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Cardiac Arrhythmias and Aerosol "Sniffing"

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Aerosol "sniffing," a variant of glue "sniffing," involves the deliberate inhalation of aerosol products and propellants. Approximately 65 deaths have been attributed to this practice. They have been predominantly sudden and generally lack conclusive autopsy findings. The cause of death has not been defined in most cases; however, various mechanisms have been postulated. The evidence suggests acute cardiac arrest as a frequent cause. It could result from the sudden onset of ventricular fibrillation due to sensitization of the heart to epinephrine by inhalation of high concentrations of aerosol contents. Experimental investigation revealed that the commonly used aerosol propellants, in high concentrations, are capable of sensitizing the heart to epinephrine resulting in serious cardiac arrhythmias. Therefore, it is concluded that cardiac sensitization is a likely mechanism of death in many of the aerosol-sniffing fatalities.

PEOPLE, and especially teen-agers, have been "sniffing" glue, paint thinner, gasoline, and other volatile solvents for years in an attempt to get "high" or for "kicks." More recently the practice has been extended to

the "sniffing" of aerosol products or aerosol product propellants for the same purpose. "Sniffing," incidentally, is a misnomer, since the practice involves the deliberate, deep inhalation of highly concentrated vapors, but the term has received popular usage.

Occasional fatalities have resulted from the various forms of solvent sniffing. That fatalities could also occur from the sniffing of aerosol products and aerosol product propellants was somewhat of a surprise, since these have been noted for their low toxicity. Thus far, approximately 65 deaths have been attributed to this fad. The first were reported in early 1967. In that year seven deaths occurred and all followed the sniffing of a product used to chill cocktail glasses. In 1968 and 1969 there were 31 and 27 deaths, respectively. During these two years, the practice encompassed numerous aerosol products including fry pan lubricant, hair spray, deodorant, antiseptic, and others.

The principal technique used in sniffing aerosols is to spray an aerosol product into a balloon or bag and then deeply inhale the contents. This procedure results in the inhalation of a high concentration of gas and vaporized liquid from the aerosol. The "gas," in most cases, would consist of a high proportion of aerosol propellant. Propellants used widely in aerosol products include such halocarbons and hydrocarbons as fluorocarbon 12, fluorocarbon 11, fluorocarbon 114, isobutane, propane, and vinyl chloride.

The aerosol sniffing deaths have been pre-

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Table 1.—Compounds Tested for Cardiac Sensitization Properties

A. Those Considered Most Active

✓ Benzene *K2661P* Potent sensitizer in animals and is even active without epinephrine^{1,4}; cases of sudden death in industry where mechanism could be ventricular fibrillation^{7,10}

✓ Heptane *K40408P* Similar to benzene in potency in animals¹; no deaths reported in industry but industrial use is limited

✓ Chloroform *K2511P* Similar to benzene in potency in animals^{1,4,11}; known to be a cause of sudden death in man due to ventricular fibrillation; this experience comes from its use as an anesthetic; acute mortality is reported to be about 1:3,500 when the agent is used as the sole anesthetic agent in a concentration of 1.0%-1.65%¹²

✓ Trichloroethylene *K2520P* Little animal data are available but sensitization has been shown to occur^{13,14}; sudden deaths have occurred in industry following exposure to high concentrations of this agent and these deaths are compatible with ventricular fibrillation^{13,14}; perhaps because of its wider use, more deaths are recorded for this agent than any of the others

B. Those Considered Intermediate in Potency

Carbon tetrachloride *K2516P* Because of a sparsity of animal data it is difficult to classify this compound¹⁵; it has caused sudden death in man¹⁶; but considering its earlier wide use, experience would suggest that it is not as active as trichloroethylene

✓ Halothane (or Fluothane) *KQ4793P* Shown to cause sensitization in animals^{17,18} and in humans in the 0.5%-1.0% range¹⁹; not used in industry; should perhaps be classified in group A but because of close supervision during anesthesia untoward results are rare

C. Those Considered Weak Sensitizing Agents or Where Data Make Classification Difficult

✓ Methyl chloride ¹⁹ <i>K2525P</i>	✓ Isopropyl chloride ¹⁹ <i>K1987P</i>	✓ Methyl bromide ¹⁹ <i>K481P</i>
✓ Methylene chloride ¹⁹ <i>K1712P</i>	✓ Primary butyl chloride ¹⁹ <i>K10070P</i>	✓ Ethyl bromide ¹⁹ <i>K1752P</i>
✓ Ethyl chloride ¹⁹ <i>K2522P</i>	✓ Secondary butyl chloride ¹⁹	✓ Methyl iodide ¹⁹ <i>K1750P</i>
✓ Ethylene chloride ¹⁹ <i>K1785P</i>	Isobutyl chloride ¹⁹	✓ Ethyl iodide ¹⁹ <i>K2533P</i>
✓ Propyl chloride ¹⁹ <i>K1986P</i>	Tertiary butyl chloride ¹⁹	
✓ Ethane ²⁰ <i>K3199P</i>	Isobutane ²⁰ <i>DD198P</i>	✓ Cyclopentane ²⁰ <i>K51917P</i>
✓ Propane ²⁰ <i>K3200P</i>	cis- or trans-butene-2 ²⁰ <i>DD324P</i>	✓ Isopentane ²⁰ <i>DD335P</i>
✓ Propylene ²⁰ <i>K2501P</i>	Cyclobutene ²⁰	2,2-dimethyl-butane ²⁰ <i>K54013P</i>
✓ Butane ²⁰ <i>K3072P</i>	Cyclobutane ²⁰	
✓ Acetylene ²⁰ <i>K2503P</i>	✓ Vinyl chloride ²⁰ <i>K171P</i>	Methyl cyclobutane ²⁰
✓ Spiropentane ²⁰	Isopropenyl chloride ²⁰	
Trifluorochloroethylene ²⁷ <i>K13648P</i>	Trichloromonofluoroethylene ²⁷ <i>K11658P</i>	trans-dichloroethylene ²⁷ <i>K9387P</i>
Monochlorodifluoroethylene ²⁷ <i>K32817P</i>	cis-dichloroethylene ²⁷ <i>K9388P</i>	

D. Compounds Which Did Not Cause Sensitization

✓ Ethylene ²¹ <i>K2504P</i>	
✓ Tetrafluoroethylene ²⁷ <i>K79756P</i>	Difluoroethylene ²⁷ <i>K67872P</i>
✓ Ethylene oxide ²⁶ <i>K1708P</i>	✓ Propylene oxide ²⁶ <i>K1709P</i>
Alcohol (very weak) ²² <i>K2544P</i>	Acetone (very weak) ²² <i>K258P</i>

