tribué au fait qu'après le laps de temps étudié, l'effet propre de la tétrabénazine n'a pas encore entièrement disparu. En effet, les valeurs moyennes du taux plasmatique (11,5 ± 1,8 γ%) et de la production surrénalienne (1,65 ± 0,15 γ) après administration de tétrabénazine ne diffèrent pas significativement des valeurs obtenues après le traitement combiné tétrabénazine-réserpine.

Les observations effectuées 20 h après l'injection de réserpine sont encore plus nettes et dans ces conditions l'effet inhibiteur de la tétrabénazine est total. Sous l'influence de la réserpine les taux moyens de corticostérone plasmatique libre et de la production surrénalienne horaire atteignent encore respectivement 21,0 ± 1,6 γ% et 3,3 ± ± 0,31 γ, contre 5,1 ± 0,8 γ% et 1,22 ± 0,23 γ chez les rats témoins. L'administration de tétrabénazine 1 h avant la réserpine inhibe entièrement ces effets prolongés de la réserpine. Les valeurs moyennes obtenues dans ces conditions pour le taux plasmatique (7,2 ± 1,9 γ%) et pour la production surrénalienne horaire (1,85 ± 0,27 γ) ne diffèrent pas significativement de celles observées chez les témoins. Que la tétrabénazine ne possède plus d'effet propre après ce laps de temps est prouvé par l'absence de différence notable pour les deux paramètres étudiés entre les rats traités uniquement à la tétrabénazine (valeurs moyennes respectives de 7,3 ± 1,4 γ% et 1,8 ± 0,23 γ) et les animaux témoins.

On peut conclure de ces observations que la tétrabénazine administrée chez le rat 1 h avant la réserpine, tout en possédant une action propre, mais de plus courte durée, inhibe fortement et même totalement l'effet stimulant prolongé de la réserpine sur la fonction corticosurrénalienne. Cet effet est à rapprocher du pouvoir inhibiteur du prétraitement par la tétrabénazine envers l'action sédative centrale de la réserpine.

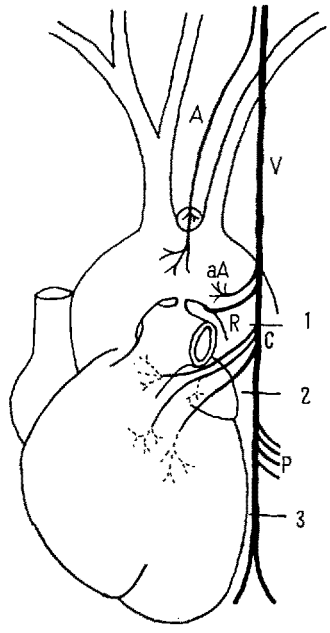
Summary. Reserpine provokes an intense and long-lasting (more than 20 h) stimulation of the adrenocortical activity of the rat. Tetrabenazin (50 mg/kg) also produces an adrenocortical stimulation which is, however, of a much shorter duration. The injection of tetrabenazin 1 h before the injection of reserpine (5 mg/kg) prevents the prolonged stimulating effect of reserpine on the adrenal cortex. This effect can be compared with the blocking effect of tetrabenazin, a short-acting central depressant with monoamine-liberator properties, against the prolonged central sedative influence of reserpine.

W. EECHAUTE, E. LACROIX et I. LEUSEN

Laboratoires de Physiologie Normale et Pathologique de l'Université de Gand (Belgique), le 8 janvier 1962.

Cardiopulmonary Origin of Vagal Afferent Fibers Exerting a Tonic Reflex Influence on the Circulation[1]

In a previous report[2] we have presented evidence suggesting that the pressor release phenomenon induced by cervical vagal interruption may not result from section of intermingled afferent fibers originating from the aortic arch. More crucial evidence to this effect, and direct data on the actual origin of these afferents have been sought in a series of experiments where the left vagus nerve has been cut at different levels along its intrathoracic course, below or above its various branchings towards heart and lungs.



