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VI. Electrocardiographic Study of Heart and Effect of Vagotomy in Phosgene Poisoning.*

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(Introduced by I. S. Ravden.)

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Bradycardia, salivation, vomiting, urination, and defecation regularly appear during or shortly after exposure to phosgene.[1-6] The bradycardia persists up to the critical anoxic phase and is clearly of neurogenic origin since vagotomy or atropine prevent or abolish it. These very early signs suggest an over-all, abnormally high parasympathetic tone which, therefore, was investigated by electrocardiography in order to: (1) confirm this clinical impression and assess the importance of parasympathetic tone in the etiology of the lung damage and (2) evaluate this sign of poisoning in relation to prognosis. The electrocardiograph used in conjunction with the electro-encephalograph also offered a means of detecting whether the central nervous system or heart was more affected by anoxemia in the critical and terminal stages.

Methods†. Thirteen healthy dogs were studied electrocardiographically using the 3 standard leads and the apical-left leg lead with the dog placed in the supine position on a shaped wooden board. This position according to preliminary experiments gave reproducible tracings. Lead II was used for following changes at short intervals. Samples of the other 3 were taken at longer intervals as indicated. Following several control tracings the dogs were exposed to phosgene in a dynamically operated chamber as previously described.[7] In the low concentration (0.5 mg per liter)—long duration (30 minutes) exposure, the leads were passed into the chamber and tracings were made throughout the gassing. In the equivalent high concentration (5.0 mg per liter)—short duration (3 minutes) exposure, tracings were started within 2 minutes after the end or 5 minutes from the beginning of gassing. Both exposures are an L(CT)99 for dogs.

The dogs on which electro-encephalographic records‡ were also made had recovered fully from an operation at which metal guide plugs had been screwed in the temporal bones. Chlorided silver electrodes thrust through the overlying skin were used for recording.

Results. Excessive sinus arrhythmia was seen regularly as soon as 1½ minutes after beginning exposure to the low concentration. This was followed by sinus bradycardia which attained its maximum within the first half of the 30 minute exposure. The PR interval lengthened about 0.03 seconds during the middle of 10 minutes gassing and then shortened somewhat. Changes of the ST interval (or ST + T, because of difficulty in determining the onset of T) paralleled the

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1 Laqueur, E., and Magnus, R., *Z. f. d. ges. exp. Med.*, 1921, **13**, 31.

2 Underhill, F. P., *The Lethal War Gases*, Yale Univ. Press, New Haven, 1920.

3 Meek, W. J., and Eyster, J. A. E., *Am. J. Physiol.*, 1920, **51**, 303.

4 Gibbon, M. H., Bruner, H. D., Boche, R. D., and Lockwood, J. S., To be published in *J. Thor. Surg.*

5 Patt, H. M., Tobias, J. M., Swift, M. N., Postel, S., and Gerard, R. W., *Am. J. Physiol.*, 1946, **147**, 329.

6 Rothlin, E., and Suter, E., *Helvetica. Physiol. et Pharm. Acta.*, 1946, **4**, 147.

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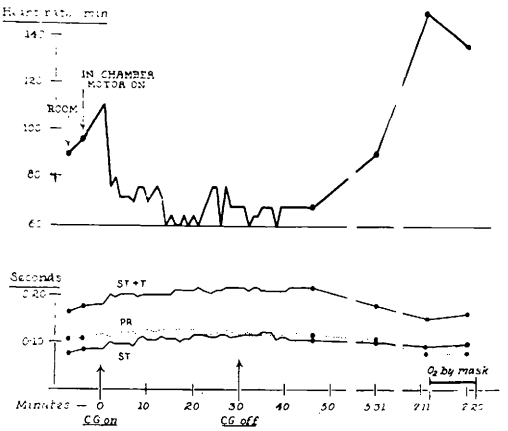

FIG. 1.

Changes in heart rate, PR, ST, and ST-T electrocardiographic waves (Lead II) during exposure to phosgene (0.52 mg per liter for 30 minutes, a L(CT)99 dose) and at subsequent representative intervals.

PR changes as shown in Fig. 1. Other electrocardiograph values remained essentially constant.

The first tracings taken in air after gassing at the high concentration for 3 minutes showed sinus bradycardia and lengthened PR and ST + T intervals, which attained their maximum during the next 5 to 10 minutes and then slowly regressed. The magnitude of change is of the same order as that in Fig. 1. The 2 types of exposure to phosgene evoked essentially identical cardiac responses regardless of the fact that the animals gassed by the high concentration technique were again breathing air when the maximal changes occurred.

In 2 dogs during the height of the bradycardia, ectopic areas assumed the pacemaker role—the ventricle in one case and probably the upper part of the bundle or the A-V node in the other. A third dog showed A-V block temporarily some 20 minutes after gassing began.

This combination of sinus arrhythmia, sinus bradycardia and prolonged conduction time may be considered pathognomonic or heightened vagal activity.

