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Effects of Cat Exposure and Cat Odors on Subsequent Amphetamine-Induced Stereotypy

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WILLIAMS, J. L. AND R. G. BARBER. *Effects of cat exposure and cat odors on subsequent amphetamine-induced stereotypy.* PHARMACOL BIOCHEM BEHAV **36**(2) 375–380, 1990.—The effect of exposure to a cat, as a predatory stressor, was examined in male and female rats during subsequent tests of amphetamine-induced stereotypy in which cat odors were present or absent. Rats in Group C/O were given a 15-min exposure session to a male cat while they were protected in a wire cage. They were then given an IP injection of d-amphetamine (1 mg/kg) and tested 30 min later for stereotypy in the presence of cat odors (soiled cat litter). Rats in Group NC/O were given a no-cat-exposure control session, and amphetamine tested with cat odors. Groups C/NO and NC/NO were both tested without cat odors (fresh litter), with the former group having been previously exposed to a cat. During the 90-min test sessions, female rats showed significantly more stereotypy than males. More importantly, the male subjects in group C/O exhibited significantly more stereotypy than the males in the other groups, and group NC/NO males showed the least amount of stereotypy. These findings clearly indicate that amphetamine reactivity is influenced by prior exposure to a predator, the presence of predatory odors during testing, and the subject's sex.

Stress Cat exposure Cat odors d-Amphetamine Response stereotypy Sensitization Contextual cues Dopamine Predator Fear

EXPOSURE to aversive stimulation, particularly when the instigating stimulus is uncontrollable, may induce subsequent alternations in learned and unlearned behaviors. In rats and mice, inescapable electric shock has been shown to modify later escape learning (2,32), appetitive operants (29), and a variety of agonistic (33,34) and defensive behaviors (35,36). Attention is recently being devoted to the neurophysiological mechanisms that underlie, or are at least correlated with, these types of behavioral disruptions, as well as those produced by a variety of other painful stressors, such as physical restraint, cold-water swim, and mild pressure to the tail [see (3,4) for reviews]. Repeated exposure to some of these inescapable stressors has been found to induce increases in corticosteroids and acetylcholine, decreases in norepinephrine (NE), dopamine (DA), and serotonin (1, 2, 32), and endogenous opioid and nonopioid analgesic reactions to nociceptive stimuli that are mediated by either hormonal or nonhormonal systems (20,25).

Stress-induced analgesia, and many of the previously mentioned biochemical disturbances, have also been found to result in profound changes in an organism's reactions to various pharmacological agents. For example, prior exposure to inescapable shock, but not escapable shock, has been shown to result in a hyperanalgesia (20) and exaggerated withdrawal reactions (37) to a small dose of exogenous morphine. Moreover, a number of studies have shown that these stress-induced behavioral and pharmacological reactions are influenced by the context or cues in the test environment. For example, Fanselow and other investigators (11, 13, 14) have repeatedly shown that shock-induced analgesia is mediated by the presence of conditioned contextual stimuli that were previously present at the time of conditioning. Williams (35, 36, 38–40) postulated that experimentally manipulated or inadvertent stimuli associated with stress (e.g., stress odors) are important for the mediation and/or sensitization of behavioral and physiological aberrations during subsequent testing.

Of particular relevance to the present research are studies that have examined the influence of stress exposure and stress-associated cues on an organism's subsequent reactions to d-amphetamine. For example, Antelman *et al.* (4) found that the stress produced by repeated applications of mild pressure to a rat's tail produces sensitization of amphetamine-induced sniffing that is virtually identical to that seen after long-term amphetamine administration. Conversely, a single dose of amphetamine was found to sensitize tail-pressure reactions (3,4). Other types of nociceptive stressors also appear to be interchangeable with amphetamine in terms of their ability to augment certain behaviors. Repeated exposure to footshock, particularly if it is uncontrollable, enhances or alters a number of subsequent manifestations

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of amphetamine, such as rearing (24), unilateral circling (9), sniffing (24), and stereotypic head and body movements (3, 21, 22, 24). It is believed that most forms of stress-induced amphetamine sensitization occur because the neurochemicals effected by uncontrollable stress, such as norepinephrine and dopamine, are the same ones that are effected by catecholamine stimulants, such as amphetamine (1, 3, 4, 21, 22, 24). Moreover, Anisman, Hahn, Hoffman and Zacharko (1) have reported that uncontrollable shock, followed by an amphetamine challenge enhanced response perseveration in a maze, provided that the shock and testing environments were similar. This finding parallels the results of the previously cited behavioral and analgesia studies in which long-term reactions were found to be mediated and/or further potentiated by presenting stress-associated cues in the test environment (11, 13, 14, 40).

