reflect the activation of central motor pathways, because active movements that occurred independent of the stimulus were not associated with unit discharge (Fig. 1D). It is unlikely that we failed to recognize neuronal activity related to active movement, because we were easily able to recognize neurons with discharges preceding limb movement in recordings from the adjacent ventrolateral (VL) thalamic nucleus. All VPL and VPM neurons we studied could be excited in the absence of movement by adequate stimulation applied only to discrete cutaneous receptive fields. The discharges of these nine VPL neurons, therefore, must signal the occurrence of noxious cutaneous mechanical stimuli. The anatomical location from which these neurons were recorded is shown in Fig. 2.

In previous studies, neurons differentially responsive to noxious stimuli have not been found in the VP thalamus of unanesthetized primates (*3, 11*). It is possible that nociceptive VP neurons were missed because of an inadequate search procedure or because of an inadequate sample size. Indeed, the report by Kenshalo *et al.* (*9*) suggests that nociceptive neurons may constitute a very small proportion of all VP cells. We found no NS neurons, but our failure may be due to our small sample of nociceptive cells and the fact that, in the awake animal, noxious stimuli cannot be applied continually while searching for neuronal responses. It is also possible that nociceptive neurons were not evenly distributed throughout the VP or that, relative to cells responding to innocuous stimuli, a higher proportion of nociceptive neurons may be found in regions dominated by spinothalamic rather than dorsal column nuclear input (*15*). The cells we recorded were in fact found in the posterior and lateral part of VP in an area described by Berkley (*15*) as receiving a relatively high proportion of spinothalamic tract fibers.

It may be significant that the WDR neurons we recorded are different from those described in recordings from medullary and spinal dorsal horn since none of the cells we recorded responded to hair movement; all required mechanical stimulation of the skin. This finding suggests that the less intensive hair-elicited discharges of spinal or medullary WDR neurons projecting in the spinothalamic tract may not produce the postsynaptic temporal and spatial summation necessary to discharge VP neurons. Additional experiments will be necessary to resolve this issue.

Neurons of the medial and intralaminar thalamus and of the posterior group of thalamic nuclei respond differentially to noxious stimuli in cats, rats, and monkeys (*4, 16*). Because these neurons typically have wide receptive fields that may include both ipsilateral and contralateral portions of the body surface, their role in pain mechanisms is uncertain. Neurons of the VPL and VPM thalamus, however, precisely encode the location and time of somatic stimuli and project specifically and somatotopically to the somatosensory cortex. This suggests that the VP nociceptive cells we have recorded could subserve the sensory-discriminative component of pain (*17*). This hypothesis would gain support if future experiments show that VP nociceptive neurons encode intensity within the noxious range and if their responses are selectively modified during analgesia produced by brain stimulation (*18*), analgesic drugs, or behavioral methods.

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19. This work was supported by the Veterans Administration and by grant NS 12581 from the National Institutes of Health. The assistance of L. Sorkin and Li Chun-yuan is gratefully acknowledged.

20 December 1982; revised 23 March 1983

Alcohol Self-Administration Disrupts Reproductive Function in Female Macaque Monkeys

Abstract. *Female macaque monkeys self-administered high doses of alcohol (2.9 to 4.4 grams per kilogram per day) for 3 to 6½ months. Amenorrhea, atrophy of the uterus, decreased ovarian mass, and significant depression of luteinizing hormone levels were associated with chronic alcohol intoxication. Reproductive system failure in female primates following self-induced dependence on alcohol parallels the results of clinical studies of alcoholic women.*

Alcoholism in women is often associated with several derangements of reproductive function, including amenorrhea, infertility, and spontaneous abortions (*1, 2*). The mechanism of amenorrhea in alcoholic women is unknown, and there are conflicting opinions as to whether reproductive system dysfunction primarily reflects toxic effects of alcohol on the ovary (*3*) or at the hypothalamic pituitary level (*1*). Moreover, since alcoholic women are often malnourished and have liver disease, it has been difficult to determine the relative contribution of alcoholism and of these related disorders to the spectrum of reproductive system derangements (*1*). Either malnutrition associated with profound weight loss (*4*) or hepatic dysfunction can disrupt menstrual cycle regularity (*1*). These clinical findings indicate that an animal model of alcoholism is necessary to systematically evaluate the effects of alcohol dose and exposure duration on female reproductive function under controlled conditions. Since the reproductive physiology of female macaque monkeys is similar to that of human females, and since the neuroendocrine regulation of primate reproductive function has been studied extensively (*5*), we chose this species to develop such a model. We found that self-induced alcohol dependence led to reproductive system dysfunction in these female monkeys.

