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# THE MECHANISM OF SUDDEN DEATH IN EXPERIMENTAL ACUTE BENZOL POISOSISG

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It is a well established fact that exposure to the vapors of the coal tar distillate, benzol ($C_6H_6$), produces both acute and chronic poisoning and that the acute poisoning often terminates in death. More than half of the cases of benzol poisoning analyzed by the Benzol Poisoning Committee of the National Safety Council (1) terminated fatally. This report, as well as those of McCord (2j and Hamilton (3), showed that low concentrations of benzol vapor often caused sudden death, while in other cases high concentrations failed to do so. Bamesreiter (4) obtained similar results in an experimental study of acute benzol poisoning. Physical exertion was also often associated with a fatal terminstion. In many instances members of a rescue party were fatally poisoned while the original victims, sometimes unconscious for a considerable period of time, survived. Finally it is necessary to point out that the emotional state of the gassed person may have an important bearing on the outcome in such cases. Such a typical case is cited by Feil (5) in which the victim burst suddenly out of the space where he had been working, cried several times that he was burning and dropped dead.

It seems difficult in the light of these observations to accept the view that sudden death in acute benzol poisoning ensues from respiratory paralysis, and consequently the present investigation was undertaken in an effort to find an explanation for these hitherto unexplained facts. It was our belief that, in such cases, cardiac and not respiratory failure might be a more logical cause of death. This opinion has been completely substantiated by thepresent investigation.

## METHOD

These experiments were conducted on cats and monkeys (Macaca mulatta), ten of the former and two of the latter being used. The animals were anesthetized with amytal or were decerebrated at the mid-collicular level by the trephine method. Decerebration was performed under ether and the animals were fully recovered from their anesthetic before being used.

The animals were fitted with a tracheal cannula which was connected by means of rubber tubing to a wash bottle containing benzol in such a manner that the air drawn into the lungs passed over the surface of the benzol. The supply of benzol vapor was turned on and off for varying periods of time in order to study the the period of induction and recovery as well as that of narcosis. Electrocardiograms were taken at regular intervals, from lead II, with the animal lying on its right side.

## RESULTS

*A. The effect in the intact animal.* Within less than a minute after inhalation of benzol vapor was started ventricular extrasystoles appeared from one or more foci in the node, bundle branches, deep down in the Purkinje system, or from various foci in succession (fig. 2, *A*). The pacemaker and the auricles were not affected, and normal P waves appeared at a regular rhythm, with now and then a completely normal heart beat occurring between the ventricular extrasystoles. With recovery from the extrasystoles the aberrant foci occasionally ascended in the bundle until a normal rhythm was reestablished. At other times the extrasystoles gradually ceased allowing the normal mechanism to reappear.

As narcosis deepened extrasystoles usually disappeared and a normal rhythm was reestablished. If inhalation was continued, a quickening of the rate together with a reduction in voltage of all complexes occurred and finally after five to ten minutes respiration ceased.

If the inhalation was stopped prior to the onset of respiratory failure or just subsequent to it so that resuscitation by means of