The importance of the stress-induced sensitization reactions to amphetamine, particularly in terms of their potential application to various types of behavioral and psychological pathologies (21, 22, 24), clearly depends on the extent to which they occur using other stressors, particularly those that an organism might encounter in its natural environment. Much of the current research conducted in our laboratory has examined the behavioral and physiological effects of various types of natural or ethological stressors as a function of the presence, versus the absence, of stress-related cues in the subsequent test environment. Using rats as subjects, we have found that repeated intruder defeat by a dominant colony resident (i.e., an alpha conspecific) increases the occurrence of defensive responses, decreases exploration, and retards the learning of escape behavior, if the odors of the alpha rat are later present in the test setting (38). Other experiments have also established that even a single session of intruder defeat by a dominant conspecific produces a significant increase in freezing and a suppression in conditioned burying of a shock prod, provided that the testing apparatus contains the odors of the alpha resident (39). Recently, we have also found that these long-term, context-specific effects are accompanied by an analgesic reaction, which is partially blocked by naltrexone and can be extinguished by poststress exposure to the odors without the experience of defeat (40).

Another type of ethological stressor for a rat is exposure to a natural predator, such as a cat, when it is confined in a protective chamber without an opportunity to escape (6,8). Several investigators have reported that rats show pronounced defensive reactions to a cat, even though they have not had previous experience with such a predator (6, 8, 15, 23). Furthermore, the presence of cat odors, without prior exposure to a cat, has been recently reported by Williams and Scott (39) to disrupt adaptive prod-burying behavior and result in risk-assessment exploration. Finally, cat odors have been found by several investigators to activate a variety of predatory-defensive systems (7,15), including an analgesia reaction that is mediated by endogenous opioid mechanisms (15,23).

In light of some of the previously mentioned similarities in the behavioral and biochemical processes that modulate the effects of various laboratory and ethological stressors, the overall objective of the present research was to determine (a) if an augmentation in amphetamine reactivity occurs in the rat following protected exposure to a cat, serving as a natural predatory stressor; and (b) if this hyperreactivity might be further enhanced and/or persist for a longer period when cat odors are present in the test environment following an amphetamine challenge. The use of cat exposure as an innately feared stressor, without the rat experiencing any actual physical pain, is of special interest because previous stress-amphetamine research has exclusively employed artificial, nociceptive stressors (e.g., footshock, cold-water swim, pressure to the tail).

The present experiment used a factorial design to test the effects of cat exposure, cat odors, and their possible interactive effects on subsequent drug reactivity. Two groups of rats were exposed to cats and the remaining two were not. Thirty-five min later, drug testing was done with two subgroups having cat odors from soiled cat litter on the floor of the test apparatus, whereas the other two subgroups were tested with fresh litter that had no cat odors. Based on the findings and theorizing of several ethoexperimental researchers (15, 34, 36, 39), it was hypothesized that the fear produced by exposing a rat to a cat, while being protected from physical harm by being in a small cage, would later exacerbate the animal's reactions to a relatively small dose (1 mg/kg) of d-amphetamine sulfate. In addition, it was predicted that the presence of cat odors in the drug-testing environment would further augment the predicted potentiation of amphetamine reactivity resulting from exposure to a predator. Because previous research has reported that rats show sex differences in terms of their reactivity to amphetamine (5, 16, 27, 28), both male and female subjects were used as subjects in this experiment.

METHOD

Subjects

Sixty-four Sprague-Dawley, Holtzman albino rats, approximately 150 days old, were used as subjects. The 32 male rats had a mean weight of 569 g, and the mean weight of the 32 females was 351 g. The rats were bred in the laboratory facilities of the Psychology Department at Kenyon College, and they were housed individually in wire cages with free access to food and water for two months prior to the experiment. In addition, four adult neutered male cats, housed in a separate laboratory area, were used as predatory stressors.

