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# CARDIOVASCULAR RESPONSES TO ELECTRICAL STIMULATION OF THE BRAIN STEM

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The significant role of the medulla oblongata in the regulation of cardiovascular function was first clearly defined by the classical transection studies of Dittmar (1870, 1873) and Owsjannikow (1871). Beginning with localization of pressor and depressor points in the floor of the fourth ventricle by Ranson & Billingsley (1916), many workers have contributed to current concepts of a diffuse distribution within the lateral reticular formation (pressor) and the caudal part of the medial reticular formation (depressor) of a network known as the vasomotor centre (Wang & Ranson, 1939; Monnier, 1939; Alexander, 1946; Bach, 1952). Chen, Lim, Wang & Yi (1936, 1937) proposed that this reactive region is a general sympathetic area inducing extensive sympathetic activation. Bach (1952) reported that stimulation of points within the diffuse network of the vasomotor centre yields simultaneous cardiovascular, respiratory and somatic (knee jerk) responses. Much of this work suggests that the medullary reticular formation in which the vasomotor centre is enmeshed is a relatively non-specific system. However, recent neuro-anatomical studies (Scheibel & Scheibel, 1958), which reveal the extensive synaptic connexions of a single reticular neurone, and which permit estimation of the large number of such neurones activated by commonly used stimulation procedures, suggest that such an interpretation of functional activity within the reticular formation should be made with caution.

Recent writers (Cotten, 1953; Randall & Rohse, 1956; Anzola & Rushmer, 1956) have re-emphasized the significance of the sympathetic outflow to the heart. On the basis of these studies, it appears that the more important functional effect of sympathetic activation of the heart is augmentation of myocardial contraction. When the left stellate ganglion is stimulated, cardio-augmentor responses with large increases in systolic pressure are recorded, while diastolic pressure and heart rate remain relatively unchanged. Similar

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responses have been reported during stimulation of the brain stem reticular formation (Peiss, Middo, Randall & Jones, 1956; Peiss, 1956).

In reviewing the current status of bulbar regulation of cardiovascular function in the light of these studies, several important facts appear. There has been no description of cardio-augmentor responses following brain stem stimulation. With few exceptions, workers in this field have measured pressor or depressor activity with no attempt to analyse these responses. Moreover, the majority of these workers, having used inadequate recording techniques, could not analyse pulse pressure changes so as to interpret possible cardio-augmentor effects. In several instances (Alexander, 1946; Pitts, Larrabee & Bronk, 1941) electrical activity in the inferior cardiac nerve has been recorded as a measure of cardio-accelerator discharge. However, optical pressure pulses simultaneously measured often show no change in either heart rate or pulse pressure. The conclusion seems warranted, therefore, that increased electrical discharge in the inferior cardiac nerve is not necessarily a valid criterion of cardio-acceleration or cardio-augmentation. Finally, there is little direct evidence of a cardio-accelerator centre at the medullary level. This latter point will be treated in detail in a separate communication. One must conclude, therefore, that the concept of cardiac regulating centres in the diffuse network of the vasomotor area is largely based on inference from reflex studies.

It is the purpose of this report to describe cardio-augmentor responses to stimulation of the brain stem, to demonstrate activation of specific types of cardiovascular responses, and to assess the relation of these findings to cardiovascular reflexes and specificity of the reticular formation.

## METHODS

Fourteen dogs and fifty-three cats were used. Various anaesthetic agents were used, but the majority of experiments were performed on animals under sodium pentobarbital or alpha-chloralose anaesthesia. There were no significant differences in response, regardless of the anaesthetic employed. Arterial blood pressure was recorded from a carotid artery with a Sanborn electromanometer adapted to drive a Sanborn EKG optical galvanometer. Square-wave stimulation pulses were delivered from an American Electronics Model 104 square-wave generator, which was continuously monitored by an oscilloscope connected across the electrodes. Actual stimulation voltages were read from the oscilloscope. Experiments on dogs were performed by surgical exposure of the floor of the fourth ventricle and manual placing of unipolar electrodes on or just ventral to the floor of the ventricle. All cats were positioned in a Johnson stereotaxic apparatus. In some cases small holes were made in the cranium and electrodes inserted stereotaxically into the areas desired. In other experiments occipital bone was removed, part of the cerebellum aspirated by suction, and electrodes then positioned under stereotaxic control. In the cat experiments electrodes were of the coaxial type, the outer shell (reference electrode) being 22-gauge hypodermic-needle tubing completely insulated except for the terminal portion of the ring. The active electrode consisted of fine stainless steel wire projecting 1 mm beyond the reference electrode and insulated except for the terminal 0·5 mm, which tapered to a dull point. Electrodes were routinely tested for integrity of insulation. Stimulation voltages varied from