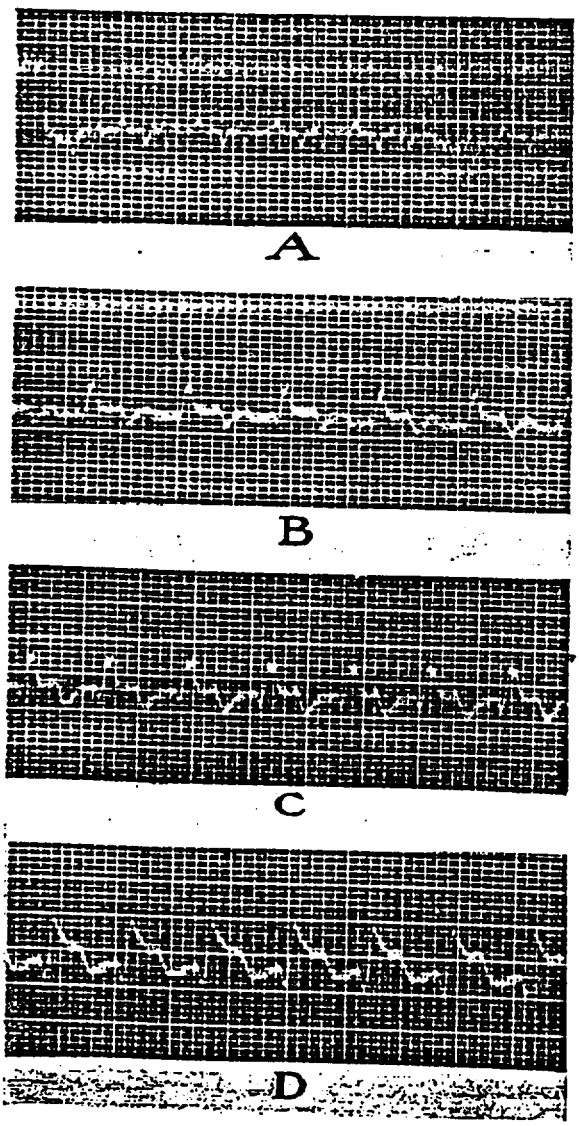


FIG. 1. Experiment 60. Monkey (Macaca mulatta). Amytal anesthesia. Progressive anoxemia developing during benzol inhalation as shown by elevation and alteration of S-T segment. A shortening of the P-R interval indicating downward shift of pacemaker.

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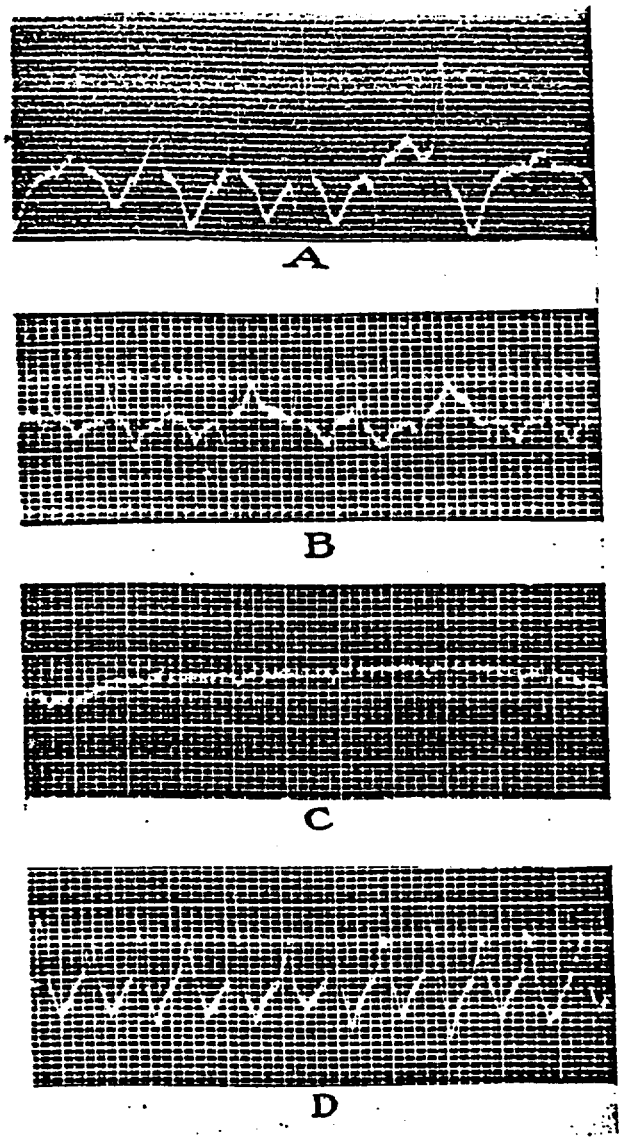


FIG. 2. *A*. Experiment 62. Monkey (Macaca mulatta). Amytal anesthesia. Adrenals removed a half-hour before inhalation of benzol. Characteristic ventricular extrasystoles from multiple foci. Independent auricular rhythm.