Five sexually mature female macaques

(4.6 to 7.5 kg) were adapted to laboratory conditions for 12 to 18 months (*6*). Menstrual cycles were stable for at least 10 months before the study began, and all monkeys had normal ovulatory menstrual cycles, as indicated by a mid-cycle surge in the level of luteinizing hormone.

The monkeys were trained to work for 1-g banana pellets in an operant paradigm. Once food-maintained responding was stable, each monkey was surgically implanted with an intravenous catheter under ketamine anesthesia (25 mg/kg, intramuscularly) using aseptic procedures. Eight to 10 days after surgery, the monkeys were given access to alcohol during menstruation or the late luteal phase of the menstrual cycle. The monkeys learned to self-administer alcohol intravenously on the same operant schedule of reinforcement used for food acquisition (*7*). An average of 64 responses was required for each food pellet or alcohol injection (0.12 g/kg per injection) under a second-order schedule of reinforcement [FR 4 (VR 16:S)] (*8*). Food and alcohol each were available during four 1-hour sessions per day. Food sessions began at 1100, 1500, 1900, and 2300 hours; alcohol sessions at 1200, 1600, 2000, and 2400 hours. The nutritionally fortified banana pellet diet was supplemented with fresh fruit, vegetables, biscuits, and multiple vitamins each day.

Vaginal swabs were done daily to determine the onset and duration of menstrual bleeding. Venous blood samples were collected periodically for radioimmunoassay of neuroendocrine hormones and to determine levels of alcohol in blood (*9*). Also, the status of liver function, lipid and carbohydrate metabolism, electrolyte homeostasis, and hematologic function was monitored with laboratory tests.

Of the five monkeys studied, three began to self-administer relatively high doses of alcohol immediately. During the first month of alcohol availability, these monkeys self-administered an average of 2.29 ± 0.26, 3.15 ± 0.27, and 3.24 ± 0.38 g/kg per day. The three monkeys developed amenorrhea that persisted for 84 to over 180 days. Two others self-administered relatively low doses of alcohol that averaged 1.35 ± 0.26 and 1.66 ± 0.38 g/kg for 119 and 173 days, respectively. These two monkeys continued to have stable menstrual cycles (28 ± 0.89 and 31 ± 1.35 days), cycles that were almost identical to the ten menstrual cycles that preceded the study (27 ± 1.41 and 31 ± 1.14 days).

Each monkey that developed amenorrhea self-administered alcohol to the point of intoxication; blood alcohol levels measured after an alcohol session ranged from 266 to 438 mg/dl. These levels are comparable to those observed in alcoholic men during intoxication (*10*). After the 11-hour interval between the midnight and noon alcohol sessions, each monkey showed signs of physical dependence on alcohol evidenced by gross tremor of the extremities and nystagmus (*11*).

Figure 1 shows patterns of alcohol and food self-administration over successive 10-day intervals by the amenorrheic monkeys for 84, 93, and 160 consecutive days. Despite daily intoxication, two monkeys showed no change in operant food self-administration from baseline during the first 50 to 60 days of alcohol exposure. Monkey 10-80 worked for significantly more food than baseline ($P < 0.01$ to 0.001, *t*-test) after 70 days of alcohol self-administration. After 80 consecutive days of alcohol self-administration, monkey T681 showed a significant decrease in food intake for 20 days ($P < 0.02$ to 0.001). However, after 100 days of intoxication, this monkey worked for pellets at levels that were not significantly different from baseline. Then, after 140 and 150 days of intoxication, food acquisition significantly exceeded baseline levels ($P < 0.02$ to 0.001). Only monkey B428 reduced operant food intake significantly ($P < 0.05$ to 0.001) after the first 10 days of alcohol self-administration. After 60 days, banana pellet intake returned to levels not significantly different from baseline. Each monkey also continued to eat daily supplements of fruit, vegetables, and biscuits.