2 to 7·5 V. Pulse duration was usually kept constant at 2 msec, with the exceptions noted in the text. Frequency of stimulation was varied from 50 to 100 c/s in the experiments reported here, and the duration of stimulation was 15 or 20 sec. At termination of the experiments the brain stem was fixed with formalin for subsequent histological work-up. In order to limit cardiac responses to those mediated by the sympathetic nervous system, bilateral vagotomy was carried out on all animals.

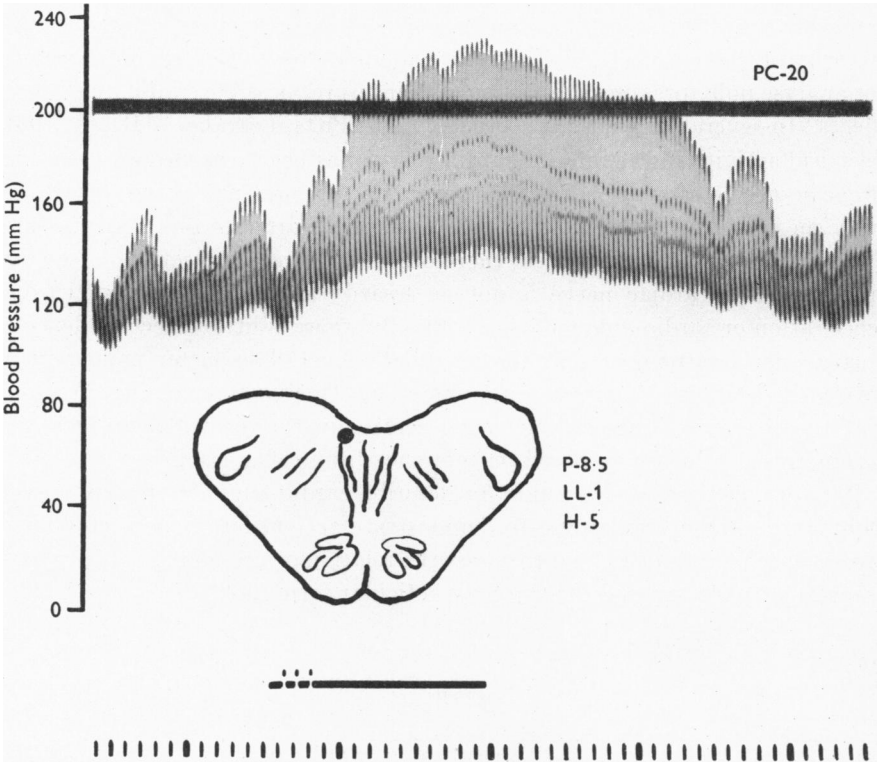


Fig. 1. Cardio-augmentor response elicited by stimulation (3 V, 2·0 msec, 70 c/s) of cat's lower brain stem at breaks in lower horizontal bar. Black dot in cross-section of brain stem indicates site of stimulation in Horsley–Clark co-ordinates. Time marker 1 sec.