Apparatus

Subjects were exposed to a cat in a wire-cloth cage that was 31 cm long × 20 cm wide × 20 cm high. This small exposure cage was placed directly in front of a larger kennel cage, containing one cat. The wire cloth sides of the subject's exposure cage and the large opening in the front of the cat's cage allowed for visual contact between the rat and cat, but actual physical contact was not possible because of the small openings in the wire cloth. A shallow tray containing soiled cat litter was placed beneath the wire floor of the rat's cage. During this session, the cat and rat cages were located in a room that was used exclusively for this purpose. After the amphetamine injection, the subject's stereotypic reactions were continuously monitored using the Omnitech Activity Monitor, interfaced with an Apple IIe microcomputer. Based on the results of a pilot study, the activity monitor was primarily programmed to record the number of repetitious head and body responses (i.e., response stereotypy) and the amount of time that the rat engaged in this type of activity. The Plexiglas activity chamber, 41 cm long × 41 cm wide × 31 cm high, was located in a separate room from the monitor and microcomputer.

Standardization studies have been done on measures of stereotypic behaviors recorded by Omnitech's Digiscan Analyzer (10, 26, 30). The photocell activated Analyzer defines two stereotypic variables: (a) number of stereotypic responses, which corresponds to the number of times the monitor observes the rat breaking the same beam repeatedly, and (b) stereotypy time, which consists of the total number of seconds that such behavior is detected by the monitor. The stereotypy-inducing effects of d-amphetamine, as measured by the Analyzer, have also been shown to correlate significantly with visual stereotypic ratings, using a scale developed by Creese and Iversen (10,26). Furthermore, the Digiscan system was found to differentiate the effects of d-amphetamine

dosages ranging from 1.00 to 10.00 mg/kg, and these data were not confounded by changes in other responses (e.g., locomotion, rearing).

Drug Dosage

The d-amphetamine sulfate for this study was obtained from Sigma Chemical Company (St. Louis, MO). A pilot study, involving two male and two female rats, was conducted to find the optimal dosage of d-amphetamine sulfate to be used as the challenge injection in this experiment. The behavioral effects of IP doses of 1, 2, 4, 10 mg/kg, and a saline injection were recorded every 15 min over a 2-hr period. Based on the results of this study, it was decided that a 1 mg/kg should be used as the challenge injection for all subjects in the present experiment. This dosage produced significantly more stereotypic responses than was found for the subjects in the saline control group, and yet it seemed to allow sufficient room to assess the possibility of higher levels of stereotypy due to stress.

Procedure

Sixty-four subjects were randomly assigned to four groups that comprised a 2×2 factorial design, with 8 male rats and 8 female rats being assigned to the cat (C) and no-cat (NC) exposure conditions that were crossed with the cat-odors (O) and no-cat-odors (NO) test conditions. The subjects were weighed and individually taken to the cat-exposure or the control-exposure rooms. After the cat litter, which was soiled for two C groups and fresh for the remaining NC groups, was placed in the tray beneath the exposure cage, the subject was removed from its home cage and placed in the exposure cage. For the C groups, a carrying cage, containing one randomly selected male cat, was placed directly in front of the exposure cage, forcing close proximity (i.e., 5 cm) between the rat and the cat. The proximity of a predator, or predatory imminence, has been shown by several investigators to be a very important factor in determining the type and the intensity of fear-elicited, defensive reactions in rats (7,15). The exposure session continued for 15 min, after which the cat was removed and the subject was placed in its home cage for 5 min in the exposure room, while the experimenter evenly distributed 2 liters of soiled cat litter (fresh from the litter box) or clean cat litter on the floor of the activity chamber that was to be used for drug testing. Subjects in the NC groups were given the same confinement procedure in a separate room, without the presence of a cat and with clean cat litter in the tray.

Following the cat-exposure and control-exposure sessions, subjects were individually taken to the room containing the activity chamber. A 1.0 mg/kg IP injection of d-amphetamine sulfate was administered, and then the subject was placed in the activity chamber, containing either soiled or clean cat litter. The Omnitech monitor and computer, in the adjacent room, recorded the number and duration of stereotypic head and body responses that occurred during successive, 15-min intervals. After each subject was tested for 2 hr, the activity chamber was thoroughly cleaned with a 5% ammonium hydroxide solution, that has been found to be effective in controlling for odors (12,23).