*B*. Experiment 56. Amytal anesthesia. Both stellate ganglia removed five hours before benzol inhalation. Multiple foci ventricular extrasystoles.

*C*. Experiment 62. Adrenals removed an hour and fifteen minutes and stellate ganglia removed ten minutes before benzol inhalation. Normal mechanism.

*D*. Experiment 62. One and one-half cubic centimeters adrenaline injected subcutaneously, with no abnormal beats for fifteen minutes. Inhalation of benzol immediately produced ventricular tachycardia of the pre-fibrillation type.

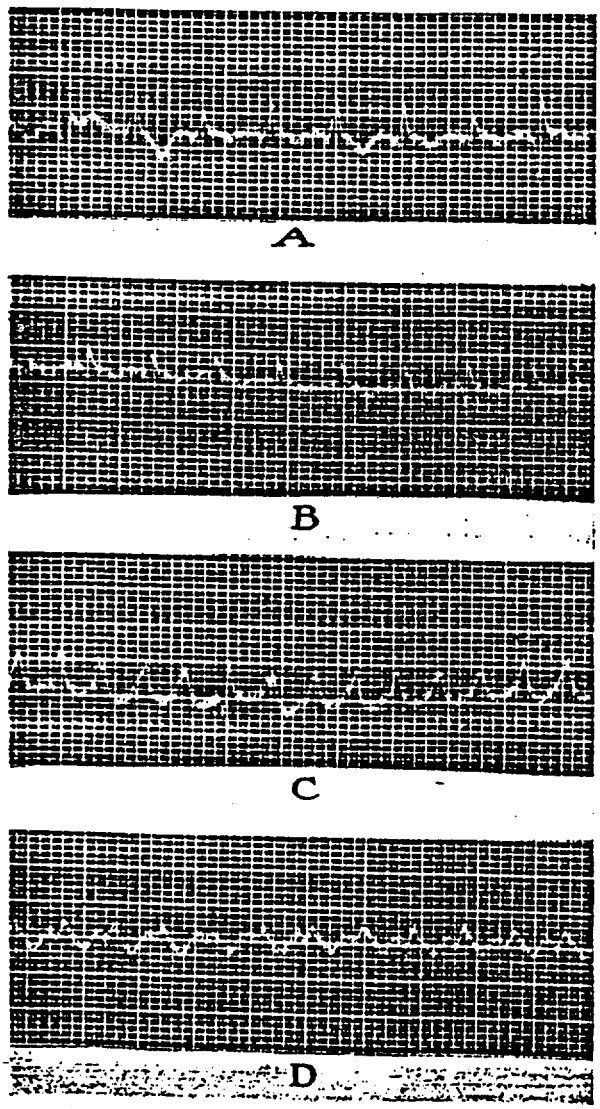


FIG. 3. Experiment 57. Cat. Amytal anesthesia. *A*. Ventricular extrasystoles from multiple foci following benzol inhalation.
*B*. One-half cubic centimeter adrenaline injected intrnvenously upon appearance of extrasystoles. Ventricular tachycardin.
*C* and *D*. Development of ventricular fibrillation in five minutes.

artificial respiration was successful, the animal passed through a stage similar to that occurring on induction, characterized by the appearance of multiple-foci ventricular extrasystoles or periods of ventricular tachycardia which occasionally terminated in ventricular fibrillation (fig. 3).

When inhalation was continued through the induction stage of narcosis and the animal became deeply narcotized, a progressive displacement of the S-T segment was noticed in three experiments, terminating in complete disorganization of the QRS and T complexes. These changes (fig. 1) evidently indicate progressive anoxemia of the myocardium.

*B. Effect of benzol inhalation after removal of both suprarenal glands.* Inasmuch as the rôle of adrenaline had been shown by Levy and Lewis (6) to be of great significance in the production of ventricular extrasystoles and ventricular fibrillation during light chloroform narcosis, it seems desirable to determine whether a similar mechanism was responsible for the appearance of the same type of irregularities in acute benzol inhalation.