## RESULTS

### *Cardio-augmentor responses*

Over 100 different points (Horsley–Clark co-ordinates) in the pons and medulla have been stimulated. Owing to the large number of responses obtained, it is impossible to do more than illustrate certain types of response common to a large number of animals. Detailed mapping of reactive points awaits the completion of the histological examination. The significant points to be made from these experiments are illustrated in the figures below. Fig. 1 shows the effect

of stimulation in the rostral medulla just ventral to the floor of the fourth ventricle, and 1 mm to the left of mid line. This response is the closest we have come to eliciting a 'pure augmentor' effect, and looks strikingly like those obtained by Randall & Rohse (1956) when the left stellate ganglion was stimulated. Systolic pressure rose from a control level of 150 to 230 mm Hg, while diastolic pressure changed only from 110 to 140 mm Hg. Heart rate remained constant during and after stimulation. The change in pulse pressure strongly suggests that the primary effect of stimulation at this point in the brain stem was activation of neurones which eventually terminate as post-ganglionic fibres on the myocardium, and which induce greatly increased myocardial contraction. There was no evidence of significant vasoconstriction. The latency between the onset of stimulation and the first augmented beat of the heart was less than 4 sec. Since both augmentation and acceleration of the heart beat also occur secondary to adrenal secretion, it is essential to restrict interpretation of direct sympathetic augmentation of the heart to those responses occurring within 6 sec of onset of stimulation. It is quite common to find latencies as short as 2 sec (see below), a value which compares closely with latencies observed during sympathetic trunk stimulation.

Although it is tempting to compare responses to restricted stimulation of the isolated stellate ganglion and a generalized stimulation in the brain stem, the comparison is weakened by the fact that brain stem stimulation may influence vascular function in wide-spread areas of the body. This is due in part to the profuse interconnexions within the reticular formation. Moreover, it is not known whether the point stimulated is on an afferent or an efferent pathway. In order to extend the comparison, the spinal cord was transected at the T4–T5 level in six animals. This procedure eliminates nervous excitation of the adrenal medulla and also eliminates a large fraction of peripheral vasoconstrictor fibres. Although hypotension results from the transection, it was still possible to elicit significant cardio-augmentor responses. Within a few seconds of onset of stimulation augmented pulse pressure was observed. The effect of stimulation was of long duration, a common finding when the stellate ganglion is stimulated. Thus, although the magnitude of the response in a 'transected' animal was always less than in the 'intact' animal, it is clear that significant cardio-augmentation can occur in animals with cord transection at the T4–T5 level.

*Adrenal responses*

Figure 2 (dog no. 14) indicates a type of response which should not be interpreted as a direct nervous cardio-augmentation. For 18 sec following the onset of stimulation no significant change was observed in either pulse pressure or heart rate. A modest vasoconstriction occurred, resulting in a small rise in arterial pressure. At the end of this period of time a simultaneous increase occurred both in pulse pressure and heart rate. The timing of these events

suggests that the long-latency response was due to secretion of adrenaline from the adrenal medulla, with subsequent inotropic and chronotropic effects on the heart, and with a further vasoconstriction of peripheral blood vessels. Responses of this type have been eliminated by acute bilateral adrenalectomy (Peiss, 1957). The late onset of augmentation and/or acceleration is a common occurrence. In most cases it is preceded by a short-latency vasoconstriction, presumably of splanchnic origin. These delayed responses are sometimes attri-

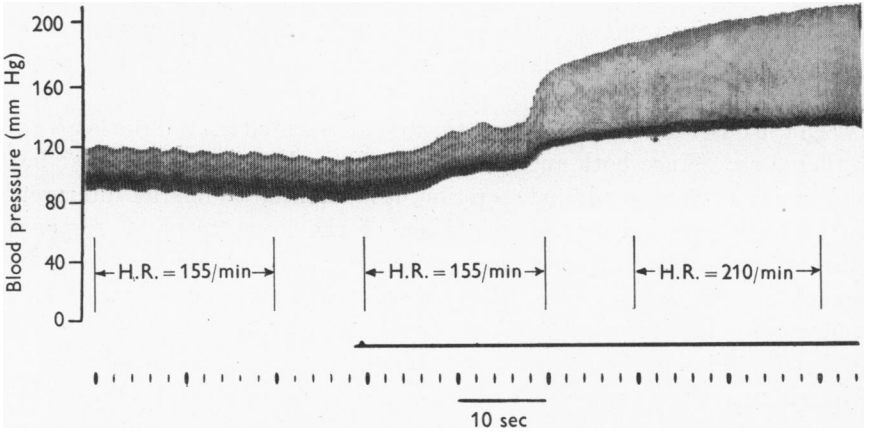


Fig. 2. Delayed augmentation and acceleration of dog's heart elicited by stimulation (3 V, 2 msec, 100 c/s) of brain stem, horizontal bar. See text for discussion.

buted to direct sympathetic stimulation with delayed peripheral transmission. It is our experience, however, that brain stem stimulations of direct sympathetic pathways to the heart show latencies as low as 1·8 sec. Responses occurring with latencies approaching the animal's circulation time should be considered to be of adrenal origin unless evidence to the contrary is presented.