Schematic drawing of the intrathoracic branching of the left vagus in the cat. A: aortic nerve; aA: accessory aortic fibers; C: cardiac twigs; P: pulmonary twigs; R: inferior laryngeal or recurrent nerve; V: vagal trunk. 1, 2, 3 indicate the levels of different intrathoracic sections of the vagus nerve. For further explanations see text.

Methods. Animal preparations, cholinergic blockade, blood pressure and respiration recordings were as previously reported[2]. Under artificial ventilation the left hemithorax was opened in the fourth intercostal space, and the vagus nerve dissected free of the surrounding tissue. A suitable instrument was hooked to the nerve at the selected level, its handle protruding from the external surface of the thorax, which was thereafter sutured. After reduction of the pneumothorax, spontaneous ventilation was resumed, so that thoracic dynamics was normal when by pushing on the handle's shaft a sharp blade was moved to cut the nerve without any undue stretching or pressure. In a few animals two such instruments were placed at different vagal levels, and operated in succession from the outside of the closed thorax. Intrathoracic section of the left vagus was always performed after severing the right vago-aortic-sympathetic trunk and the left aortic nerve. In several experiments also carotid sinus influences were removed by bilateral ablation of the carotid sinuses.

Results. The main intrathoracic branchings of the left vagus nerve in the cat have been schematically represented in the Figure. While most of the afferent fibers from the aortic arch and body run, on the left, along the aortic nerve (A), some accessory fibers have been described by NONIDEZ[3] to reach directly the left vagus nerve just above

[1] This research has been sponsored in part by Wright Air Development Division of the Office of Aerospace Research, United States Air Force, through its European Office, with Contract No. AF 61 (052)-253, and by Consiglio Nazionale delle Ricerche.

[2] M. GUAZZI, A. LIBRETTI, and A. ZANCHETTI, Exper. *18*, 185 (1962).

[3] J. F. NONIDEZ, Amer. J. Anat. *57*, 259 (1935).

the entrance of the inferior laryngeal or recurrent nerve (R); these have been depicted in our Figure and labelled aA. A few mm below the branching of the recurrent nerve, three or more thin twigs are noted to diverge from the main vagal trunk. These can be traced in proximity to the atria, ventricles and pulmonary artery, although their actual ending cannot be identified owing to their abundant anastomosing in the cardiac plexus. Therefore, they have loosely been labelled as 'cardiac' vagal fibers (C). Shortly below the 'cardiac' vagal branches, several twigs depart from the main trunk directed toward the pulmonary hilus. As for the so-called 'cardiac' fibers, their actual ending cannot be determined exactly, although some of them appear to originate from the bronchial tree[4], their section being associated with the known respiratory changes due to the interruption of the Hering-Breuer reflex. We have loosely labelled these fibers as 'pulmonary' (P). Caudad of the 'pulmonary plexus' and near to the diaphragm, the main vagal trunk itself bifurcates into two divisions which enter the abdomen after uniting with similar divisions of the right vagus nerve.

The effect of intrathoracic vagus sectioning at three different levels was studied (I) on the amplitude of the pressor response to carotid occlusion, in animals with the carotid sinuses intact, or (II) on the basal level of arterial pressure, in animals with previous removal of the carotid sinus receptive regions. Both tests gave concordant results. Left vagus interruption just above its terminal supradiaphragmatic division (section 3 in our Figure) was always without effect, while a slightly more rostral section (2 in our Figure), above the 'pulmonary' twigs, constantly induced either an increased pressor response to carotid occlusion or an enduring augmentation of basal arterial pressure. Further pressor effects were, however, induced by subsequent section of the cervical vagus. Intrathoracic vagal severing just above the cardiac twigs, well below the entrance of the inferior laryngeal nerve and the aortic arch (section 1), elicited pressor reactions which were often larger than those produced by section 2 ('pulmonary' fibers), but then no further pressor change could be induced by subsequently cutting the left cervical vagus. Any substantial contribution of accessory aortic fibers to the circulatory effects of intrathoracic or cervical vagus sectioning was finally ruled out by showing that vagal severing above the pulmonary hilus had conspicuous effects, unmodified by later cutting of the cervical trunk, also after the aortic arch had been surgically denervated by stripping and all vagus branches from its entrance into the thorax to a level just above the pulmonary hilus had been resected.