Laboratory test results were normal. After 98 days of alcohol self-administration, one monkey had a slight elevation of alkaline phosphatase, but concentrations of serum glutamic oxaloacetic transaminase and serum glutamic pyruvic transaminase were normal. No monkey had evidence of liver disease (hepatitis or cirrhosis) (*12*). These data indicate that alcohol rather than malnutrition or liver disease accounted for the observed disruption of menstrual cycle regularity. It is also unlikely that seasonal factors contributed significantly to these results, since amenorrhea was observed between fall and spring—the usual breeding period in the Northern Hemisphere (*13*).

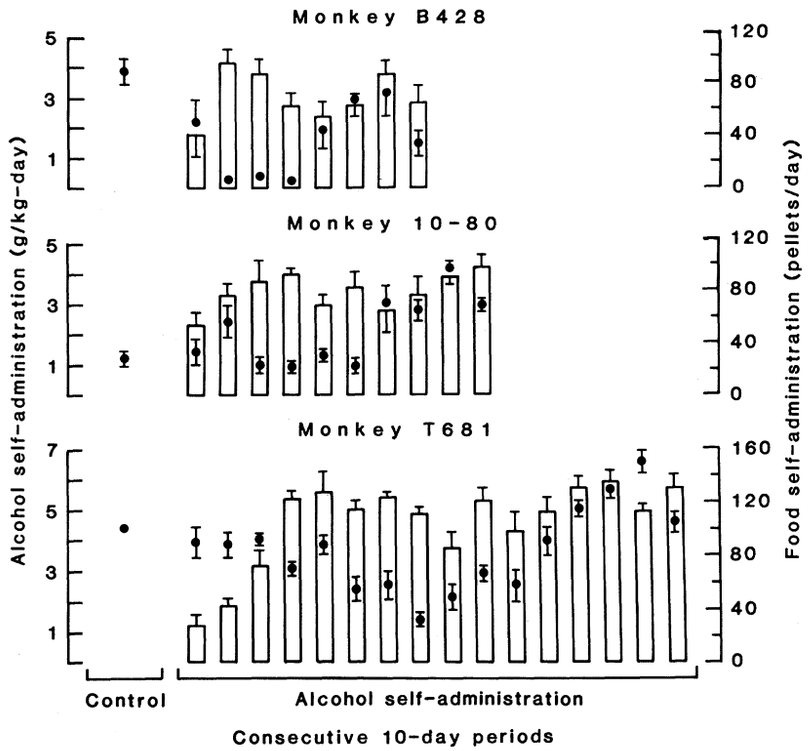

Fig. 1. Alcohol and food self-administration by three alcohol-dependent amenorrheic monkeys. The average daily dose of alcohol self-administered over 10-day periods in an operant paradigm is shown by the bars and the average number of 1-g banana pellets self-administered during the same period is shown by the circles. Each data point is the mean (± standard error) of ten values, except for the final data point for monkey 10-80, who died of an alcohol overdose (the average food and alcohol intake during the final 3 days are shown). Each monkey was first given access to alcohol (0.12 g/kg per injection) during menstruation or during the late luteal phase of the control menstrual cycle, and did not menstruate subsequently.

Two of the three amenorrheic monkeys died after 84 and 93 consecutive days of alcohol self-administration. One monkey (10-80) apparently died of an alcohol overdose (the postmortem blood alcohol level was 502 mg/dl). A second monkey (B428) died of alcohol-related pulmonary disease. Necropsy revealed pathological changes in the reproductive systems of both monkeys. The uterus was markedly atrophied: there was a paucity of glands and the endometrial stroma was dense (Fig. 2A).

There was also evidence of decreased ovarian mass. A photomicrograph of a right ovary containing multiple graafian follicles is shown in Fig. 2B. No corpora lutea were present in either ovary, which strongly suggests that ovulation did not occur. This pathological picture is consistent with that seen in early menopause. Decreased ovarian mass and an absence of corpora lutea have also been observed in alcoholic women at autopsy (*14*), and in rodents (*15*) after prolonged alcohol exposure in a forced alcohol feeding paradigm.