In three experiments which showed characteristic multiple-foci ventricular extrasystoles when benzol was inhaled, both adrenal glands were removed. After a recovery period of a half-hour or more, benzol vapor was again administered. Ventricular ectopic beats quickly made their appearance, although at times they seemed less numerous than previously, arose from fewer foci, and did not completely supplant the normal mechanism (fig. 2). After removal of the adrenals benzol inhalation no longer led to well established ventricular tachycardia of the type known to precede ventricular fibrillation. In one such experiment an abnormal rhythm failed to develop at all during the induction phase but appeared during the recovery period.

*C. Effect of bilateral removal of the stellate ganglia on the production of ventricular rhythms.* In one experiment typical of four both stellate ganglia were excised; and five hours later the animal was exposed to benzol vapor. There was an *immediate* quickening of the *rate,* leading after one minute to the appearance of ventricular extrasystoles from two foci, frequently interrupting the normal rhythm. Ventricular tachycardia did

not occur, although it had appeared regularly following benzol before the accelerantes were interrupted by stellate ganglionectomy. Excision of the stellate ganglia was in every case somewhat less effective in preventing the appearance of ventricular tachycardia than was the removal of the adrenals (fig. 2, *B*).

*D. Removal of both adrenal glands and the stellate ganglia.* In three animals both the adrenal glands and the stellate ganglia were removed. In the first of these, where the benzol inhalation was begun before a half-hour after the operation, a few ectopic ventricular beats appeared. In the other two experiments the interval following the operative procedures was longer, and no ventricular rhythms occurred. In all three experiments, however, there occurred a slight increase in the heart rate (fig. 2, C), a flattening of the T wave, and a downward shift of the pacemaker.

*E. The effect of decerebration.* Further to eliminate the effect of cerebral stimulation on the peripheral mechanism experiments were performed on four decerebrate cats. In every instance the inhalation of benzol vapor produced the characteristic ventricular rhythms obtained in the intact animal.

*F. The effect of benzol inhalation in animals With adrenals and stellate ganglia removed, before and after the injection of adrenaline.* It was pointed out earlier that, after a sufficient interval following the removal of the adrenal glands and the stellate ganglia, inhalation of benzol vapor produced none of the ventricular rhythms characteristic of benzol inhalation in the intact animal. In experiment 62 (monkey), inhalation of benzol vapor in the intact animal gave rise to ventricular tachycardia of the type recognized as prefibrillation. After both stellate ganglia and adrenals were removed inhalation of benzol led to an increase in rate but not to the occurrence of ectopic beats. A slight decrease in the P-R interval from 0.08 to 0.06 second occurred.

The animal was allowed to recover from the benzol vapor and 1.5 cc. adrenaline was then injected subcutaneously. The characteristic cardio-accelerator effects ware obtained, such as tachycardia and shortening of the P-R-and QRS complexes. After an interval of ten minutes during which no other changes took place the administration of benzol was begun, and was imme-

diately followed by the picture usually obtained in the intact animal (fig. 2, *D*): ventricular tachycardias, first from one focus and then from multiple foci. At this point 0.5 cc. additional adrenaline was injected intravenously and there occurred characteristic ventricular tachycardia leading to ventricular fibrillation (fig. 3).

## DISCUSSION

The appearance of the ventricular rhythms in the above experiments evidently depends on two essential factors; first, a direct influence of benzol on the myocardium, and, second, the presence of sufficient adrenaline in the blood. Evidence of the direct influence of benzol on the myocardium is seen in the increase in rate, the flattening of the T wave, and the downward shift of the pacemaker, in animals without adrenal glands and stellate ganglia. While benzol inhalation in the presence of small quantities of adrenaline will give rise to ventricular extrasystoles and ventricular tachycardia, it is only when large quantities of adrenaline are present in the blood that ventricular fibrillation ensues.