RESULTS

Computer-obtained raw data from the activity monitor provided the number of stereotypic responses and the total duration of these responses for each of the 15-min intervals during the 2-hr test session. The first two intervals were not analyzed because the results of our pilot research indicated that 30 min was required for the subjects to habituate to the activity chamber and recover from the stress of the injection. Figure 1 presents the mean number of stereotypic responses for each group over the remaining six 15-min intervals.

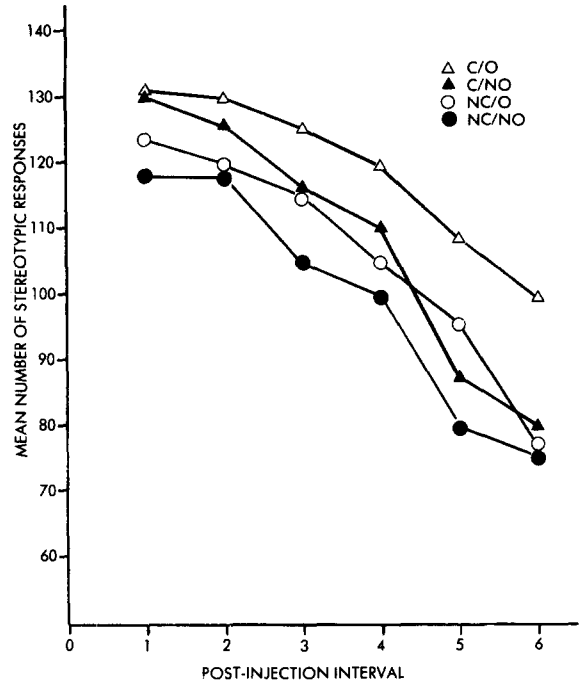

FIG. 1. Mean number of stereotypic responses made by groups of rats that were given cat (C) or no-cat (NC) exposure and subsequently injected with 1 mg/kg of amphetamine before a 2-hr test session with cat odors (O) or no cat odors (NO) in the activity chamber. All six successive intervals were for 15 min, and Interval 1 began 30 min after the amphetamine challenge.

The results of a $2 \times 2 \times 2 \times 6$ mixed design analysis of variance revealed statistically significant between-groups effects of sex, $F(1,56) = 48.72$, $p<0.001$, cat exposure, $F(1,56) = 7.31$, $p<0.01$, test odor, $F(1,56) = 5.15$, $p<0.05$, and an interaction of sex by cat exposure, $F(1,56) = 8.01$, $p<0.001$. Significant within-subjects effects were found for test interval, $F(5,280) = 79.19$, $p<0.001$, and the interactions of sex by interval, $F(5,280) = 5.53$, $p<0.001$, and odor by interval, $F(5,280) = 2.45$, $p<0.05$. The findings from a series of planned-comparison tests (41) of the group differences, over the six test intervals, indicated that Group NC/NO showed significantly ($p<0.01$) fewer stereotypic responses than Groups NC/O and C/NO, with the latter two groups not differing from one another. Group C/O was found to make significantly ($p<0.01$) more stereotypic responses than the other three groups. In addition, the female rats showed significantly ($p<0.01$) more stereotypy than the male rats, and there was a significant ($p<0.01$) decrease in stereotypy, for both the sexes in each group, across the six test intervals.

Although the above pattern of statistically significant findings is consistent with our predictions about stress and stress-odors enhancing amphetamine reactions, the significant sex by cat interaction suggests that males and females responded differently to the amphetamine challenge following exposure to a cat. Figure 2 shows the mean number of stereotypic responses, averaged across all intervals, for the four experimental groups and for the sexes within each group. Consistent with our hypotheses, the male rats clearly showed greater stereotypy to amphetamine if they had been previously exposed to a cat or were tested with cat odors, and the combination of these two variables produced the greatest amount of stereotypy. Planned-comparison tests (41) further revealed that the males in Groups NC/NO and C/O significantly differed from the males in the remaining two groups at the 0.01

