corded; if an intermediate fall occurred, an instance of inconclusive control; if amplitude remained high, no control.

The rationale for selection of drugs was primarily based upon reference materials in Goodman and Gilman (*14*). We anticipated (i) that inhaled isoproterenol would control both allergic and conditional attacks; (ii) that a conditional attack, presumably parasympathetically mediated, would respond to cholinergic blocking agents possessing both central (atropine as a sulfate) and peripherally restricted (methscopolamine as a bromide) sites of action; (iii) that methysergide, a peripherally acting congener of LSD and a potent blocker of serotonin, would prevent allergic attacks; and (iv) that an antihistamine (Benadryl, diphenhydramine hydrochloride) would prevent neither form of attack. Although the first two expectations were confirmed, the last two were not.

Immunologists generally agree that allergic asthma occurs when an allergen and a specific antibody engendered by it combine in some fixed tissue of the airway. The combination releases a chemical irritant that constricts smooth muscle of the airway. Although histamine is implicated as an irritant of tissues in other hypersensitivities such as urticaria and angioedema, its importance as a bronchoconstrictive trigger in human asthma has been minimized; the role of trigger has been ascribed to other agents such as serotonin (*15*). The failure of methysergide to prevent allergic attacks and the implication that histamine and not serotonin is the guinea pig's bronchoconstrictive trigger suggest that asthmas in man and guinea pig are precipitated by a different chemical irritant. The data are open, however, to another interpretation. Asthma in the human being, at least when failing to respond to antihistaminic premedication, may be the classically conditioned aftermath of earlier provocations by an allergen. Perhaps histamine is a bronchoconstrictive trigger in early stages of human asthma; perhaps, too, the strong emotional states that usually accompany an attack of asthma are subject to classical conditioning. If so, their subsequent evocation in the absence of allergenic stimulation may be paralleled by activation of vagal or other parasympathetic pathways investing smooth muscle of the airway. This alternate interpretation is fully consonant with recently reported findings based upon human beings (*16*). Increased impedance of the airway as measured by whole-body plethysmography occurred in 13 of 29 chronically asthmatic patients when challenged by physiological saline. This psychogenic constriction of the airway, which was repeatedly but selectively occasioned when the patient believed he was being challenged by his allergen, was selectively abolished by controlled injections of atropine.

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8. The amplitude of basal plethysmograms was highly consistent for a given animal and usually was higher in the case of heavier animals. Because of this individual variation, absolute pressures were not used as criteria of changed airway impedance. Instead, the basal amplitude for each animal was used as the control reference for a plethysmogram generated during an experimental treatment.
9. Although all sensitized guinea pigs have a strong, and often mortal, reaction to the initial provocative challenge, approximately half are completely desensitized by the time a second challenge is presented. The basis for the desensitization is unknown but has been reported previously (*2*, *5*). We did find that when the concentration of the albumin solution was reduced from 800 to 300 mg/100 ml during the first provocative challenge, none of the 17 treated animals died. Subsequent challenges by a solution of 800 mg/100 ml have invariably been well tolerated. All animals that exhibited allergic attacks to a second provocative challenge continued to do so to subsequent challenges by the protein.
10. Plethysmographic measurements were kept short because accumulation of expired CO_2 in the closed chamber might have led to an artifactual constriction of the airway [G. N. Loofbourrow, W. B. Wood, I. L. Baird, *Amer. J. Physiol.* **191**, 411 (1957)].
11. Both UR's and CR's occurred as essentially all-or-none rises in plethysmographic amplitude, the actual increment being three- to fourfold for most animals. The absence of graded levels may have been due to the relatively lengthy, 3-minute presentations of CS's and US's and to the testing of UR's only after blocks of five trials had been conducted; however, even "on-line" plethysmographic recordings taken from human asthmatic patients exhibit the same all-or-none changes of pressure (*16*).
12. A short-lived experiment involved bilateral section of the vagus nerve in four guinea pigs and unilateral section in two controls. Sections were made in the neck a few millimeters caudad to the lower mandible. None of the four experimental animals recovered from anesthesia; both controls did. The guinea pig's apparent critical need for a unilaterally intact vagus prevented us from learning whether its fibers participate, as we suspect, in the conditional attack.
13. A sensitized animal reacting to provocative challenges may concomitantly develop a conditional attack; to control for such a dual occurrence, when pharmacologically treating an allergic attack we always first presented sham challenges to ensure absence of a CR. To control for the possibility that the CR had extinguished, when pharmacologically treating a conditional attack, we always presented a second sham challenge 1 to 3 days later, after dissipation of a drug, to insure the existence of the CR.
14. We refer to L. S. Goodman and A. Gilman, Eds., *The Pharmacological Basis of Therapeutics* (Macmillan, New York, ed. 3, 1965), sect. 4, chap. 21–28; *ibid.*, sect. 5, chaps. 29 and 30.
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17. These data were originally presented at the Annual Meeting of the American Psychological Association in San Francisco on 1 September 1968. The paper is based in part upon thesis research performed by E.W.B. for the Kansas University School of Medicine and was supported by 8200 Research Funds from the Veterans Administration and by a grant from the Kansas University Medical Center. We thank B. Ascough, E. B. Brown, D. C. Greaves, G. N. Loofbourrow, E. J. Walaszek, and E. L. Wike for technical or material assistance. We thank Prof. H. Lal for helping us select and evaluate effects of drug treatments.