* Compound given in high concentration (15% to 90%) and arrhythmias produced in 100% of dogs tested.

dominantly sudden and only in two cases has an explanation for the deaths been demonstrated at autopsy. Although the cause of death has not been defined in most cases, various mechanisms have been postulated. These include anoxia, narcosis, oxygen displacement from the lungs, freezing injury to the respiratory epithelium, laryngeal spasm or edema, and acute cardiac arrest (ventricular fibrillation). The latter four are listed among possible mechanisms of death in the *National Clearinghouse for Poison Control Centers Bulletin*.¹

Under the conditions in which these aerosols are inhaled, ie, taking several deep breaths of a highly concentrated compound from a bag or balloon, it is easy to see that anoxia and narcosis with their accompanying symptoms could occur. However, should these conditions progress to the point that the individual would become incapacitated, the bag or balloon should fall free from the breathing zone and the person would resume breathing fresh air and regain complete consciousness. In addition, the fact that some of these subjects were walking or running immediately before death occurred is evidence that anoxia or narcosis were not causes of death in these instances. For both reasons, it seems that anoxia or narcosis could not account for more than a small percentage of these deaths.

Since previous animal experiments² with sulfur hexafluoride did not demonstrate that this heavy gas displaced air from the lungs, it is doubtful that the gases inhaled in the aerosol-sniffing cases would have had this effect. In regard to damage of the respiratory epithelium by freezing, there has been no evidence that this was a causal factor in the aerosol-sniffing deaths.

Laryngeal spasm or edema could result from aspiration of yet unvaporized droplets of the aerosol product or propellant causing shock to or freezing of the larynx sufficient to produce laryngeal edema or spasm and, thus, cause death by blocking the flow of air in and out of the lungs. This has reportedly been shown to have occurred in two cases as indicated by the autopsy findings.

The clinical picture plus the general lack of autopsy findings suggests that an acute cardiac arrest such as would occur in ventricular fibrillation may be a frequent cause

of death. This could be caused by sensitization of the heart to epinephrine with the sudden onset of cardiac arrhythmias resulting from the inhalation of high concentrations of propellant compounds in the presence of elevated levels of epinephrine. This phenomenon is referred to as cardiac sensitization.

The phenomenon of cardiac sensitization is not new. It has been known from some time that the inhalation of certain hydrocarbons, for example cyclopropane and chloroform among inhalation anesthetics, can make the mammalian heart abnormally reactive or sensitive to epinephrine, resulting in cardiac arrhythmias. These arrhythmias are usually ventricular in origin and may result in sudden death.

Cardiac sensitization was first demonstrated by Levy^{3,4} in the early years of this century when he showed that in cats the intravenous injection of an amount of epinephrine that alone was nonhazardous would, during chloroform inhalation, cause ventricular fibrillation. Since then, a growing number of unsubstituted and halogenated hydrocarbons have been found which sensitize the heart to epinephrine, resulting in the production of ventricular arrhythmias.

A list of chemicals (not all inclusive) which have been reported in the literature as being capable, experimentally, of producing cardiac sensitization is found in Table 1. The majority of these compounds have merely been rated as causing or not causing sensitization. A few studies have been more quantitative and where a judgment has been made as to whether a compound is a strong or weak sensitizer, this has been noted. If there is relevant information on human experience with the test compound, this is also noted.

As indicated in Table 1, experience in medicine and industry has shown that the phenomenon of cardiac sensitization occurs in man as well as laboratory animals. In view of this plus the clinical picture and nondiagnostic pathological findings associated with most of the aerosol-sniffing deaths, it was decided to study the cardiac sensitization potential of the aerosol propellants generally involved in these deaths as well as other aerosol propellants. The purpose of this study was to determine if these com-

A. These
Benze

Heptane

Chlorofo

Trichloro

B. These
Carbon t

Halothar
(or F

C. These

Methy.
Methy.
Ethyl c
Ethyle
Propyl
Ethane
Propan
Propyl
n-Buta
Acetyl
Spirop
Trifluo
Monoc

D. Comp

Ethyle
Tetra
Ethyle
Alcono

* Com;

Table 2.—Materials Used for the Screening Experiment and Their Sources

Designation	Chemical Name	Source
Fluorocarbon 11	Trichlorofluoromethane	E. I. du Pont de Nemours & Co.
Fluorocarbon 12	Dichlorodifluoromethane	E. I. du Pont de Nemours & Co.
Fluorocarbon 22	Chlorodifluoromethane	E. I. du Pont de Nemours & Co.
Fluorocarbon 114	1,2-dichlorotetrafluoroethane	E. I. du Pont de Nemours & Co.
Fluorocarbon 115	Chloropentafluoroethane	E. I. du Pont de Nemours & Co.
Fluorocarbon C-318	Octafluorocyclobutane	E. I. du Pont de Nemours & Co.
Fluorocarbon 152a	1,1-difluoroethane	E. I. du Pont de Nemours & Co.
Fluorocarbon 142b	1-chloro-1,1-difluoroethane	E. I. du Pont de Nemours & Co.
Fluorocarbon 502	Azeotrope: 48.5% Chlorodifluoromethane/ 51.5% chloropentafluoroethane by weight	E. I. du Pont de Nemours & Co.
Isobutane	2-methyl propane	Phillips Petroleum Co.
Propane	Dimethylmethane	Phillips Petroleum Co.
Dimethyl ether	Methoxymethane	Matheson Scientific
Vinyl chloride	Chloroethene	Matheson Scientific

Table 3.—General Protocol

		Standard Exposure
Control Period	Air	0 min: Start
		2 min: Administer epinephrine intravenously; the total dose (0.008 mg/kg) is contained in 1 ml of normal saline and is injected in 9 sec by an automatic infusion pump
Admin. Period	Air and Compound	7 min: Administer compound
		12 min: Administer epinephrine (challenge injection)
		17 min: Stop compound administration; end experiment
		Short-Term Exposure
Control Period	Air	0 min: Start
		2 min: Administer epinephrine intravenously; the total dose (0.008 mg/kg) is contained in 1 ml of normal saline and is injected in 9 sec by an automatic infusion pump
VAP*	Air	12 min: Administer compound; administer epinephrine (challenge injection)
		12.5 min: Discontinue vapor exposure
		15 min: End experiment

* Vapor administration period, air and compound.

pounds possess this property and thus attempt, experimentally, to verify the hypothesis that cardiac sensitization is a probable cause of death in aerosol-sniffing fatalities.