*Mixed responses*

Figure 3 is an example of the most common cardiovascular response to stimulation of the dorsal medulla. Within 2·5 sec of the onset of stimulation (3 V, 2 msec, 70 c/s) a tremendous pressor response began, reaching a maximum in about 25 sec. Careful examination of the figure reveals increased pulse pressure (augmentation) on the 6th beat after onset of stimulation. At the peak of the response pulse pressure had increased from a control level of 18 to 62 mm Hg. This is superimposed upon a marked elevation in diastolic pressure, which is interpreted to indicate increased peripheral resistance. It is characteristic that such maximum increases in blood pressure are achieved only when vasoconstriction and cardio-augmentation occur simultaneously. The electrode was then lowered 1 mm ventrally and the response illustrated in Fig. 3 changed to one in which pulse pressure remained relatively constant,

while the maximum mean pressure attained was some 50 mm less than that shown in the figure. The vertical dotted lines in Fig. 3 are spaced 10 sec apart; numbers between the lines indicate the number of heart beats in that period. It is clear that no significant increase in heart rate occurred at the time that both vasoconstriction and cardio-augmentation were induced by the stimulus.

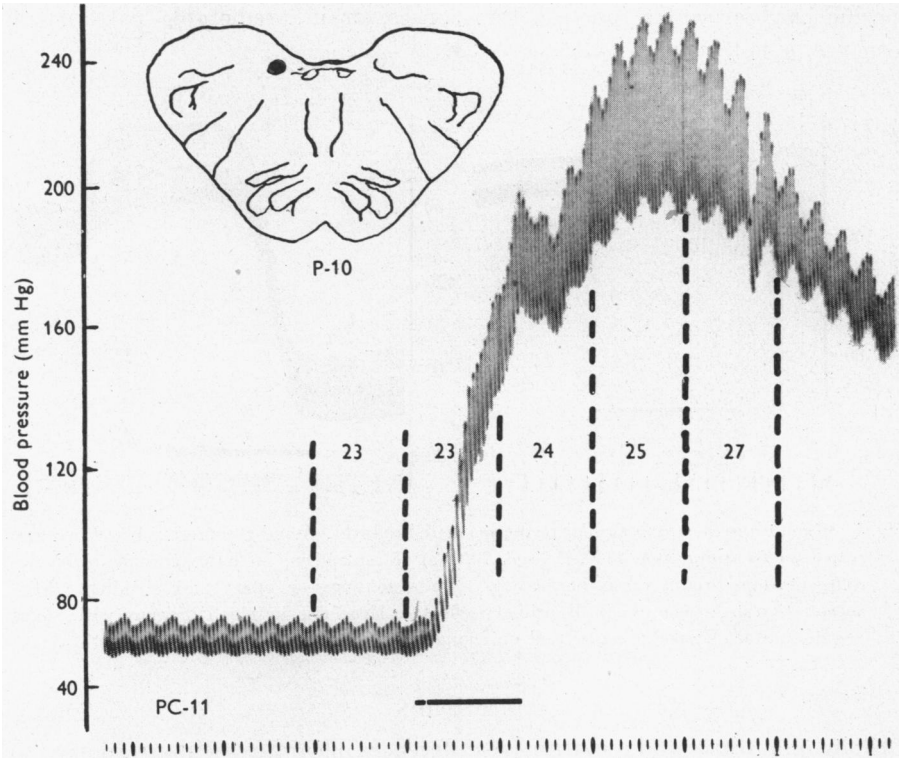


Fig. 3. Mixed cardiovascular response in the cat to stimulation (3 V, 2 msec, 70 c/s) of brain stem, horizontal bar. Note large rise of blood pressure with augmented pulse pressure and lack of significant cardio-acceleration. Broken vertical lines are spaced 10 sec apart; numbers between lines represent number of heart beats/10 sec.

