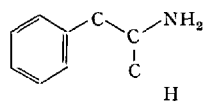
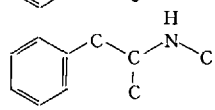
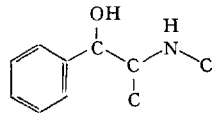
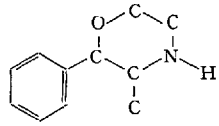
Potency of some amphetamine-like drugs. ED_{50} is determined from the log dose-response curves as the dose for which the motor activity is 45 pulses/min

Drug	Formula	ED_{50} μMol/kg	ED_{50} mg HCl salt/kg
dl-Amphetamine		9.7	1.7
dl-Methamphetamine		3.6	0.67
(−)-Ephedrine		170	34
Phenmetrazine		30	6.8

For 4 or 6 geometric increasing doses of each drug, cumulative time-response records were made and the activity determined by measuring the slope. The activity in responses/min were plotted *versus* the dose, using a logarithmic dose-scale (see Figure 4). Parallel lines were obtained over a considerable dose range. With higher doses, an auto-inhibition occurs. From the dose-response curves thus obtained (Figure 4), the dosage producing 50% effect was calculated. This dose is used as a measure for the central stimulating action. The potency of a few amphetamine-like drugs determined from dose-response curves are given in the Table.

In a number of pairs of mice, two latency times were observed for amphetamine. After 30–60 min there is again an increase in activity with moderate to high doses. This might be an indication that amphetamine could be methylated into the more potent methylamphetamine.

Time-response curves and dose-response curves of drugs and of combinations of drugs with their specific antagonists form the basis of a proper understanding of the mechanism of action of drugs in general.

The shape of drug-induced cumulative records of locomotor-activity and the dose-response curves may therefore provide valuable information on the mechanism of action and the classification of central stimulant drugs.

Zusammenfassung. Eine Methode zur kumulativen Registrierung spontaner motorischer Aktivität kleiner Tiere wird beschrieben. Die Wirksamkeitsbestimmung aus dem kumulativen Rekord und die analytische Bedeutung der Methode für die Wirkungsweise zentralstimulierender Substanzen wird diskutiert.

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Effects of Selective Intracranial Section and Stimulation of Vago-Accessory Roots. III. Course and Distribution of the Cardio-Inhibitory Fibers of the Bulbar Root of the Accessory Nerve

It has been previously reported that, in the dog, marked cardio-inhibitory effects can be obtained from, and mediated by, the bulbar root of the accessory nerve[1]. This root, fusing into a common trunk with the vagus nerve at level of the upper part of the nodose ganglion[2], seems therefore to represent an additional channel through which the pre-ganglionic cardio-inhibitory axons leave the oblongata. The arrangement of these 'accessory' fibers into the cardiac branches of the vagal trunk and the pattern of distribution to the intrinsic structures of the heart have now been investigated.

Intracranial section of either vagal or bulbar accessory root has been made unilaterally, in dogs, under aseptic conditions, and the efferent axons then allowed to degenerate. 20–30 days after, the animals were anaesthetized with chloralose and both vagi were cut at the neck. The peripheral stump of the vagal trunk ipsilateral to the chronic radicotomy (thus containing either vagal or bulbar accessory efferent fibers only) and its cardiac branches were gently dissected free and stimulated at different levels, the effects being recorded by conventional EKGraphy. Samples of vagal trunk and cardiac branches were then taken and processed according to the Marchi's method for degenerating myelinated fibers and the Cajal's method for axons.

EKGraphic records were also taken in acute preparations, subjected to selective intracranial stimulation of vago-accessory roots.

The results can be summarized as follows: (a) Cardio-inhibitory responses, including cardiac (or ventricular) arrest, can be obtained by stimulation of the vagal trunk, after degeneration of either vagal or bulbar accessory fibers, though more readily in the latter case. The same applies, generally, to the main cardiac branches (recurrent cardiac, cranio- and caudovagal nerves, on the right side; ventromedial and dorsal cervical cardiac nerves, left innominate and recurrent nerves, on the left side[3,4]) of the vagal trunk, with the exception of the ventromedial cervical cardiac and, possibly, left innominate nerves, which appear to be, after chronic vagal radicotomy, almost completely without effects. (b) After chronic section of the bulbar accessory root, no degenerated myelinated fibers have been traced into the cardiac branches of the vagal trunk (as after chronic vagal radicotomy). A small, compact group of degenerated myelinated fibers, present in the vagal trunk just cranially to the exit of the cranialmost branch (ventromedial cervical cardiac nerve, on the left; recurrent cardiac nerve, on the right side), enters the recurrent nerve. (c) Electrical stimulation of the bulbar root of the acces-

[1] L. SPERTI and E. XAMIN, Exper. *16*, 556 (1960).
[2] M. R. CHASE and S. W. RANSON, J. comp. Neurol. *24*, 31 (1914).
[3] N. J. MIZERES, Anat. Rec. *123*, 437 (1955).
[4] N. J. MIZERES, Anat. Rec. *127*, 109 (1957).