To sum up, those afferent fibers in the left cervical vagus that have been shown to exert a tonic inhibitory influence upon the circulation[2], appear to originate from intrathoracic receptive areas, which are likely to include atria, ventricles, pulmonary vessels, and, possibly, the bronchial tree. More precise identification of the receptive fields is prevented by the distribution of these vagal endings in diffuse plexuses. Accessory aortic fibers, claimed by NONIDEZ[3] to join the left vagus at the level of the recurrent nerve, would be responsible for quite an unsubstantial part, if any, of the influence.

Riassunto. Le fibre afferenti presenti nel vago cervicale, e dotate di tonica attività inibitrice sui fenomeni circolatori, originano da aree recettrici intratoraciche, non provengono in misura importante dall'arco aortico, ma si dipartono da ampie zone della regione cardio-polmonare.

M. GUAZZI, A. LIBRETTI, and A. ZANCHETTI

Istituto di Patologia Medica, Università di Siena (Italy), October 31, 1961.

[4] J. G. WIDDICOMBE, J. Physiol. *123*, 71 (1954); *125*, 336 (1954).

Day-Night Periodicity in Pentobarbital Response of Mice and the Influence of Socio-Psychological Conditions[1]

The pharmacological effectiveness of barbiturates in man and animals is known to be subject to many varied influences. Psychological factors in barbiturate responsiveness of man and of Rhesus monkeys have been cited by SHAGASS[2] and by CHEN[3] respectively. Physiological factors affecting degree of barbiturate response have been studied to a greater degree. Important influences observed in rodents include state of water balance[4,5], environmental and body temperature[5–8], adrenocortical hormone secretion[9], blood level of insulin or epinephrine[10], and circulatory state[11] in addition to basic attributes of age, sex, and strain. With such information in mind we have anticipated that one or more physiological factors displaying circadian periodicity might affect barbiturate response significantly. Various workers no doubt have considered time of day as a variable to be controlled in tests of barbiturate sleeping time prolongation commonly employed in characterizing new central nervous system drugs. Observations reported here demonstrate the importance not only of circadian physiological periodicity, but also of socio-psychological conditions in the response of mice to a standard anesthetic dose of pentobarbital sodium.

The Figure illustrates the variation in duration of response to pentobarbital with time of day detected in several strains of mice. Curves obtained from mice of inbred albino or non-albino, and non-inbred albino strains are similar. To detect such circadian patterns considerable care must be used to maintain constancy of conditions during and prior to the experimental observations. Male mice of several strains were housed in isolation or in groups with food and water available *ad libitum*. Room

[1] This work was initiated with the aid of a grant from the University of Oklahoma Faculty Research Committee and was later supported by grant B-2250, National Institutes of Health, U.S. Public Health Service.

[2] C. SHAGASS, in UHR-MILLER, *Drugs and Behavior* (John Wiley & Sons, New York 1960), p. 399.

[3] K. K. CHEN, in *Symposium on Sedative and Hypnotic Drugs* (Williams & Wilkins, Baltimore 1954), p. 54.

[4] M. F. KAUFMANN, Arch. int. Pharmacodyn. *103*, 167 (1955).

[5] J. F. BORZELLECA and R. W. MANTHEI, Arch. int. Pharmacodyn. *111*, 296 (1957).

[6] J. RAVENTOS, J. Pharmacol. exp. Therap. *64*, 355 (1938).

[7] F. A. FUHRMAN, Science *105*, 387 (1947).

[8] A. W. LESSIN and M. W. PARKES, Brit. J. Pharmacol. *12*, 245 (1957).

[9] D. M. WOODBURY, Pharmacol. Rev. *10*, 275 (1958).

[10] J. F. REINHARD, Proc. Soc. exp. Biol. Med. *58*, 210 (1945).

[11] F. N. FASTIER, Exper. *12*, 351 (1956).