Materials and Methods

Two types of experiments were performed. The first, a series of screening experiments, involved exposure of dogs to various unsubstituted and halogenated hydrocarbons at several concentrations for a duration of five minutes. This was followed by administration of a challenge injection of epinephrine and the recording of an electrocardiogram to determine the effect of this procedure on the cardiac rhythm. In the case of dichlorodifluoromethane, the duration of exposure was varied to examine the effect of this factor upon cardiac sensitization.

Following the initial screening experiments, it was decided to carry out an experiment which might closely simulate what actually happens in aerosol sniffing. It dealt primarily with those compounds most frequently used as aerosol propellants and involved the administration of a high concentration of compound for a duration of 30 seconds, accompanied by a stimulus intended to frighten the animals and thereby cause the endogenous release of epinephrine.

Screening Experiment

Materials.—The materials studied and their source are listed in Table 2. All of the compounds studied were commercial materials which were analyzed and found to meet specifications required for aerosol use.

Epinephrine (adrenaline) hydrochloride, 1:1,000, was obtained from a commercial pharmaceutical company.

Experimental Animals.—Healthy, male, beagle dogs, 13 to 26 months old, weighing 7 to 14 kg (15.4 to 30.9 lb) were used in this study. The dogs were kept in a laboratory kennel environment for several weeks prior to their use. They were trained to maintain a standing position while lightly supported by a cloth sling, to wear a mask over their nose and mouth, and to accept a venipuncture (Fig 1 and 2).

Generation and Administration of Compound.—Except for fluorocarbon 11, all of the compounds studied exist in the vapor or gaseous phase at normal ambient temperature and pressure and, therefore, were stored in pressure cylinders. The desired concentrations (calculated concentrations) were achieved by delivering

a metered volume of the gas from the cylinder and diluting it with a known volume of air (Fig 3 [gases]). The diluting airflow was fed through a flowmeter fitted with a feedback differential pressure regulator so that the flow downstream from the regulator remained constant despite changes in the upstream pressure. The diluting flow was maintained at a level of 10 to 20 liter/min except in the case of exposure to 50.0% fluorocarbon C-318 where the flow was 8 liter/min.

Where necessary, a heating tape was wrapped around the copper tubing leading directly from the cylinder to ensure complete vaporization of the material.

The flowmeters used for monitoring the volume of test material were calibrated with each compound using a dry test meter. The flowmeter used for monitoring the diluting air was calibrated in a similar manner.

The final compound-air mixture then passed into a 1-inch bore copper tube about 3 feet in length and was carried to the dog mask.

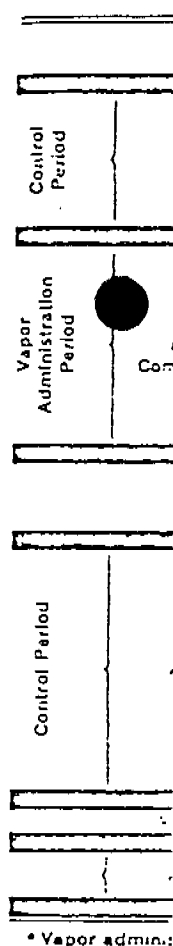
Since the concentrated and diluting flows entered this tubing within a few centimeters of each other, mixing of the two flows occurred rapidly. The compound-air mixture was exhausted to the outside atmosphere by means of an exhaust fan. A 20.5-gal drum with an opening to the laboratory atmosphere was placed in the exhaust line to absorb changes in flow rates due to the dog's respiration. The relatively high rate of the combined vapor (gas) and airflow, coupled with a slight negative pressure applied to the exhaust tube from the mask, assured an adequate air supply to the dog and rapid removal of the expired air.

The vapor of fluorocarbon 11 was generated by passing air through the compound which was contained in a gas-washing bottle (Fig 3 [liquids]). The bottle was partially immersed in a water bath maintained at the optimum temperature for generation of the desired concentration. The water bath was heated by an electric heater for immersion, agitated by an electric stirrer, and the temperature was maintained by a temperature controller. Once the optimum bath temperature was established, the concentration of vapor being generated was controlled by varying the airflow through the test compound. A heating tape was wrapped around the stainless steel tubing just beyond the vaporizer to overcome evaporative cooling and, thus, prevent condensation of the vapor.

A short distance beyond the vaporizer, a tube fitted with a toggle valve led to the exhaust reservoir. This enabled the airflow from the vaporizer to bypass the dog and thus permitted only fresh air to pass through the dog mask at

Designation
Fluorocarbon 11
Fluorocarbon 12
Fluorocarbon 22
Fluorocarbon 11
Fluorocarbon 11
Fluorocarbon C-3
Fluorocarbon 15
Fluorocarbon 14
Fluorocarbon 50