The literature contains many references to the excitement accompanying the induction stages of benzol narcosis, similar to that found in ether and chloroform anaesthesia. In chloroform anaesthesia only those concentrations which produced excitement have been found to give rise to extrasystoles (Levy (7)). Such central stimulation is probably associated with an adrenaline discharge varying in intensity with the degree of excitement, for it has been shown that stimulation of hypothalamic centres produces secretion of adrenaline, (Houssay and Molinelli (8), and Beattie, Brow and Long (9)). A further secretion of adrenaline probably takes place reflexly through the carotid sinus due to the fall in blood pressure (Dautrebande (10)) caused by the peripheral action of benzol on the arterioles. It is thus apparent that in the intact animal benzol produces its effects by causing the liberation of adrenaline and at the same time sensitizing the myocardium to its toxic action.

These experiments provide a rational interpretation of the mechanism of sudden death associated with excitement and vigor-

ous muscular exercise in acute benzol poisoning so frequently cited in the literature. In muscular exercise there is a reflex cardio-acceleration (Bainbridge (11)), with a liberation of sympathin (Cannon and Bacq (12)), while in excitement there is in addition to this a well marked liberation of adrenaline into the blood stream. The adrenaline and sympathin contribute to the production of ventricular extrasystoles, and the amount liberated determines the severity of the attack. It is therefore probable that the individual variations in susceptibility to benzol poisoning frequently reported (Committee on Benzol Poisoning (1)) may be due largely to variations in the adrenaline response.

In both the clinical reports and in these experiments the danger of death from ventricular fibrillation occurs during the phase of induction or recovery from the narcosis; periods of hyperexcitability and increased adrenaline liberation.

Sudden death is known to occur in many forms of heart disease. It may well be that in some such cases, as in these studies, a sensitized heart has responded to the action of adrenaline by the development of ventricular fibrillation.

## SUMMARY

1. Ten cats and two monkeys were exposed to benzol vapor in high concentration.

2. In the intact animal such exposure invariably led to the appearance of ventricular extrasystoles and ventricular tachycardia of a pre-fibrillation type. These irregularities appeared during the period of induction or recovery.

3. The removal of the adrenal glands in three animals reduced, but did not abolish, the ventricular extrasystoles, and the removal of both stellate ganglia in four cases was not effective in reducing the frequency of ventricular rhythms.

4. With the adrenal glands and the stellate ganglia both excised, in three experiments, ventricular rhythms no longer appeared. They were immediately produced after the subcutaneous injection of adrenaline. When benzol was not inhaled such doses of adrenaline had only cardio-accelerator effects.

5. During the stage of narcosis respiratory failure occurred

and associated with it were progressive anoxemic changes in the electrocardiogram.

## CONCLUSIONS

Benzol effects the liberation of adrenaline and sensitizes the myocardium to its action. Death from acute benzol poisoning may occur suddenly from ventricular fibrillation in the presence of sufficient amounts of adrenaline or accelerantes stimulation or both during the stage of induction or recovery. Death may also occur during the stage of narcosis from respiratory failure.

The authors wish to express their thanks to Professor Lucien Dautrebande for suggesting the study of the cardiac effects of benzol inhalation.

## REFERENCES

(1) Final Report, Committee, Chemical and Rubber Sections, National Safety Council on Benzol. May, 1926. Nat. Bur. Casualty and Surety Underwriters.
(2) McCord: Benzol (Benzene) Poisoning. Industrial Health Conservancy Lab., Cincinnati, 1932.
(3) Hamilton: Industrial Poisons in the United States. New York, Macmillan & Co., 1925.
(4) Bamesreiter: Arch. f. Hyg., 108, 199, 1932.
(5) Feil: Presse méd., 41,[1] 129, 1933.
(6) Levy and Lewis: Heart, 3, 99, 1911–12.
(7) Levy: Heart, 4, 319, 1913.
(8) Houssay and Mollinelli: Compt. rend. Soc. de biol., 93, 1454, 1925.
(9) Beattie, Brow and Long: Proc. Roy. Soc. Med., 106B, 253, 1930.
(10) Dautrebande: Compt. rend. Soc. de biol., 111, 218, 1932.
(11) Bainbridge: J. Physiol., 50, 65, 1915.
(12) Cannon and Bacq: Am. J. Physiol., 96, 392, 1931.
(13) Levy: Heart, 12, 387, 1925.