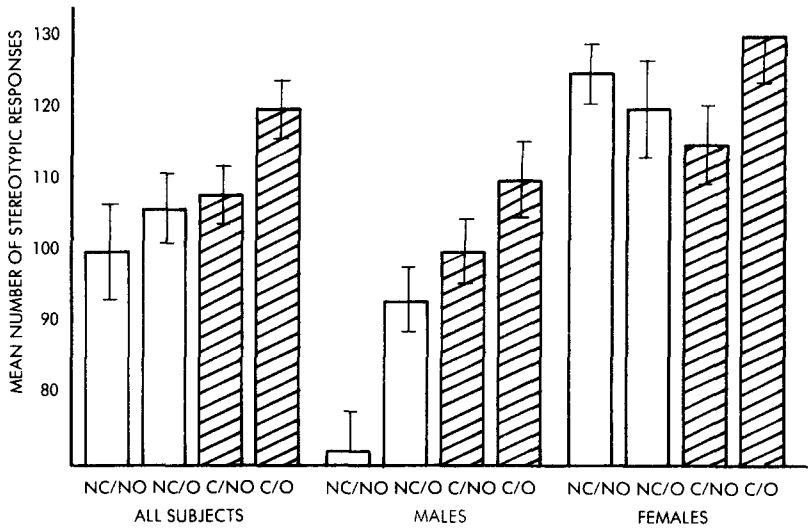

FIG. 2. Mean number of stereotypic responses per 15-min interval for groups of rats, broken down by sex, that were given cat (C) or no-cat (NC) exposure and subsequently injected with 1 mg/kg of amphetamine before a 2-hr test session with cat odors (O) or no cat odors (NO) in the activity chamber. The initial interval, used in calculating these averages, began 30 min after the amphetamine challenge.

level. However, the data from the female rats were not found to yield significant main effects in terms of cat exposure, test odors, nor was there a significant interaction effect between these variables. Thus, the observed pattern of significant results for the four groups, with the sexes combined, was due to the fact that the males showed very large differences that were consistent with our predictions, whereas this was not the case for the female subjects.

The amount of time that the rats showed stereotypy was analyzed by means of the same type of mixed-design analysis of variance as was used for the number of stereotypic responses. The significant outcomes paralleled, but were not as robust as, those found for the number of responses. Within-group correlations between these two measures were found to be highly significant for all groups (r's>.90; p's<0.01). Because of the redundancy between the findings for the number and time measures of stereotypy, it was thought that the reporting of the less sensitive stereotypy-time data would not be very informative.

DISCUSSION

The results of this experiment confirmed most of our predictions concerning stress-potentiation of amphetamine-induced stereotypy. The main effects of sex, cat exposure, and test odors were all found to influence amphetamine-induced stereotypy. However, the most important finding of this experiment, in terms of demonstrating the impact that predators and their related odors have on drug reactivity, is that Group C/O showed significantly more stereotypy than the three remaining groups. Although the exposure by test odor interaction failed to reach the 0.05 criterion of statistical significance, the combination of prior cat exposure and subsequent testing in the presence of cat odors clearly resulted in an additive effect in terms of accentuating amphetamine-induced stereotypy.

Several investigators have independently reported that exposure to inescapable footshock and other nociceptive stimuli subsequently augment stereotypy (3, 4, 21, 22, 24) and other amphetamine-induced reactions (1,9). These stress-induced increments to amphetamine are postulated to be the result of norepinephrine depletions (1) and the sensitization of mesolimbic and mesocortical dopamine systems (1, 3, 4, 21, 22, 24). The results of the present experiment expand the findings of previous shock research by showing that male rats exhibit the same type of augmentations in amphetamine-induced stereotypy following inescapable exposure to a cat, particularly when cat odors are later present in the test environment. Previous research has demonstrated that exposure to a cat and cat odors induce analgesic reactions in rats that are mediated by endogenous opioid processes (23). Other investigators have shown that stress-induced treatments, involving alterations in opioid mechanisms, are typically accompanied by changes in catecholaminergic, dopaminergic, and serotinergic systems (2, 24, 25, 32). Because many of these systems are known to influence amphetamine reactivity, it is possible that the reported augmentations in stereotypy following cat exposure and testing with cat odors may have been mediated by alterations in one or more of these neurochemical processes. More importantly, the present findings strongly imply that uncontrollable exposure to an ethologically relevant, innately feared stimulus is a sufficient condition to produce biochemical changes that are known to be influenced by repeated exposure to a variety of painful stressors (1, 4, 9) or injections of amphetamine (3,4).