Isobutane
Propane
Dimethyl ether
Vinyl chloride



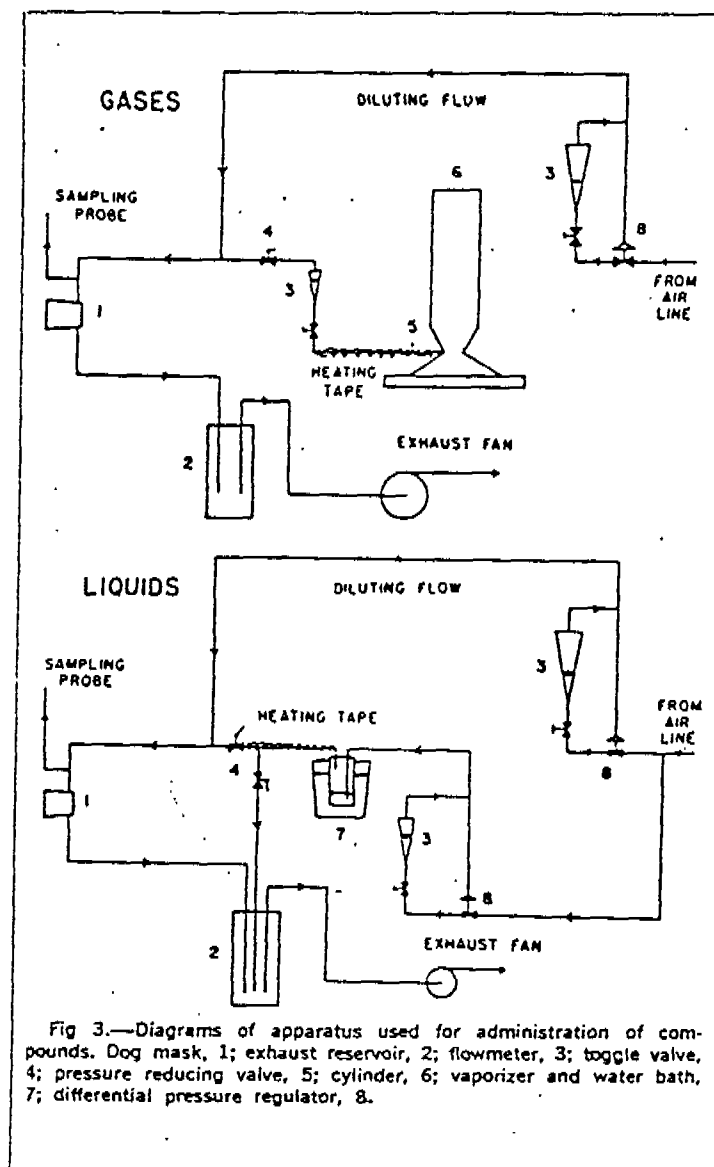


Fig 3.—Diagrams of apparatus used for administration of compounds. Dog mask, 1; exhaust reservoir, 2; flowmeter, 3; toggle valve, 4; pressure reducing valve, 5; cylinder, 6; vaporizer and water bath, 7; differential pressure regulator, 8.

those times when it was necessary for the mask to remain in place without the animal being exposed to the vapor. This arrangement also provided a means of uninterrupted vaporization and thus ensured that the desired vapor concentration could be immediately supplied to the animal by moving the toggle valves.

The diluting airflow and the rest of the delivery and exhaust system were the same as those described above.

Dog Mask.—The dog mask (Fig 4) was constructed from a standard 8-oz paper cup, fitted with intake and exhaust ports without valves, and a rubber sleeve for a tight fit over the dog's nose and mouth. The rubber sleeve was the cuff

from a standard size 7 surgeon's glove. All parts of the mask were coated with a heavy layer of epoxy resin, and the mask, although held in place by an external cloth cover, was supported by hand.

Measurement of Vapor Concentration.—A small portion of the compound-air mixture was withdrawn continuously for analysis at a point just before the mixture entered the mask. For all compounds except fluorocarbon 11, the concentration was calculated from the gas and airflows and monitored by a Haskell Laboratory thermal conductivity gas analyzer so that any significant changes in concentration could be detected. For fluorocarbon 11 and for the one-half- and one-hour fluorocarbon 12 exposures, a gas chromatograph, incorporating a hydrogen flame ionization detector with nitrogen serving as the carrier gas, was used to measure the vapor concentration. The column used was stainless steel, 5 feet in length with an outside diameter of one eighth-inch. The column material was 5% SE-30 on a celite base chromatograph column packing material (Chromasorb W). The column temperature was 110 to 115 C; the hydrogen flow rate, 20 ml/min; and a 0.5-ml sample loop was attached to the chromatograph and used to

introduce samples for analysis every 1½ to 2 minutes during the exposure. A 10-inch, linear, 1-mv range, strip chart recorder was coupled to the gas chromatograph.

Administration of Epinephrine.—The epinephrine was administered intravenously into the cephalic vein of the foreleg of the dog. The injection was made by an automatic infusion-withdrawal pump set to deliver the total epinephrine dosage of 0.008 mg/kg in a volume of 1 ml of normal saline in nine seconds.

Electrocardiograms.—An ECG was recorded continuously during each experimental run using a standard electrocardiograph in association with an oscilloscope having a low-level type

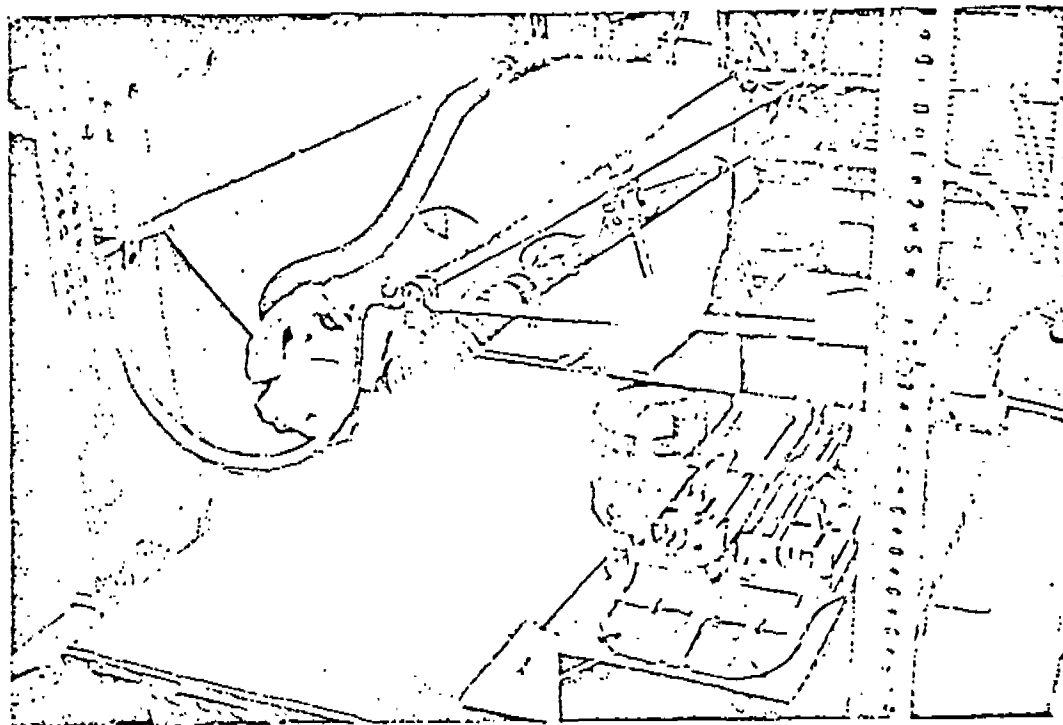


Fig 1.—Experimental equipment showing cloth sling, dog mask, and infusion pump.

Fig 2.—Experimental run showing position of dog with mask in place and injection of epinephrine.



