ward from the peduncle to terminate in the lateral mammillary nucleus. Others swing ventromedially through the lateral mammillary nucleus to terminate in the ventrolateral hypothalamic nucleus. Still other fibers course dorsomedially and terminate both in the rostral part of the medial mammillary nucleus and in the supramammillary nucleus. Laterally located degenerated fibers of the mammillary peduncle continue forward to terminate in the lateral hypothalamic nucleus. These fibers are distributed throughout the lateral hypothalamic area forward almost to the level of the optic chiasma.

The available experimental material indicates that the *Substantia nigra* does not contribute to the crossed component of the mammillary peduncle. Lesions in the *Substantia nigra* produce no degeneration which terminates in the contralateral hypothalamus excepting when they are located in the caudomedial part of the nigra. Lesions in this part of the nigra interrupt fibers entering the mammillary peduncle from the ventral tegmental nucleus (Fox[3]). The crossed degeneration present in 4 of our animals can be attributed in each case to the interruption of these fibers. The distribution of the fibers of the mammillary peduncle presented here is in agreement with the termination of the peduncle as described by other investigators (see review of Huber and Crosby[8]).

Careful consideration has been given in the present study to determine the exact origin of degenerated fibers in the mammillary peduncle. Experimental evidence indicates that the peduncle arises in part from the mesencephalic tegmentum. Fox[3] has shown the ventral tegmental nucleus to be the specific nucleus of origin for these fibers. Tegmental lesions located lateral and rostral to this nucleus produce no degeneration in the mammillary peduncle. Likewise no degeneration occurs in the mammillary peduncles of animals with multiple lesions in the pons, caudal to the nigra. Thus the degeneration produced within the mammillary peduncle in animals with nigral lesions apparently results from injury to the nigral cells.

Summary. Degenerated fibers, resulting from lesions located in the *Substantia nigra,* ascend to the hypothalamus by way of the homolateral mammillary peduncle. These fibers terminate in homolateral nuclei of (a) the mammillary bodies, (b) the infundibular region and (c) the lateral hypothalamic area. None of the degenerated nigral fibers appear to enter the contralateral hypothalamus.

8 Huber, G. C., and Crosby, E. C., *Arch. Neur. and Psychiat.*, 1929, **22**, 187.

14021

Influence of Respiratory Inspiration on the Heart Rate.

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It is well known that deep sustained inspiration is associated with a slowing of the heart rate. Of the recognized mechanisms having this effect the following may be mentioned: (1) overdistention of the lungs, evoking the cardioinhibitor reflex described by Anrep, Pascual and Rössler[1] and by von Saalfeld;[2] (2) the "Lungenentlastungsreflexe" of Schwiegk,[3] in which an increase of pressure in the pulmonary vessels slows the heart; and (3) the carotid sinus and aortic cardioinhibitor reflexes activated by a rising systemic arterial pressure. Certain effects of inspiration would tend to accelerate the heart: (1) increased venous inflow into the thorax evoking the Bainbridge reflex; (2) moderate distention of the lungs, stimulating the accelerator reflex of Anrep *et al.*[1] and von Saalfeld;[2] (3) inhib-

1 Anrep, G. V., Pascual, W., and Rössler, R., *Proc. Roy. Soc.*, 1936, **119B**, 191, 218.

2 von Saalfeld, E., *Pflügers Arch.*, 1932, **231**, 724.

3 Schwiegk, H., *Pflügers Arch.*, 1935, **236**, 206.

itory irradiation from the respiratory center to the cardiac vagus center;[1] and (4) the voluntary effort exerted in the act of inspiration. In an attempt to evaluate these factors in human subjects, the effects of chest position and of reduction of intrapulmonary pressure in various chest positions was studied.

The intrapulmonary pressure, assumed to be atmospheric when the chest was held in any given position with the glottis open, was reduced by the following procedure: the nose was clamped and a mouthpiece connected with a mercury manometer was held in the mouth; the subject, lying in the supine position, watched the manometer and made a voluntary inspiratory effort sufficient to reduce and maintain the pressure at −20 mm Hg for at least 30 seconds. Observations were made with the chest held voluntarily in the position of full inspiration, with and without reduction of intrapulmonary pressure, and in the position of full expiration with and without reduction in intrapulmonary pressure. Heart rate was recorded continuously on a kymograph by means of a Gaertner sphygmograph. Arterial pressures were determined by the auscultatory method. Before each experiment the subject rested for 15 minutes, at the end of which control heart rate and arterial pressure determinations were made. Between trials, sufficient time was allowed to elapse for the normal levels to return. Eleven experiments were performed on 6 subjects, 4 males and 2 females.

The average values for heart rate, and systolic and diastolic pressures, at various times after the assumption of the appropriate chest position (with and without reduction of intrapulmonary pressure), are shown in the accompanying figures. The following discussion will be confined to consideration of the heart rate 20 seconds after the beginning of the trial, since the arterial pressures at this time were not yet affected by the respiratory arrest.