The significant cat-odors by test-interval interaction, found in the present experiment, implies that the cat odors were important in terms of maintaining a high level of amphetamine reactivity in the male rats throughout the 2-hr test session. Anisman *et al.* (1) has reported that contextual cues, previously associated with a series of inescapable shocks, were effective in enhancing subsequent behavioral manifestations of amphetamine. In addition, much of the senior author's previous ethoexperimental research (34–36, 38, 39) indicates that exposure to uncontrollable fearful situations results in the fear-conditioning of contextual cues (e.g., odors, handling) that have numerous behavioral (35,38), motivational (36,38), affective (32,33), and physiological (40) consequences. The prolonged level of stereotypy seen during the course of testing in the present study, might therefore be due to conditioned fear elicited by the cat odors during testing. However, it is important to note that the presence of cat odors during testing produced increased amphetamine stereotypy in male rats, regard-

less of whether or not they were previously exposed to a cat. This implies that the cat odors were unconditioned stimuli that were capable of innately eliciting a moderate level of fear. Recent research from our laboratory has shown that cat odors produce fear-mediated disruptions in the defensive behaviors of rats, regardless of whether or not the rats were exposed to a cat (39). This finding, in conjunction with the lack of a statistically significant cat-exposure by cat-odors interaction, strongly suggests that the effectiveness of cat odors in maintaining stereotypy throughout the test session was the result of a fear-sensitization process that may have been supplemented, to a moderate degree, by fear conditioning. More research needs to be done, perhaps involving a longer interval between the stress-exposure and the test sessions, in order to determine if stress-induced hyperreactivity to amphetamine is the result of nonassociative (sensitization) and/or associative (conditioned) processes elicited by the stress odors during testing.

As noted earlier, the overall levels of amphetamine-induced stereotypy were found to be significantly greater for the female rats in each of the four groups. A number of other researchers have reported that female rats consistently show more sensitivity to amphetamine, as well as other stimulants (e.g., cocaine), in terms of stereotypy (5) and rotation (16–18). Although the sexes differed in terms of their body weight, it is unlikely that this produced the observed sex differences in stereotypy because the amphetamine dose was adjusted according to each subject's weight. However, several alternative explanations of this sex difference merit discussion. First, sex differences in the accumulation and excretion of amphetamine in the brain and in its metabolism may account for the differences in stereotypic behavior. For example, Meyer and his associates (27,28) have reported that amphetamine produces greater stimulation of motor activity in female rats, which also causes anorexia and hyperthermia. These researchers have related these differences to a longer half-life of amphetamine in the brain and to slower metabolism in females. Second, the observed sex differences in stereotypy may have occurred because amphetamine released greater amounts of dopamine from the nigrostriatal terminals in females than in males. This interpretation is suggested by the fact that DA levels are higher in the striatum of female rats (19). Finally, sex differences in reactivity to stimulants have been postulated to occur because of sex-dependent, functional asymmetries in mesocortical dopamine projections that are known to be selectively activated by amphetamine (16,31), cocaine (17), and footshock (9). Regardless of the reasons for why the female rats in this experiment showed significantly more stereotypy, it is believed that their hyperreactivity may have produced a ceiling effect that precluded the possibility of their showing differential levels of stereotypy as a result of our cat-exposure and test-odor manipulations.

The findings of this research indicate that male rats clearly show an exaggerated reaction to a small dose of amphetamine following a relatively brief encounter with an innately feared predator. Specifically, it appears that exposure to a cat, as well as subsequent testing with cat odors, can increase stereotypic responses that are known to be modulated by dopaminergic systems which have been implicated as having an important role in amphetamine psychosis (22) and schizophrenia (21). This is the first demonstration that ethological stressors, and their innately associated odors, are capable of producing hyperreactions to amphetamine as a result of fear-sensitization and/or conditioning processes that do not involve nociceptive stimulation. Further investigations, using other types of ethological stressors, are needed to provide a more complete understanding of the influence of fear and pain, on an organism's sensitivity to amphetamine, as well as to other stimulants and psychoactive drugs.

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