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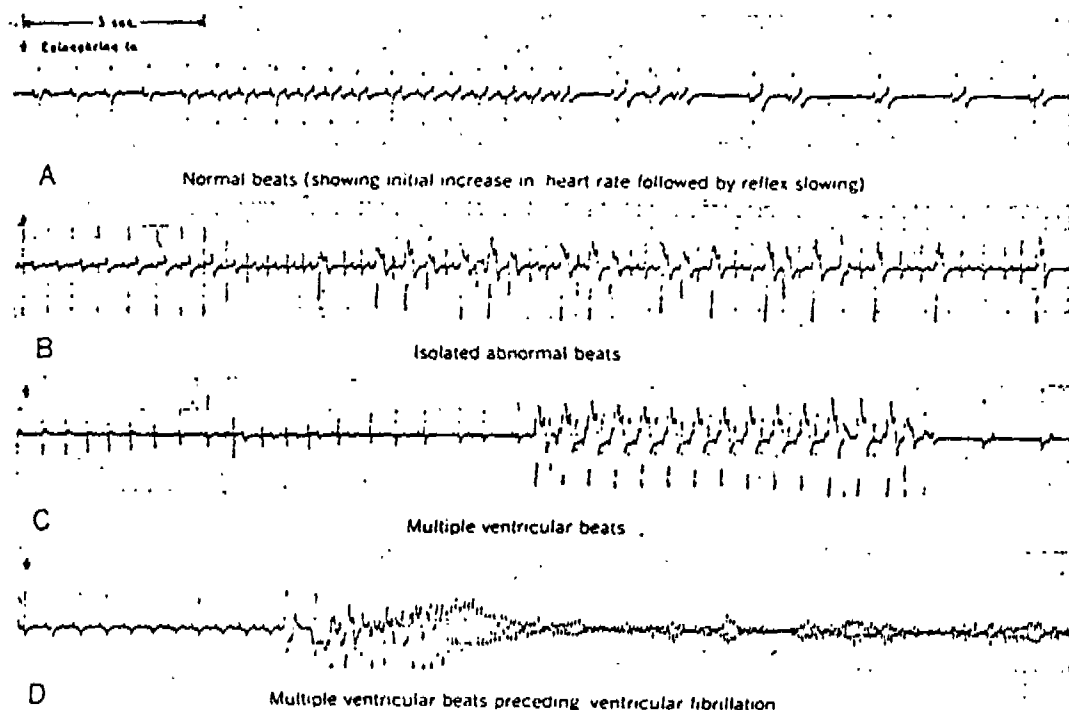


Fig 5.—Examples of electrocardiographic patterns recorded following challenge injection of epinephrine.

that occurred after the second injection of epinephrine as compared to the first. Therefore, in order to evaluate the effect on cardiac rhythm of the second injection of epinephrine alone, an experiment was done in which the usual protocol was followed except that the animals breathed only fresh air the entire time. The results of 13 dog exposures show that although no marked responses occurred, a significant number of mild responses (6[46.2%]) resulted from the second injection of epinephrine in an exposure to air alone. In view of this, only marked responses were considered to represent a significant cardiac sensitization effect in the screening experiments. There is little doubt that the marked responses which followed the challenge injection of epinephrine resulted from exposure to the test material since no serious arrhythmias followed any control injection of epinephrine and none occurred following the challenge injection in the control experiment with air alone.

The results for the various compounds studied in the screening experiments were tabulated as shown in Table 4 and those for the variable exposure durations using fluorocarbon 12 in Table 5. Using marked re-

sponses as the indicator, the results show that all of the compounds studied are capable of sensitizing the mammalian heart to epinephrine. Of this group of compounds, fluorocarbon 11 has the greatest cardiac sensitization potential since it produced this phenomenon in 8.3% and 41.7% of the dogs at concentrations of 0.5% and 1.0% while fluorocarbon C-318 which produced this effect in 16.7% and 83.3% of the animals at concentrations of 25.0% and 50.0% was at the opposite end of the spectrum. Most of the remaining compounds caused sensitization to epinephrine at concentrations in the range of 5.0% to 20.0%.

The results obtained with fluorocarbon 502, an azeotrope of fluorocarbon 22 and fluorocarbon 15 (Table 2), suggest that there may be a potentiating effect when sensitizing compounds are administered simultaneously.

The sensitization potential of a compound apparently depends partly on the degree and type of halogenation. Those compounds containing chlorine atoms produced the greatest degree of sensitization while those containing only fluorine atoms were among compound in the presence of a relatively

differential amplifier input for base-line stabilization. The electrodes were held in place on the dog by a rubber strap extending around the body and were positioned over shaved areas as follows: (1) two active electrodes—one on each side of the chest just behind the foreleg; and (2) one indifferent electrode—over the sternum.

General Protocol.—A so-called standard exposure which was similar to those done in the past by other investigators in this field was given for each compound (Table 3). For fluorocarbon 12 only, additional exposures of 30 seconds (Table 3) and one-half and one hour were carried out to determine what effect duration of exposure might have on the cardiac sensitization potential of a compound.

Since the experimental procedure required relatively quiet and cooperative animals, the maximum concentration of each agent used in these studies was that which the animals would tolerate for about ten minutes without undue struggling or incoordination. The lower test levels studied were chosen to determine a concentration at or near which no significant cardiac arrhythmias developed.

Endogenous Epinephrine Experiment

The compounds studied in this experiment included fluorocarbon 11, fluorocarbon 12, and fluorocarbon 114 which are commonly used aerosol propellants. Fluorocarbon 142b was also tested for comparison purposes since it, in the presence of epinephrine, produced a high percentage of serious cardiac arrhythmias in the screening experiment. Generation and administration of the desired vapor or gas concentrations was carried out in essentially the same manner as described above. However, in the case of fluorocarbon 11, the vapor was generated from a 1-liter, high-pressure cylinder which was fitted with a pressure relief valve (60 pounds per square inch [psi]) and wrapped with a heating tape maintained at a temperature sufficient to produce adequate vaporization of the material. The dogs were exposed to a mixture of 80% compound and 20% oxygen for 30 seconds while simultaneously being frightened by a loud noise provided by an amplified sound-effects tape recording having sounds of sirens, gongs, jet takeoffs, etc. Monitoring of the compound concentration was carried out indirectly by maintaining the oxygen concentration at 20% using an oxygen analyzer. Since the fright was intended to stimulate the release of endogenous epinephrine, no epinephrine was administered exogenously. Electrocardiograms were obtained in the same manner as described above.