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Glue Sniffing Causes Heart Block in Mice

Abstract. *In mice, the inhalation of airplane glue or toluene fumes slows the sinoatrial rate, prolongs the P-R interval, and sensitizes the heart to asphyxia-induced atrioventricular block. In humans who sniff glue or solvents, similar mechanisms may be a cause of sudden death.*

Bass reported on 110 cases of sudden death in youths turning on by inhaling the vapors of airplane glue, aerosol propellants, and various solvents (*1*). Although the fatal mechanism is unknown, the combination of rapid death and negative autopsy findings suggests that a cardiac arrhythmia might be responsible. To test this possibility, we investigated the electrocardiographic effects of glue sniffing in mice.

Adult ICR mice (26 to 37 g) were anesthetized with 0.5 ml of 0.3 percent sodium pentobarbital and secured in the prone position to an operating table. Needle electrodes were inserted subcutaneously. A photographic recorder (Electronics for Medicine DR-12) was used to record the electrocardiogram (leads II, aVF, and a unipolar thoracic lead, simultaneously) at a paper speed of 200 mm/sec with 20-msec time lines. Asphyxia was induced with a form-fitting plastic bag wrapped tightly around the nostrils and mouth, rostral to the ears. Mice inhaled airplane glue fumes from a large plastic bag that was open to room air and had its inner surface freshly coated with 4 ml of glue, either Amco Cement or Testor's Cement, both of which contain toluene.

During a 10-minute inhalation of glue fumes in room air, the sinoatrial (SA) heart rate of 12 mice slowed from (mean $\pm$ S.E.) 462 ± 9.9 to 416 ± 17.3 beat/min ($P < .005$) and the P-R interval lengthened slightly. These changes, which persisted until the experiment ended 30 minutes after the mice sniffed the glue, were absent in four mice exposed to room air alone. During 24 5-minute periods of asphyxia in 12 mice not exposed to glue sniffing, the SA heart rate rose 72 ± 7.6 beat/min ($P < .001$), the P-R interval did not lengthen, and atrioventricular (AV) block never occurred. In contrast, during asphyxia begun 3 minutes after the mice had completed 10 minutes of glue vapor inhalation, the SA rate fell 57 ± 18.9 beat/min ($P < .025$), the P-R interval lengthened, and, after an interval of asphyxia ranging from 35 to 135 seconds and averaging 79 ± 10.6 seconds, all 12 animals tested developed 2 : 1 AV block (one ventricular beat, or QRS complex, for every two atrial beats, or P waves) (Fig. 1). When asphyxia was immediately stopped, this block disappeared but reappeared after asphyxia was again applied. The interval from onset of asphyxia to appearance of 2 : 1 AV block lengthened progressively over time, so that by 22 ± 2.0 minutes (range 16 to 30 minutes) after the end of glue inhalation, six mice tolerated 5 minutes of asphyxia without developing 2:1 AV block. In the remaining six mice, although asphyxia was stopped, the 2:1 AV block rapidly progressed to complete AV block and they died.

Substitution of 1 ml of toluene for glue evoked the same responses, before and during asphyxia, as did glue. After four mice had sniffed toluene for only 1 minute, asphyxia induced 2:1 AV block within 45 to 90 seconds (average 68 seconds). When four mice, previously untreated, were asphyxiated with a plastic bag coated on the inside with glue, all developed 2:1 AV block within 30 to 62 seconds (average 42 seconds). None of the 20 mice that inhaled glue or toluene fumes had ventricular extrasystoles.