The assumption of the chest position of full inspiration is followed by a reduction of the heart rate averaging 11 beats per minute at 20 seconds. This fall is statistically significant, the probability of chance occurrence being less than 1 in 1000. None of the three

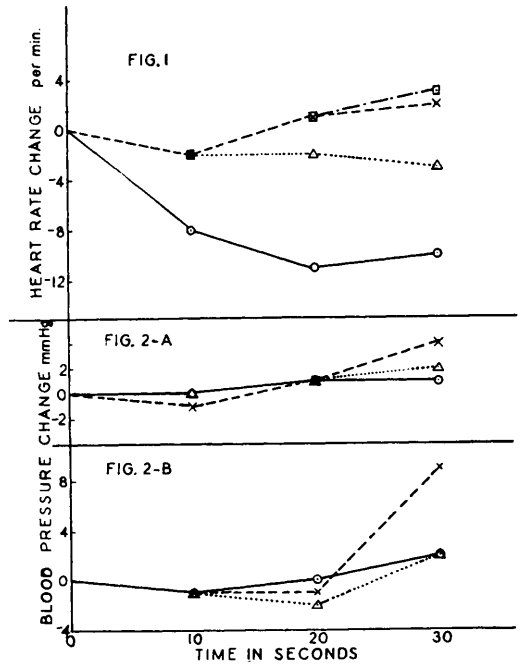

FIG. 1.

Changes in heart rate and blood pressure accompanying changes in chest position and intrapulmonary pressure: Fig. 1, heart rate; Fig. 2-A, systolic pressure; Fig. 2-B, diastolic pressure. Continuous line, inspiration at atmospheric pressure; Dotted line, inspiration at −20 mm Hg.; broken line, expiration at atmospheric pressure; alternate dots and dashes, expiration at −20 mm Hg.

other maneuvers produced statistically significant changes in heart rate.

Are any of the known cardioinhibitor reflexes which might be evoked by inspiration adequate to explain the concomitant slowing of the heart rate? Since the arterial pressure is not altered, the carotid sinus and aortic reflexes cannot be responsible. It is improbable that the degree of pulmonary distention which could be brought about under these conditions would be adequate to evoke the reflex slowing of the heart, for it requires, according to Anrep and his associates,[1] inflation with a positive pressure which in an open chest would cause the lungs to bulge out of the thorax. There remains only the reflex of Schwiegk,[3] which might be activated by a rise in pressure in the pulmonary vessels produced by increased output of the right ventricle resulting from the greater venous inflow into the chest in inspiration. In order to be effective in slowing the heart, the Schwiegk

reflex must outweigh the accelerator influence of the Bainbridge reflex which would also be elicited under these conditions.

If inspiration slows the heart by the consequences of reduction in intrathoracic pressure, the slowing should appear when the intrathoracic pressure is reduced by other means. Voluntary inspiration against resistance is one such means and the one which we have employed. However, when the intrapulmonary pressure is reduced to −20 mm Hg with the chest in the expiratory position, there is no slowing of the heart. Probably the Bainbridge reflex and the Schwiegk reflex, both of which are doubtless evoked, cancel each other's effect on the heart rate.

Thus we arrive at the conclusion that none of the cardioinhibitor reflexes discussed can explain the slowing under consideration. Some other factor must be postulated, such as the position of the chest itself or of the diaphragm as suggested by Sylla,[4] or some secondary consequence of the inspiratory position other than those already discussed.

In support of this conclusion may be cited the finding that the heart rate when the chest is in the inspiratory position with an intrapulmonary pressure of −20 mm Hg is somewhat slower than when the chest is in the expiratory position with the same intrapulmonary pressure. The fact that the slowing is not as great as when the intrapulmonary pressure is atmospheric may be attributed to the greater voluntary effort required to reduce the intrapulmonary pressure to −20 mm Hg when the chest is in the inspiratory position than when it is in the expiratory position. The cardiac acceleration accompanying the greater voluntary effort, it may be suggested, would increase the inhibitory irradiation from the respiratory center to the cardiac vagus center and so in part counteract the decelerating influence of the inspiratory chest position.

Summary and Conclusion. The slowing of the heart produced by sustained deep inspiration is not due to the reflex consequences of lowered intrathoracic pressure nor to any other hitherto recognized reflex mechanism. It is probably caused by some influence activated by the assumption of the inspiratory position of the chest.

[4] Sylla, A., *Klin. Woch.*, 1936, **15**, 849.

14022 P

Concentrations of Sulfadiazine in Human Saliva Attained by Chewing Paraffin Containing Sulfadiazine.

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It is now recognized that the sulfonamides are effective in the therapy of many severe infections of hemolytic streptococcic origin. The results with these compounds have been less satisfactory in the treatment of patients with streptococcic upper respiratory diseases. This is especially true of the milder types of infections such as acute pharyngitis and tonsillitis. In our own clinical experience, the ingestion of moderate doses of the sulfonamides by patients having acute pharyngitis and tonsillitis has occasionally been attended by disagreeable side effects from the drugs, which overshadowed the questionable therapeutic responses. We have attempted to treat such individuals by the local application to the pharynx of powdered sulfonamide preparations, or solutions and suspensions of the compounds. The results have been disappointing.

The possibility arose that more desirable therapeutic responses might be obtained if the tonsillar tissues and oral pharynx were subjected to high concentrations of a suitable