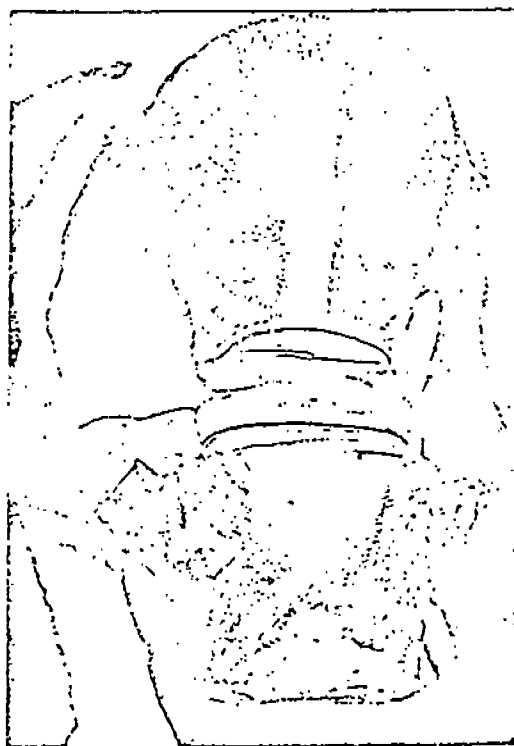


Fig 4.—Dog mask showing intake and exhaust ports.

Results

The first step in assessing and tabulating the results in the screening experiments was to establish response criteria. Based upon the ECG recorded during each experimental run, a "mild response" was recorded when there was an increase in the number of isolated, abnormal beats (abnormal complexes) following the second or challenge injection of epinephrine as compared to the control injection (Fig 5,B). A "marked response" was recorded when an arrhythmia developed which was considered to pose a serious threat to life (multiple consecutive ventricular beats) or which ended in cardiac arrest (ventricular fibrillation) (Fig 5,C and D). The ECG shown in Fig 5,A, illustrates a frequent pattern observed after the challenge injection of epinephrine and would not constitute a response. No serious arrhythmias were observed to follow any of the control injections of epinephrine.

In the screening experiments, many of the responses were mild, consisting of only a slight increase in the number of isolated abnormal beats (frequently by one or two)

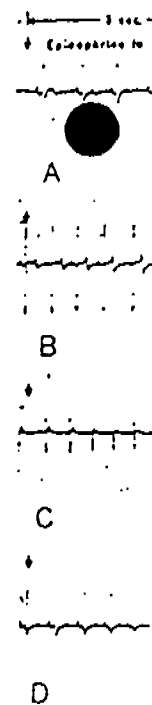


Fig 5.—ECG

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The resu studied in tabulated a the variable carbon 12

Table 5.—Cardiac Sensitization: Results of Variable Duration of Exposure to Fluorocarbon 12

Duration of Exposure	0.5 Min			5 Min		0.5 Hr	1 Hr
Concentration, % V/V	7.0*	7.0	13.5	2.5	5.0	(2.48-2.58)†	(2.48-2.50)†
No. of dog exposures	6	7	7	12	12	6	6
No. of marked responses	1	0	2(1)‡	0	5(1)‡	0	0
Percent marked responses	16.7	0.0	28.6	0.0	41.7	0.0	0.0

* Oxygen concentration reduced to approximately 8.0%.

† Analytic concentration.

‡ Numbers in parentheses indicate number of cases of ventricular fibrillation and cardiac arrest included in marked responses.

Table 6.—Cardiac Sensitization: Results of Endogenous Epinephrine Experiment 80% Compound/20% Oxygen for 30 Seconds With Noise

Compound	No. of Dog Exposures	No. of Mild Responses	No. of Marked Responses	Percent Responses		No. of Convulsions	Percent Convulsions
				Mild	Marked		
Fluorocarbon 11	12	9	2*	75.0	16.7	0	0.0
Fluorocarbon 114	12	1	1*	8.3	8.3	5	41.7
Fluorocarbon 12	12	2	0	16.7	0.0	9	75.0
Fluorocarbon 142b							
Compound & noise	12	4	5	33.3	41.7	9	75.0
Compound alone	12	3	1	25.0	8.3	5	41.7
Noise alone	6	1	0	16.7	0.0	0	0.0

* Bigeminal rhythm with areas suggestive of multiple ventricular beats.

normal oxygen concentration. The results, which are included in Table 5, suggest that the combination of hypoxia and exposure to the compound makes the heart more sensitive to epinephrine.

An autopsy was performed in all cases which ended in sudden death. The heart was examined grossly and microscopically and in each instance appeared to be normal, thus giving no indication that a pathological condition existed which might have made these animals more susceptible to cardiac arrhythmias.

The results of the fright experiment are presented in Table 6. In this experiment, the severity of the response was categorized in the same manner as in the screening experiments. Fluorocarbon 142b was the most potent compound tested, resulting in 41.7% marked responses. Of the three compounds most frequently used as aerosol propellants, fluorocarbon 11 resulted in two cases of questionable marked responses and fluorocarbon 114 in one. No marked responses were seen with fluorocarbon 12. The questionable marked responses observed with fluorocarbon

11 and fluorocarbon 114 were not the classical multiple consecutive ventricular beats seen in the screening experiments but consisted mainly of a bigeminal rhythm with some areas highly suggestive of multiple ventricular beats. A marked tachycardia (300 to 350 beats per minute) was frequently observed with exposure to fluorocarbon 12 and fluorocarbon 114.

The effect of the noise was studied using fluorocarbon 142b. It was apparent that noise was a contributing factor since in combination with fluorocarbon 142b it resulted in 41.7% marked responses as compared to 8.3% with compound alone and none with the noise alone (Table 6).

The convulsions observed with fluorocarbon 142b and fluorocarbon 12 were severe, generalized clonic, tonic seizures, occasionally associated with fecal and urinary incontinence. Those seen with fluorocarbon 114 were mild and characterized by spasticity of the extremities. Although fluorocarbon 11 did not result in convulsions, the dogs did not tolerate the compound and struggled violently.