These findings regressed to normal as the heart rate increased during the second to sixth hour and showed no further change despite subsequent development of tachycardia coincident with development of pulmonary edema, anoxemia and a shock-like state of the circulation. Occasional transient inversions of the QRS and/or T waves in leads II and III occurred in the anoxic phase but nothing characteristic of cardiac anoxia.[7] Similarly in the electro-encephalographic tracings the waves characteristic of the dog continued despite severe cyanosis associated with stupor. The electro-encephalographic waves, however, died out shortly before the animal ceased to breathe whereas normal electrocardiographic complexes continued until after complete respiratory failure. The heart then showed bizarre ectopic and premature beats, various types of block and finally ceased. Terminal ventricular fibrillation was very brief or absent.

Oxygen therapy sufficient to abolish the cyanosis (Fig. 1) made no significant changes in the tracings and slowed the heart only slightly. Apparently the heart was not critically impaired even though the animal, as in Fig. 1, was soon to die.

No correlation could be discovered between changes of electrocardiographic measurements and either rate of development or severity of the syndrome. This confirms Underhill's[2] study of heart rate changes in relation to survival.

To investigate the possible role of excessive parasympathetic tone in the genesis of pulmonary damage, detailed histologic studies were carried out on the lungs of animals gassed before or after unilateral or bilateral cervical vagotomy done under local or evipal anesthesia. In other dogs the vagi were temporarily blocked during gassing by infiltration with procaine. In still other dogs atropine or physostigmine was administered to block or exaggerate, respectively, parasympathetic tone. Most of the dogs had been devocalized previously to eliminate complications from laryngeal paralysis.

The bradycardia was absent whenever the vagi were cut, or blocked by procaine, or the end organs blocked by atropine. Physostigmine appeared to have no special effects.

[7] Harris, A. S., and Randall, W. C., *Am. J. Physiol.*, 1944, **142**, 452.

All the other signs of parasympathetic response were present. Bradycardia developed as the procaine wore off *after* gassing was ended.

Interpretation of all these sections with reference to appropriate ungassed controls suggests that the pulmonary effects of vagotomy resemble phosgene poisoning[8,9] and leads to the conclusion that vagal efferent fibers to the lung and afferents from the lung, trachea and larynx have little, if any thing, to do with the pulmonary tissue's response to phosgene.[7] Unilateral vagotomy failed to produce detectable differences between homolateral and heterolateral lungs. These studies fail completely to confirm the claim of Laqueur and Magnus[1] that bilateral vagotomy before, but not after, gassing protects against phosgene poisoning.

Discussion. The bradycardia is not peculiar to phosgene poisoning since it has been noted in poisoning by chlorine, chlorpicrin and other lung irritants.[1,2,10] Presumably the same is true of the other cardiac signs of excessive parasympathetic tone. In man it has been reported to occur soon after gassing in combat,[1,11] but nevertheless it was not present in a large number of serious but nonlethal accidental exposures to phosgene.[12] Possibly among the latter the psychic response to being "gassed" may have contributed to the somewhat increased heart rates.

The cardiac reactions appear to be a reflex response. Vagotomy appears to sever only the efferent side of the arc as the other parasympathetic signs still occur. Therefore cranial nerves I, V, IX, parts of X and possibly sympathetic afferents[13] may serve as the afferent limb of the arc. Alternatively, there is produced in the tissues by action of phosgene a chemical which activates the parasympathetic centers or their specific afferents. While this humoral mechanism seems improbable to us (c.f.[6]), we are not able to suggest a complete explanation for the continued development of bradycardia *after* the stimulus, the phosgene, has been withdrawn.

Regardless of whether a state of exaggerated parasympathetic tone exists in the pulmonary as in the cardiac vagal fibers, the above data demonstrate that such innervation is not essential to the typical pulmonary reaction to phosgene. In particular, broncho- and bronchiolar constriction, if occurring at all,[7] is of no special significance.

Summary. By use of the electrocardiograph, vagotomy, and atropine, it was shown that the early bradycardia of experimental phosgene poisoning was mediated by efferent vagal fibers. Excessive parasympathetic tone appears to have no special significance in the genesis of the pulmonary response to phosgene.

8 Coman, D. H., Bruner, H. D., Horn, R. C., Jr., Friedman, M., Boche, R. D., McCarthy, M. D., Gibbon, M. H., and Schultz, J., *Am. J. Path.*, 1947, **23**, 1037.

9 Wieser, J., *Pflug. Arch. ges. Physiol.*, 1933, **321**, 68.

10 Fleming, A. J., *Industrial Med.*, 1943, **12**, 127.

11 Cole, H. H., *Am. Rev. Tuberc.*, 1923, **7**, 230.

12 O'Connor, J. A., Personal communication, 1943.

13 Miscall, L., and Rovenstine, E. A., *Surgery*, 1943, **13**, 495.