### *Reflex responses*

Figure 4 shows that separation of cardiovascular responses can also occur by reflex stimulation. In parts A and B of this experiment, taken from two different dogs, the central end of the cut left vagus nerve was stimulated at 5 V, 2 msec, 100 c/s. In each case the right vagus nerve had also been cut. Part A shows primarily a modest pressor effect and a most striking cardio-acceleration occurring within a few seconds of the onset of stimulation. The origin and central connexions of the afferents in the left vagus nerve, whose

stimulation results in sympathetic cardio-acceleration, are not known. In part B similar central left vagus stimulation in another animal resulted in a prompt large pressor response with slight augmentation of the pulse pressure but with no increase in heart rate. In each animal, moreover, variation of stimulation parameters resulted in marked changes in the type of cardiovascular response. Whether or not specific cutaneous and visceral afferents result in activation of specific cardiovascular functional responses, or in predictable patterns of response, is not known.

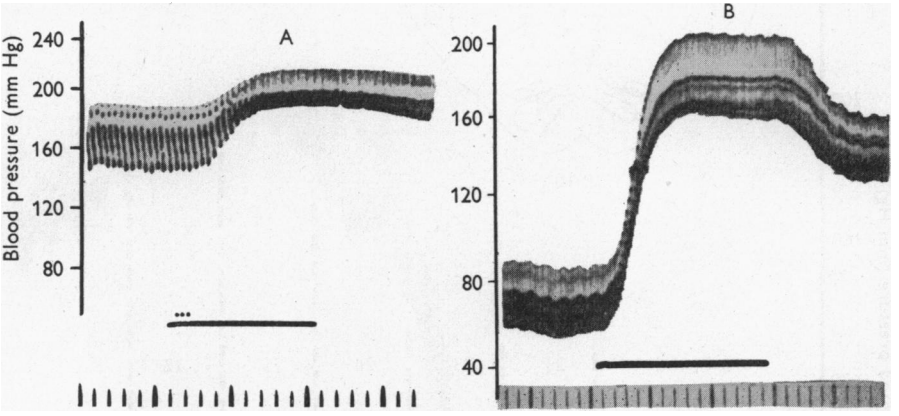


Fig. 4. Mixed types of cardiovascular response elicited reflexly. A and B represent blood pressure responses to stimulation (5 V, 2 msec, 100 c/s) of central end of left vagus nerve in two different dogs; right vagus nerve cut. Note slight pressor effect and striking cardio-acceleration in A, whereas in B primary effect is large rise in blood pressure with slight augmentation of pulse pressure and no change in heart rate. Time marker, 2 sec.

## DISCUSSION

Despite qualitative and quantitative differences in cardiovascular responses to electrical stimulation throughout the medulla, certain generalizations are permissible.

(1) The most commonly elicited response is vasoconstriction, either alone or associated with cardiac and adrenal effects. For the present it seems most reasonable to ascribe this to the relatively large number of central fibres or cells representing vasoconstrictor innervation of the blood vessels.

(2) Analysis of pulse pressure changes, correlated with reports of dynamic effects of sympathetic trunk stimulation, indicates that within the network of the vasomotor centre are cells or fibres whose stimulation results in increased force of myocardial contraction. Although commonly associated with simultaneous vasoconstriction, such cardio-augmentor activity is sometimes seen as the only significant result of brain stem stimulation. This response is readily seen in animals with spinal cord transection at the T4–T5 level.

(3) These experiments confirm anew the concept of cells or fibres in the lower brain stem whose activation results in secretion by the adrenal medulla. In addition, they indicate that the common occurrence of adrenal secretion necessitates careful attention to the latency of response to stimulation of the brain stem. Adrenal secretion results in both chronotropic and inotropic changes in cardiac activity. The determination of cardio-acceleration or cardio-augmentation on the basis of sympathetic activation via stimulation of the brain stem requires one of two procedures: (*a*) the preparation must be adrenalectomized and vagotomized, or (*b*) only those responses which occur within a few seconds after onset of stimulation can be considered valid.