Table 4.—Cardiac Sensitization: Results of Screening Experiments*

Test Compound	Concentration, % V/V	Duration of Exposure (min)	No. of Dog Exposures	No. of Marked Responses	Percent Marked Responses
Fluorocarbon 11	(0.09-0.13)†	5	12	0	0.0
	(0.35-0.61)	5	12	1 (1)‡	8.3
	(0.96-1.21)	5	12	5 (3)	41.7
Fluorocarbon 12	2.5	5	12	0	0.0
	5.0	5	12	5 (1)	41.7
Fluorocarbon 22	2.5	5	12	0	0.0
	5.0	5	12	2	16.7
Fluorocarbon 114	2.5	5	12	1	8.3
	5.0	5	12	7 (2)	58.3
Fluorocarbon 115	15.0	5	13	1	7.7
	25.0	5	12	4	33.3
Fluorocarbon C-318	10.0	5	12	1	8.3
	25.0	5	12	2	16.7
	50.0‡	5	6	5 (1)	83.3
	50.0‡	5	6	5	83.3
Fluorocarbon 152a	5.0	5	12	0	0.0
	15.0	5	12	3	25.0
Fluorocarbon 142b	2.5	5	6	0	0.0
	5.0	5	12	5	41.7
	10.0	5	12	12	100.0
Fluorocarbon 502	5.0‡	5	6	0	0.0
	10.0	5	12	5	41.7
	20.0	5	12	12	100.0
Isobutane	2.5	5	12	0	0.0
	5.0	5	12	4 (1)	33.3
	10.0-20.0	5	6	6 (3)	100.0
Propane	5.0	5	6	0	0.0
	10.0	5	12	2	16.7
	20.0	5	12	7 (1)	58.3
Vinyl chloride	2.5	5	12	0	0.0
	5.0	5	12	6	50.0
	10.0	5	6	6 (1)	100.0
Dimethyl ether	10.0	5	6	0	0.0
	20.0	5	12	2	16.7
	30.0	5	6	2	33.3

* The duration of all exposures prior to challenge injection of epinephrine is five minutes.

† Concentrations in parentheses are analytical.

‡ Numbers in parentheses indicate number of cases of ventricular fibrillation and cardiac arrest included in marked responses.

§ Oxygen concentration reduced to approximately 10%.

‡ Oxygen concentration enriched to 20%.

¶ Represents concentration of azeotropic mixture.

the weaker sensitizers. However, halogenation is not necessary for the production of cardiac sensitization since propane and isobutane produced a similar measure of sensitization as compared to many of the halogenated compounds.

Using fluorocarbon 12, it was demonstrated that an exposure of only 30 seconds was sufficient to produce cardiac sensitization; however, the concentration of the compound had to be somewhat higher to produce the same effect as that observed after the stan-

dard five-minute exposure (Table 5). On the other hand, increasing the duration of exposure to one-half and one hour did not produce a sensitization effect at a concentration of 2.5%.

A series of 30-second exposures to fluorocarbon 12 was conducted in which the oxygen concentration was reduced to a level of about 8% to determine whether hypoxia combined with exposure to the compound would make the heart more sensitive to epinephrine than would exposure to the

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Table 7.—Epinephrine Dosage

Epinephrine Dose	Vehicle	Rate of Injection	Author
0.03 mg/kg	Not stated	"Rapidly"	Hermann & Vial ¹⁹
0.01 mg/kg	5 cc normal saline	1 cc/10 sec	Meek et al ¹¹
0.01-0.04 mg/kg	Dilute HCl	"Made as rapidly as possible"	Chenoweth ³
0.01-0.04 mg/kg	Not stated	Not stated	Philips et al ²⁰
0.01 mg/kg	Not stated	"Made during 25-40 sec"	Krantz et al ²¹
0.004-0.017 mg/kg	5 cc normal saline	1 cc/10 sec	Raventos ²²
0.01-0.05 mg/kg	5 cc normal saline	1 cc/10 sec	Bamforth et al ²³

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sures suggest that there is a threshold concentration independent of the duration of exposure which must be reached before an effect will be produced.

Limitations of Protocol.—The protocol adopted is considered to provide a sensitive and rigorous screening test for determining the cardiac sensitization potential of a compound and as such is intended mainly to identify compounds which are capable of producing cardiac sensitization. Even though it does permit a rank order of the sensitization potential of the compounds tested, its limitations should be considered in attempting to establish significant effect levels on the basis of the results obtained. The demonstration of cardiac sensitization without the use of injected epinephrine in the fright experiment lends support to the validity of the standard exposure as a screening tool.

Mechanism of Cardiac Sensitization.—Even though a precise explanation cannot be given for cardiac sensitization, it seems apparent that the underlying mechanism involves a disturbance in the normal conduction of the electrical impulse through the heart, probably due to a local disturbance in the electrical potential across the cell membrane.

As suggested by Garb and Chenoweth,²³ during the inhalation of hydrocarbons, which markedly reduce myocardial irritability, some portions of the myocardium are less irritable than others, and, therefore, small, temporary blocks may be produced which could result in a conduction disturbance giving rise to cardiac arrhythmia. Their work showed no evidence that the hydrocarbons themselves induced ventricu-

lar arrhythmias, thus demonstrating the necessity for the concurrent presence of epinephrine or norepinephrine to achieve this phenomenon.

Price¹⁴ states, the term cardiac "sensitization" (to the actions of catecholamines) is unfortunate because there is no aspect of the intrinsic cardiac response to catecholamines which is actually increased by the administration of a "sensitizing" anesthetic. Instead, the functional parameters thus far measured have been found to be depressed. He bases his conclusion upon the work of Smith et al²⁴ which demonstrates that in the myocardium the threshold to electrical stimulation is increased, conduction velocity reduced, and latency increased by most anesthetics, and the reports of Riker et al²⁵ and Vick.²⁷ These reports indicate that the important feature of the action of the sensitizing agents is that they somehow suppress the ability of the sinus and atrioventricular nodes and the ventricular conducting system to respond to a primary increase in cardiac rate and automaticity, thus permitting the emergence of other ectopic foci of pacemaker activity.

Significance of Cardiac Sensitization.—As indicated in Table 1, there is ample evidence which indicates that cardiac sensitization is not simply an interesting laboratory finding, but that it can and has occurred in humans during periods of stress while being exposed to certain unsubstituted and halogenated hydrocarbons. Many unexpected deaths due to the sudden onset of ventricular fibrillation have occurred in humans during the administration of certain volatile, hydrocarbon anesthetic agents such as chloroform. There are also case histories of sudden deaths in

Whether the loud noise by itself resulted in sufficient endogenous epinephrine to produce cardiac sensitization is questionable. It is probable that the convulsions and struggling which occurred at these high concentrations also resulted in an increase in the level of endogenous epinephrine. Thus, it is felt that most likely a combination of these factors was involved and that the noise increased the severity of the struggling and convulsions. This reasoning is supported by the finding that the number and severity of the convulsions seen with fluorocarbon 142b and noise together were greater than those with either noise or compound alone.

