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# Alleviating nausea and emesis by Pavlovian conditioning

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Prescribed antiemetic drugs, used to counteract nausea and emesis from radiation, chemotherapy and potentially life-threatening hyperemesis gravidarum, increase patients' drug burden and are often only partially effective. Our laboratory has found that an antisickness response — that is, a homeostatic "antisickness" aftereffect of sickness — can be conditioned, thus alleviating nausea and emesis without drugs.[1] This conditioning is accomplished by "forward pairing" of a nonemetogenic cue and an emeto-

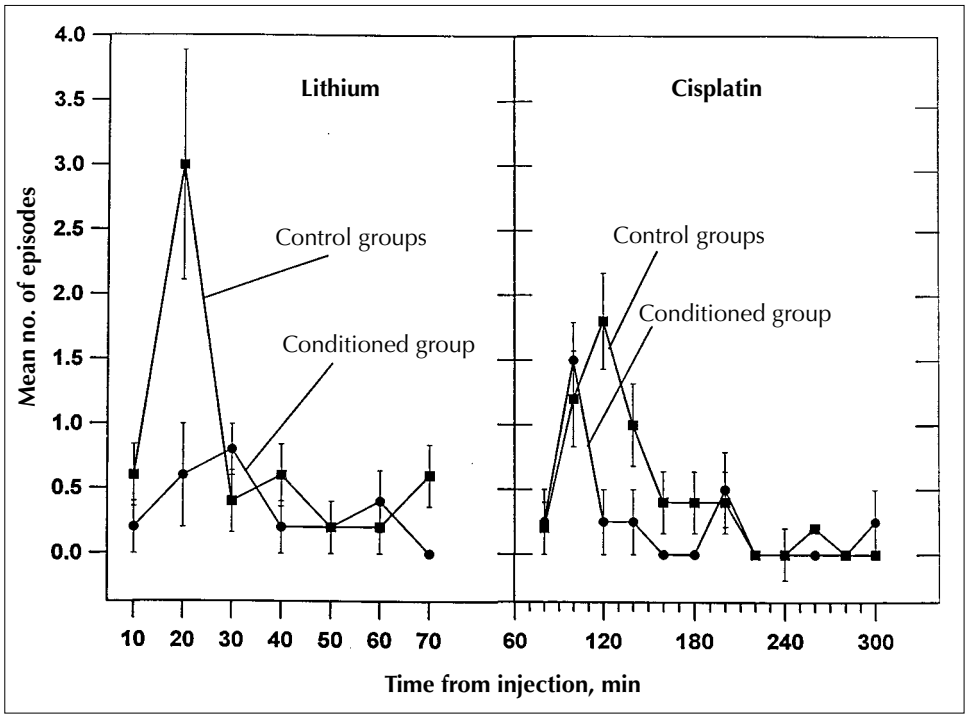


**Fig. 1: Mean number of episodes of emesis during test trials after injections with pentobarbital and lithium (left) or pentobarbital and cisplatin (right) in ferrets conditioned to have an antisickness response (conditioned group) and those not conditioned (control groups). During the training sessions, the conditioned ferrets underwent repeated sessions of "forward pairing," during which a nonemetogenic cue (pentobarbital) was given first, followed 30 minutes later by an emetogenic stimulus (lithium); the control ferrets received the drugs either in a "backward paired" arrangement (the emetogenic stimulus first) or an "unpaired" arrangement (drugs given 24 hours apart).**

genic stimulus: in other words, subjects do not become nauseated and do not vomit in response to a stimulus that is usually nausea-inducing through the consistent introduction, in repeated training sessions, of a nonemetogenic cue (a drug or event that does not cause emesis) followed by an emetogenic stimulus (a drug or event known to cause emesis). Previous attempts at validation of conditioned antisickness have relied on indirect measures of feeding or drinking behaviour in rats, a nonvomiting species.[2] We report the first direct evidence that conditioned antisickness alleviates emesis in ferrets, a vomiting species accepted as a model for human emesis,[3] and have replicated these results in humans.

Five adult male ferrets were conditioned by forward pairing of pentobarbital, the nonemetogenic cue, followed 30 minutes later by lithium, the emetogenic stimulus, in each of 5 training sessions. The nonconditioned controls consisted of 3 ferrets that received the drugs in a "backward paired" arrangement (i.e., the emetogenic stimulus was presented consistently before the nonemetogenic cue) and 3 others that received the drugs in an "unpaired" arrangement (i.e., 24 hours apart). On testing, with all ferrets receiving pentobarbital followed by lithium, the conditioned ferrets had significantly delayed onset (21.0 v. 8.8 minutes, $p < 0.05$), fewer episodes (2.4 v. 5.6, $p < 0.01$) and less time in emesis (47.0 v. 158.0 seconds, $p < 0.01$) than the nonconditioned ferrets. The 2 control groups did not differ statistically on any measure, and so their results were pooled. Similar differences between the conditioned ferrets and the control ferrets were seen after testing with the highly emetogenic anticancer drug cisplatin[4] (Fig. 1).

In a double-blind experiment involving 7 human subjects, we used caffeine as the nonemetogenic cue and virtual rotation as the emetogenic stimulus. The project was reviewed and approved by an ethics committee at the University of Toronto. During half of the 8 training sessions each subject was given either a high dose (350 mg/kg) or a low dose (100 mg/kg) of caffeine orally, followed 30 minutes later by virtual rotation (produced by seating the participant inside an optokinetic drum). During the other training sessions the subject was given the other of the 2 doses, followed 30 minutes later by sham rotation (accomplished by instructing the participant to close his or her eyes while in the drum). In this way, half of the participants had the high dose of caffeine as the conditioning dose paired with virtual rotation, and the low dose as the nonconditioning control dose paired with the sham rotation. Each subject then underwent 2 test trials: one with low-dose and the other with high-dose caffeine followed by virtual rotation. During each test trial, subjects completed a questionnaire that assessed motion sickness using a 5-point scale (5 indicating the highest degree of nausea).[5] The mean scores were 0.9 with the nonconditioning dose and 0.6 with the conditioning dose ($p = 0.059$). Six of the subjects showed a reduction in motion sickness symptoms on the test trial using the conditioning dose. Future clinical studies should assess the efficacy of antisickness conditioning using more intense emetogenic stimuli.

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