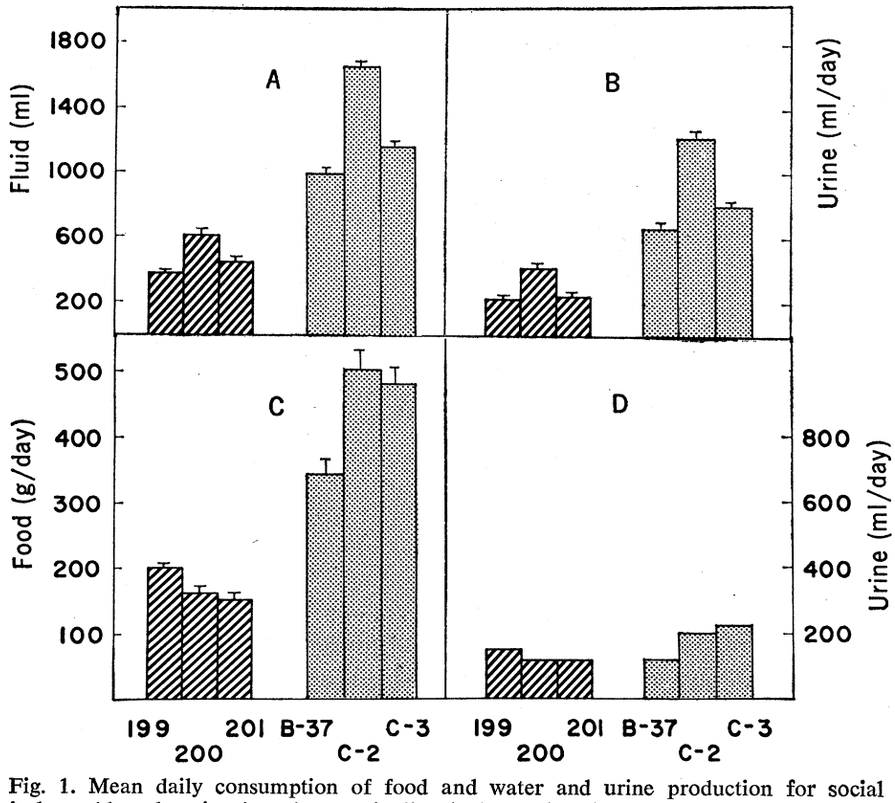


Fig. 1. Mean daily consumption of food and water and urine production for social isolates (dotted regions) and controls (hatched areas). (A) Mean and standard error of daily water consumption over 135 days; (B) mean and standard error of urine output per day during 135 days; (C) mean and standard error of consumption of monkey food pellets in grams per day over 20 days; (D) mean urine production per day during 24 hours of water deprivation.

At the conclusion of that experiment they were returned to individual metabolism cages (28 by 34 by 25 inches) within the quarters of the primate colony. Except for routine cleaning and handling for tuberculin testing, and so forth, these animals have not been disturbed for the past 15 months. One of the isolates, C-2, has required tranquilization on four occasions because he repeatedly bites and tears at his arms and thighs. Oral administration of 20 mg of chlorpromazine twice a day for several consecutive days effectively terminates such bouts of self-destructive behavior.

The monkeys were fed daily at 3:30 p.m. and received a vitamin sandwich, either an apple or an orange, and approximately 150 g of a commercial monkey pellet (Purina). A graduated 1-liter bottle was fixed to the back of the cage with a bracket. A stainless-steel tube 0.64 cm in diameter extended from the water bottle into the cage approximately 5 cm. This drinking system was designed to prevent spillage or leakage, and the monkey was required to suck on the tube to receive water. The water in the bottles was measured (Fig. 1A), refilled to 1000 ml, and replaced on the cage at 9:30 a.m. and at 3:45 p.m. daily. Urine samples were collected with the metabolism trays and plastic containers; the volumes were measured each day at 9:30 a.m. (Fig. 1B), and the samples were filtered and frozen for future analysis. Occasionally a sample was lost when a monkey managed to pull the drinking spout out of the reservoir bottle or shook its cage out of line with the urine container. If either measure was lost, that day's data were not included in the analysis for that animal.