Comment

Design of Protocol.—In considering the experimental investigation of cardiac sensitization, a number of somewhat arbitrary decisions must be made in designing a suitable protocol. Three of these which are of some importance are (1) the animals used; (2) the dosage of epinephrine used; and (3) the duration of exposure.

Animals.—For a variety of practical and pharmacological reasons, large animals are preferred for this type of experiment and traditionally two species have been used almost exclusively. Earlier work was done with cats, but recent work utilized the dog. Meek et al¹¹ state that "all the evidence with which we are familiar indicates that conclusions from experiments with anesthetics on the dog may be applied to man with much more certainty than those from the cat."

Dose of Epinephrine.—Since epinephrine can cause ventricular fibrillation when injected alone in sufficient quantity, it is necessary to use a smaller dose when looking for possible synergistic effects. Representative amounts of epinephrine used by other investigators studying cardiac sensitization are given in Table 7. As can be seen, the majority of investigators have used an intravenous dose of 0.01 mg/kg or greater given over a period ranging from "as rapidly as possible" to about one minute.

The dosage of epinephrine used in the screening experiments reported herein was 0.008 mg/kg which is similar to that used by other investigators. As mentioned under

"Materials and Methods," the total dosage was contained in 1 ml of normal saline and was injected in nine seconds.

In extending these experimental results to human exposures, there would be some advantage in using dosages of epinephrine that would yield blood concentrations similar to those resulting from adrenal gland secretion. In practice, however, it has been technically very difficult to assay naturally occurring epinephrine, and this difficulty has been compounded when attempting to measure peaks of epinephrine output such as occur in emotional states.

In Starling and Evans' textbook, *Principles of Human Physiology*,³¹ it is stated that the rate of epinephrine secretion from the adrenal gland in time of stress may reach a level of 0.004 mg/kg/min. Also, Cannon³² estimated that the reflex secretion of epinephrine might reach the level of 0.005 mg/kg/min. The rate at which the dose of 0.008 mg/kg was given in our experiments would provide a dose of about 0.050 mg/kg/min. Even though this dosage of epinephrine probably exceeds by a number of times the maximum rate of human secretion under stress, it is, as mentioned above, similar to dosages used in other experiments in which those compounds proven to be the most potent cardiac sensitizers clinically have also been identified as such experimentally. Similarly, compounds which have produced little or no cardiac sensitization clinically have been found to be weak sensitizers in the laboratory. However, it should be pointed out that for many compounds there is still no relevant information on human experience.

Furthermore, too much emphasis probably need not be placed on the exact epinephrine dosage since, as Price et al³³ suggest, the circulating level of epinephrine may not be as important as the catecholamines released from sympathetic nerve endings within the myocardium.

Duration of Exposure.—An additional variable that was examined was the effect of duration of exposure. Using fluorocarbon 12, it was demonstrated that the length of exposure is an important variable and that cardiac sensitization can occur even with very brief exposures (Table 5). The results observed in the one-half- and one-hour expo-

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industry following exposure to such compounds as benzene and trichloroethylene in which ventricular fibrillation was suspected as the mechanism of death.

The results of the screening and fright experiments indicate that all of the aerosol propellants studied are capable of sensitizing the mammalian heart to epinephrine, resulting in serious cardiac arrhythmias. The fright experiment is particularly significant in that the cardiac arrhythmias developed without the administration of exogenous epinephrine:

On the basis of (1) the positive experimental results; (2) the historical evidence cited above; (3) the presence of the necessary requisites for cardiac sensitization, (a) exposure to high concentration of compound and (b) presence of a high circulating level of epinephrine; and (4) the lack of clinical and pathological findings associated with many of the aerosol-sniffing deaths, it is concluded that cardiac sensitization to epinephrine is a likely mechanism of death in many of the aerosol-sniffing fatalities.

It is quite probable that such factors as hypoxia and hypercarbia could be contributing elements in cardiac sensitization. Standard exposures to a 50.0% concentration of fluorocarbon C-318 (oxygen reduced to about 10%) produced 83.3% marked responses (one death included), while a similar exposure with the oxygen enriched to 20% also yielded 83.3% marked responses but no deaths (Table 4). In the case of fluorocarbon 12, a 30-second exposure to a 7.0% concentration of the compound in the presence of a normal oxygen concentration resulted in no marked responses, while a similar exposure to the same concentration with oxygen concentration reduced to about 8% resulted in 16.7% marked responses. The results of these experiments, although not conclusive, suggest that hypoxia enhances to a slight degree the cardiac sensitization potential of a compound. Some degree of hypercarbia would be expected in aerosol sniffing because of breath holding and rebreathing from a bag or balloon. Price et al²³ believe that hypercarbia is a key factor in the production of cardiac sensitization.

The question of whether components of the aerosol, other than the propellant, play

a role in these deaths should be considered. When the aerosol is sprayed into a bag or balloon for sniffing, much of any solvent present would be vaporized and, therefore, would be inhaled with the propellant and, thus, might produce a toxic effect. This factor was not explored in these experiments. However, where unvaporized liquids (droplets) from the aerosol are inhaled, they may be a factor in producing laryngeal spasm or edema.

In making a judgment about the significance of the cardiac sensitization property of a compound as it relates to humans, the following factors should be considered:

1. Translation of animal data to humans. Past experience in the field of anesthesiology indicates that compounds found to produce cardiac sensitization in dogs also produce it in humans.

2. Individual susceptibility.

3. Variations in individual health.

4. Effect of combination of these compounds with caffeine, drugs, exercise, and a stress such as acute or chronic anxiety.

Overcoming the Problem of Aerosol Sniffing.—There is a special danger attending the sniffing of aerosol propellants. It is a false sense of security which is derived from the fact that numerous episodes of inhaling these materials may be carried out safely and then suddenly a fatality occurs. It can be likened to playing Russian roulette. This factor may be attributed to such things as individual susceptibility and circumstances surrounding the sniffing which may or may not give rise to increased levels of epinephrine.

The answer to this problem seems to be one of education of the public, especially teen-agers, of the potential danger associated with misuse of these materials. It is hoped that an understanding of the nature of this problem on the part of the public will lead to a better appreciation of the hazard of deliberate inhalation of aerosol products or propellants which in turn might lead to a decrease in the practice.

The experimental results reported herein in no way indicate that cardiac sensitization poses a risk when aerosol products and propellants are handled properly and used for the purposes and in the manner intended.

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