The monkey that apparently died of alcohol-induced respiratory center depression also had an unusual lesion in the adenohypophysis. Many small cells with hyperchromatic nuclei were scattered among the larger, polyhedral parenchymal cells (Fig. 2C). The small cells resembled nucleated erythrocytes and might represent extramedullary hematopoiesis. However, no comparable cells were found in the liver or spleen, which are much more common sites of extramedullary hematopoiesis.

The origin of the cells in the adenohypophyseal lesion was not determined. It is possible that this unusual pituitary lesion occurred as a direct consequence of prolonged exposure to alcohol. It is also possible that a derangement in pituitary gonadotropin secretory function induced the pathological changes observed in the ovaries and uterus.

It is likely that alcohol-induced disruptions of menstrual cycle regularity in higher primates are a consequence of its toxic effects on both the ovary and the hypothalamic pituitary axis. Luteinizing hormone levels were significantly lower than the baseline levels measured at menstruation ($P < 0.02$ to 0.001) in each monkey that developed amenorrhea. Before the introduction of alcohol, luteinizing hormone levels during menstruation ranged from 27 ± 1.06 to 36 ± 1.36 ng/ml. After the monkeys began to self-administer alcohol, the level of this hormone ranged from 18 ± 1.36 to 24 ± 1.41 ng/ml. However, in the two monkeys that self-administered low doses of alcohol, luteinizing hormone levels did not differ significantly from control levels. Single high doses of alcohol also do not suppress pituitary and gonadal hormones in female macaque monkeys (*9*) and young women (*16*).

Chronic alcohol intoxication produces similar disruptions of reproductive function in alcoholic women (*1*, *2*) and macaque monkeys. The validity of this model is especially compelling since each monkey controlled her alcohol dose and self-administered alcohol to the point of daily intoxication and physical dependence. This replication of a behavioral disorder, alcoholism, and its pathophysiological consequences in monkeys may provide an improved basis for treatment and prevention of the reproductive disorders associated with alcohol abuse once the mechanisms of alcohol's toxic effects on reproductive function are better understood.

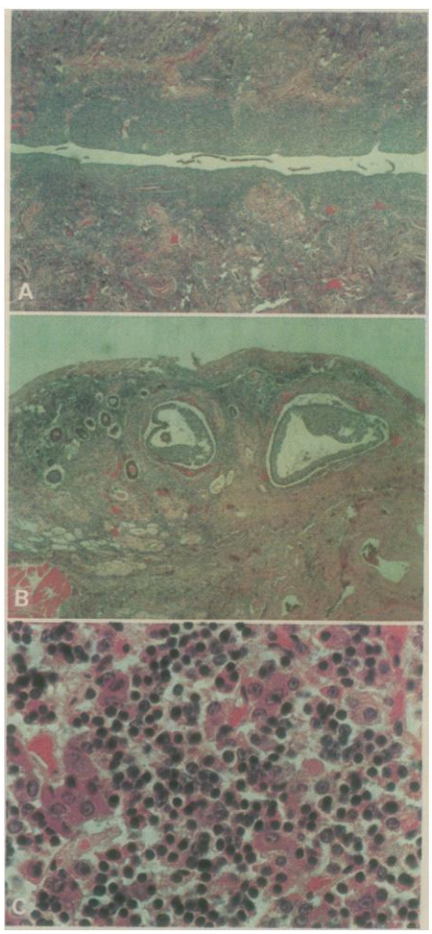

Fig. 2. Alcohol-induced pathology in a female macaque monkey. (A) Low-magnification (×100) photomicrograph of the uterus, showing an atrophic endometrium. (B) Low-magnification (×100) photomicrograph of the right ovary, showing multiple graafian follicles but no corpora lutea. (C) High-magnification (×720) photomicrograph of the adenohypophyseal lesion, showing many small cells with hyperchromatic nuclei scattered among the large polyhedral parenchymal cells.

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17. Supported in part by grant AA 04368 from the National Institute of Alcoholism and Alcohol Abuse and by NIH grant RR-00168-21.

17 February 1983