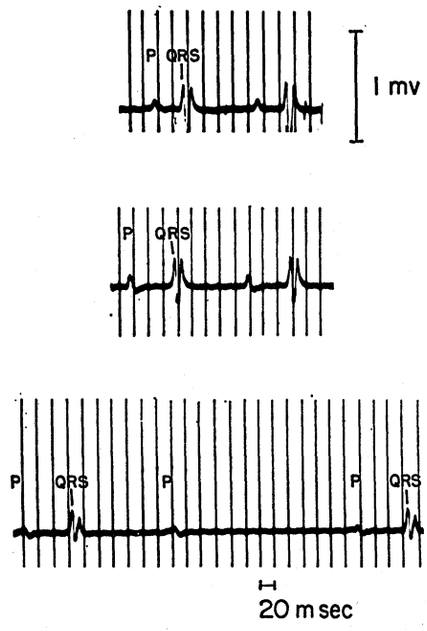

Fig. 1. Electrocardiogram (lead II) of an ICR mouse. (Top) Control, breathing room air. (Middle) Sinoatrial slowing and P-R interval prolongation during glue vapor inhalation. (Bottom) 2:1 AV block and further sinoatrial slowing during the 68th second of asphyxia, 4 minutes after end of glue sniffing.

Thus, glue sniffing by mice causes sinus bradycardia, P-R interval lengthening, and the early appearance, during asphyxia, of higher degrees of AV block. This is produced rapidly by the glue fumes and does not appear to be the result of prolonged hypoventilation. The intraperitoneal injection into four mice of 1 mg of atropine sulfate failed to alter any of these responses. After treatment with atropine and after glue sniffing, 2:1 AV block developed, on the average, after 84 seconds of asphyxia. The same dose of atropine abolished the reflex bradycardia that the elevation of arterial pressure by 2 mg of methoxamine HCl elicited in four mice. Thus, the bradyarrhythmic effects of glue or toluene vapors in mice more likely reflect a direct action on the SA node and AV conduction rather than one mediated reflexly through the vagus nerve.

The use of pentobarbital adds a pharmacological variable that may depress respiration and vary the effect of toluene. However, since all mice received pentobarbital and, yet, asphyxia without glue or toluene failed to elicit bradyarrhythmias, respiratory depression by pentobarbital could not have caused the bradyarrhythmias induced by asphyxia during or after glue or toluene inhalation. Further excluding pentobarbital as a cause were the findings in another eight mice that we restrained and studied without pentobarbital or other anesthesia. Five minutes of asphyxia without glue or toluene raised heart rate insignificantly from 672 ± 27.0 to 680 ± 30.4 beat/min. Toluene inhalation for 1 minute slowed the SA rate 36 ± 9.8 beat/min ($P < .01$). After toluene, asphyxia slowed the SA rate from 624 ± 36.4 to 314 ± 48.4 beat/min ($P < .001$) and, after an interval of asphyxia averaging 41 ± 3.5 seconds (range 20 to 55 seconds), caused 2:1 AV block in all eight animals.

Because human victims of glue or solvent inhalation die away from medical facilities (*1, 2*), electrocardiograms showing their terminal cardiac rhythms have never been obtained. Our results in mice, if applicable to man, suggest that SA slowing or AV block should be considered as one among several possible mechanisms leading to sudden death when humans sniff solvents. It must be emphasized, however, that species differences may make man more susceptible than mice to ventricular extrasystoles and fibrillation and more resistant to SA slowing and AV block. The cardiotoxic effects of hydrocarbons, alone or combined with asphyxia, probably comprise a spectrum, manifested among different species by bradyarrhythmias, ventricular tachyarrhythmias, or myocardial depression. Hydrocarbons sensitize the hearts of various mammals to ventricular fibrillation induced by epinephrine (*3–6*). Halothane, a halogenated hydrocarbon, produces SA bradycardia, AV block and dissociation, asystole and, particularly during hypercapnia or epinephrine administration, ventricular arrhythmias; it also depresses myocardial contractility (*3, 7*).

Asphyxia also affects the heart in several ways. It releases endogenous catecholamines, which may induce ventricular extrasystoles and fibrillation, especially after exposure to hydrocarbons (*5*). At least in mice, asphyxia after glue or toluene inhalation, while not causing ventricular irritability, depresses SA pacemaking and AV conduction. In humans the cardiac effects

of asphyxia after the inhalation of nonhalogenated hydrocarbons have never been determined. Although respiratory arrest is often described as a cause of acute deaths due to inhalation of hydrocarbons (*3, 8*), it is possible that many decedents first had cardiac arrest, for which they were not examined, but which stopped their breathing. If respiration fails first, the resulting hypoxemia and hypercapnia may induce arrhythmias faster than usual in the heart sensitized by hydrocarbons.