The isolated monkeys drank more fluid and excreted more urine within 24 hours than the controls. These data, in fact, do not reveal the actual amount of fluid which would have been ingested in a day since, on almost every morning, the isolated monkeys had consumed the entire 1000 ml of water received at 3:45 p.m. on the previous day, whereas the controls always had several hundred milliliters left at the morning collection (*5*). Ingestion of water and output of urine by the normal controls were well within normal limits (*5*). The isolates exceed by far any of the reported normative data on water balance.

Three tests were given to determine the ability of isolated monkeys to concentrate urine during 24 hours of water deprivation (Fig. 1D). These determinations were separated by no less than 10 days of the usual regime in which 2000 ml of water were made available to permit repletion and restabilization of water metabolism after deprivation. These data suggest that the isolates conserve fluids during the deprivation period. On the one occasion on which monkeys were deprived for 48 hours, all of the monkeys excreted similar amounts of urine; C-2 and C-3 diminished their urine production during the second 24 hours to 135 and 145 ml, respectively.

After water and urine had been collected for 135 days, food consumption was measured. The regular ration of one piece of fruit and a vitamin sandwich at 3:30 p.m. was continued. In addition, beginning at 8:30 a.m. daily, the number of food pellets in the food hopper and on the floor of the cage was counted. Then 25 fresh pellets were placed in the hopper. The hoppers were checked every hour and, if the food supply was low or exhausted, additional pellets were counted and placed in the container. At 5 p.m. the remaining supply in the hopper was brought up to 25 pellets so the animals would have an adequate supply of food overnight. Figure 1C shows the mean consumption for each of the animals over 20 days. It does not include the fruit and vitamin supplement which was the same for isolates and controls. The isolates clearly overate in comparison with their normal controls; in fact, their food consumption fell within the range reported by Hamilton and Brobeck (*6*) for hyperphagia produced in monkeys with lesions of the ventromedial nucleus.

As a further test of the polydipsic phenomenon, determinations of quinine aversion were made. Quinine sulfate was dissolved in tap water in dilutions of 0.025, 0.05, and 0.1 percent (weight/volume). The solutions were administered through the drinking tubes in sequence starting with the lowest concentration. The reservoir bottle was filled with quinine solution at 9:30 a.m. and 3:45 p.m., and the amount drunk was measured. Since there was a single tube available to the animal, the only alternative to drinking the bitter solution was to reduce fluid intake. Each concentration was administered twice, with 1 day between determinations during which plain tap water was available to permit repletion of fluids. The normal monkeys reduced their intake of fluids at lower concentrations of quinine than the isolates, but, as the concentration of quinine increased, the isolates tended to approach the same relative amount of inhibition as the controls. The absolute amounts of fluid ingested by the isolates were much greater at all concentrations of quinine than the amount accepted by the controls.

Our experiments show that one of the sequelae of total social isolation during the first year of life in the infant rhesus monkey is a marked polydipsia and hyperphagia manifest at least 6 years later. Data are not yet available concerning the age of onset and development of these abnormal ingestive patterns, but it is clear that, at the time of their arrival in this laboratory, regulatory problems were present and have continued for the ensuing 3 years.

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## Monosodium Glutamate

Olney's study (*1*) was based on the subcutaneous injection into infant mice of massive doses of monosodium glutamate (MSG), ranging from 0.5 to 4 mg/g (comparable to about 1.5 to 12 g in a newborn human infant) and doses of 5 to 7 mg/g in adult mice (corresponding to 350 to 490 g in an adult man). No mention was made of the concentration of the injected solution or of the response of control mice to the solvent alone; nor were any tests reported of the response to injected doses of equivalent amounts of sodium