sory nerve in acute preparations, as well as of the vagal trunk and cardiac branches in animals with chronic vagal radicotomy, causes EKGraphic changes which parallel those obtained from the vagal root, or from the vagal trunk after chronic radicotomy of the bulbar root of the accessory nerve, and which depend upon the side of stimulation. On the right side, sinus bradycardia develops and proceeds, as the current strenght is increased, to cardiac arrest, without significant alteration in the A–V conduction rate. On the left side, the slowing down of the A–V conduction, leading, as the current strength is increased, to partial (2:1, 3:1) and complete A–V blocks, predominates over the effects upon the sinus rythm, which become prominent only after having the A–V block fully developed; but, while the sinus rythm appears to be only moderately affected even by maximal stimulation of the ipsilateral vagal trunk in animals with chronic vagal radicotomy, a sinus arrest can still be produced in animals with chronic section of the bulbar accessory root, as in normal ones.

In conclusion, our observations indicate that the cardio-inhibitory fibers leave the medulla through both the vagal and the bulbar accessory roots. Both components enter the cardiac branches as unmyelinated fibers and show the same pattern of distribution to the intrinsic structures of the heart, the right side components involving predominantly, but not exclusively, the sino-atrial node, the left side components the atrio-ventricular node. Quantitatively, however, the vagal component is largely predominant.

Riassunto. Le fibre cardio-inibitrici della radice bulbare del nervo accessorio spinale presentano un piano di distribuzione periferica (rami cardiaci del vago-strutture intrinseche del cuore) non distinguibile da quello delle fibre della radice del vago, che rappresentano la componente numericamente predominante.

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Effects of Selective Intracranial Section and Stimulation of Vago-Accessory Roots. IV. Reflex Activity of 'Accessory' Cardio-Inhibitory Neurons

In order to analyse the reflex activity and related properties of the cardioinhibitory neurons sending their axons into the bulbar root of the accessory nerve[1,2], 24 dogs with unilateral, chronic or acute, intracranial section of the vagal root have been submitted to several experimental procedures. Vagal radicotomy has been limited to one side, in view of possible accidental lesions of the IX th nerve root during the intracranial procedure[1]. In both chronic and acute preparations vagal de-efferentation was carried out by sectioning the contralateral vagal trunk at the neck, and the dependence of the heart rate responses upon the bulbar accessory fibers was then checked by ipsilateral vagotomy.

(a) Section (or cooling) of the vagal trunk of the same side of the chronic or acute vagal radicotomy does not significantly affect, either when it is performed before or after section (or cooling) of the contralateral vagal trunk, the pre-existing heart rate in otherwise normal animals; on the other hand, a definite increase in the heart rate has been shown, in both cases, by decerebrate or morphine-treated animals, displaying low basal heart rate and marked sinus arrhythmia. (b) Electrical stimulation of the central end of the contralateral vagal trunk causes a remarkable fall in the heart rate, almost completely prevented by the division of the ipsilateral vagal trunk. (c) Section of the contralateral vagal trunk strongly increases the corresponding threshold but does not prevent the slowing of the heart rate or even the cardiac (or ventricular) arrest in response to mechanical (including Moissejeff's pouch) or electrical stimulation of either carotid sinus pressoceptors; such a response is no longer present after section of the ipsilateral vagal trunk. (d) Intravenous administration of epinephrine or nor-epinephrine (0.5–2 μg/kg body weight) induces an arterial hypertensive phase upon which a bradycardiac response, although less marked and shorter than before, still develops after section of the contralateral vagal trunk. Ipsilateral vagotomy abolishes, almost completely, such a bradycardiac response. (e) Electrical stimulation of points in the antero-lateral hypothalamus or in the pre-optic area, through bipolar, insulated except at the tip, stereotaxically placed electrodes, evokes bradycardiac responses (mostly post-stimulatory) which are not significantly affected by the division of the contralateral vagal trunk, but completely abolished by the ipsilateral vagotomy.

From the above results it is concluded that the cardio-inhibitory neurons sending their axons into the bulbar root of the accessory nerve can be activated through the same pre-synaptic channels as the vagal ones. The similarity, therefore, between vagal and 'accessory' cardio-inhibitory neurons, as far as functional properties and pattern of peripheral distribution[2] are concerned, strongly suggests that the 'accessory' neurons have to be considered as a fraction of the cardio-inhibitory center. Such an 'accessory' pool of cardio-inhibitory neurons, which is large enough to cause cardiac (or ventricular) arrest when extensively activated[1,2], does not seem to play a significant rôle in the control of the normal 'resting' heart rate, but can display relevant levels of activity in conditions of increased excitability of the cardio-inhibitory neurons (decerebrate or morphine-treated animals), and (epinephrine, nor-epinephrine), or in response to increased pressoceptors discharge.

Riassunto. I neuroni cardio-inibitori le cui fibre escono con la radice del nervo accessorio spinale possono essere attivati attraverso le stesse vie presinaptiche di quelli vagali e devono quindi essere considerati come una frazione del centro cardio-inibitore.

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Istituto di Fisiologia Umana dell'Università di Padova (Italy), July 5, 1961.

[1] L. Sperti and E. Xamin, Exper. *16*, 556 (1960).
[2] L. Sperti, M. Midrio, and E. Xamin, Exper. *18*, 96 (1962).