We postulate that some humans who sniff glue or solvent vapors die suddenly from ventricular fibrillation, sinus bradycardia, AV block, or acute ventricular failure, alone or in combination. It must be remembered that often, though not always, complete AV block ends with ventricular fibrillation. Regardless of whether ventricular fibrillation or arrest is present, external cardiac massage and vigorous mouth-to-mouth respiration, by eliminating these volatile hydrocarbons and alleviating asphyxia, may have special efficacy in acute deaths due to inhalation of solvents. Defibrillation or pacing may then return the cardiac rhythm to normal. The reviver should not inhale the victim's expired air. Prompt resuscitation might have benefited one young boy who inhaled glue fumes, cried out that his heart had stopped, and then died (*1*). Of public health importance is the possibility that in susceptible people, such as those with ischemia or other disease of cardiac pacemaking or conduction tissue, unintentional exposure to environmental hydrocarbons may lead to cardiac arrhythmias causing syncope or sudden death.

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Sexual Behavior of Male Cats after Administration of Parachlorophenylalanine

Abstract. *The behavior of 12 male cats was observed before and after six or eight daily injections of parachlorophenylalanine. Sexual performance was either unchanged or diminished; aggressive behavior was not seen. Serotonin concentrations in the brains were uniformly lowered.*

After it was shown that parachlorophenylalanine (PCPA), a tryptophan hydroxylase inhibitor, lowers serotonin concentrations in the brains of rats (*1*), a number of studies appeared dealing with the effects of this drug on various aspects of animal behavior. These included reports of increased mounting activity by male (*2*) and female (*3*) rats, as well as a rise in aggressivity (*3*); other investigators failed to find an increase in heterosexual behavior by male rats (*4*). Pronounced changes in the behavior of cats after three to five daily injections of PCPA have also been described (*5*). These included manifestations of "hypersexuality" in 15 of 26 animals, rage and vicious behavior in most of the animals, and disturbances in activity and perception. Hypersexuality was defined as the tendency to mount and attempt to copulate with another male cat. Such behavior had not been seen previously in that laboratory in untreated animals.

We studied the effects of PCPA on copulatory behavior in the male cat with the use of quantitative measures of behavior shown in standard test situations with receptive females (*6*). Observations were also made of the responses of the experimental animals to stimulus objects other than a receptive female and of any alterations in physical appearance and qualitative changes in general behavior after treatment.

Twelve healthy mature male cats (3.5 to 5.9 kg) obtained from a commercial animal dealer were housed individually under natural lighting in rooms (2.7 by 2.1 m) with one outside screen wall. Observation alcoves between adjoining rooms had sliding windows, which permitted introduction of stimulus animals for sex tests and an unobstructed view of the test area. Receptivity was induced in stimulus females by injections of 0.3 mg of estradiol benzoate every 4 to 5 days.

During a preliminary period of several weeks, each experimental male was tested several times per week in his room with a receptive female until mating performance had stabilized, as indicated by consistent latency and frequency scores. (Latency refers to the interval between the start of the test and the display of a particular behavior such as neck grip, mount, or intromission.) Thereafter each cat received a minimum of three 15- or 20-minute "standard" base-line tests as well as a 90-minute test ("extended"). Intervals between tests, generally 48 hours, were the same for each animal during base-line and drug tests. All elements of the male's sexual pattern were noted and timed so that information on frequencies, latencies, and durations was obtained. The normal sexual patterns of male and female cats, and testing procedures similar to those used, have been described (*7*). The number of intromissions achieved by male cats with the same female varies little from test to test (*7*). In additional tests, each cat was also exposed to a male cat, an anesthetized male cat, and a stuffed toy cat until mounting or attempted mounting occurred in three 15-minute tests. No attempt was made to induce mounting by manipulating the stimulus animal or toy.

After base-line data were obtained, the experimental animals received six or eight daily subcutaneous injections of PCPA (150 mg/kg) suspended in a neutral citric acid–phosphate buffer. Sex tests were then run on eight cats including the one that received two separate courses of PCPA treatment with a 6-week interval between each series. The four remaining animals were tested with receptive females after three to five PCPA injections, but scoring was limited to the latencies for the first grip, mount, and intromission. Testing was begun after the third injection in all animals because of the