(4) In the vagotomized animal cardio-acceleration via sympathetic pathways has never been observed when the dorsal half of the medulla is stimulated. The few positive responses obtained resulted from stimulation of the ventro-lateral medulla, in areas generally devoid of significant pressor activity. On the other hand, very significant sympathetic acceleration can be achieved by reflex activation.

(5) Finally, we cannot at this time assess the role of venomotor responses to stimulation of the brain stem. Until definite information on this point is available, any interpretation of central regulation of cardiovascular function must take into account the possibility of venomotor participation.

On the basis of these findings certain promising areas of investigation require further study. It will probably be necessary to re-examine cardiovascular responses to stimulation of the brain stem, using smaller electrodes. In order to differentiate types of response, it is necessary to excite far fewer fibres than is the case with usual stimulation procedures. It is possible that the different types of responses, usually occurring in various combinations, could then be elicited in 'pure' form.

It appears also that re-evaluation of the role played by different levels of the brain stem in cardiovascular regulation is necessary. Our results emphasize important medullary control of myocardial contractility. Some of our unpublished results, as well as those of McQueen, Browne & Walker (1954), indicate that this control is not restricted to the medullary level. Sympathetic regulation of heart rate does not appear to be integrated at the medullary level. A significant number of blood vessels appear to be under control of nervous mechanisms that also have no integrated representation in the medulla (Uvnäs, 1954; Lindgren, 1955). It seems essential to us that the description of cardiovascular activation must now be made in terms of what specific mechanism(s) has been activated, and what level(s) of the central nervous system is involved.

SUMMARY

1. Cardiovascular responses elicited by electrical stimulation of the lower brain stem have been studied in bilaterally vagotomized cats and dogs under sodium pentobarbital and alpha-chloralose anaesthesia.

2. Vasoconstriction is the most common response to such stimulation. Often it is associated with adrenal and/or cardiac effects.

3. Within the area studied are sites whose stimulation results in greatly increased force of myocardial contraction. This is sometimes unaccompanied by vasoconstriction and almost always unaccompanied by direct sympathetic cardio-acceleration. The cardio-augmentor responses can be obtained in animals with spinal cord transection at the T4–T5 level.

4. Adrenal responses generally result in simultaneous inotropic and chronotropic effects on the heart, and are characterized by a long latency between the onset of stimulation and the resulting cardiac effects.

5. The dorsal medulla and pons do not contain cells or fibres whose stimulation results in sympathetic cardio-acceleration. Sympathetic acceleration, however, can be activated by reflex stimulation.

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REFERENCES

ALEXANDER, R. S. (1946). Tonic and reflex functions of medullary sympathetic cardiovascular centers. *J. Neurophysiol.* **9**, 205–217.

ANZOLA, J. & RUSHMER, R. F. (1956). Cardiac responses to sympathetic stimulation. *Circulation Res.* **4**, 302–307.

BACH, L. M. N. (1952). Relationships between bulbar respiratory, vasomotor and somatic facilitatory and inhibitory areas. *Amer. J. Physiol.* **171**, 417–435.

CHEN, M. P., LIM, R. K. S., WANG, S. C. & YI, C. L. (1936). On the question of a myelencephalic sympathetic centre. I. The effect of stimulation of the pressor area on visceral function. *Chin. J. Physiol.* **10**, 445–474.

CHEN, M. P., LIM, R. K. S., WANG, S. C. & YI, C. L. (1937). On the question of a myelencephalic sympathetic centre. III. Experimental localization of the centre. *Chin. J. Physiol.* **11**, 367–384.

COTTEN, M. D. (1953). Circulatory changes affecting measurement of heart force *in situ* with strain gauge arches. *Amer. J. Physiol.* **174**, 365–370.

DITTMAR, C. (1870). Ein neuer Beweis für die Reizbarkeit der centripetalen Fasern des Rückenmarks. *Ber. sächs. Ges. (Akad.) Wiss.* **22**, 4–34.

DITTMAR, C. (1873). Über die Lage des sogennanten Gefässcentrums in der Medulla Oblongata. *Ber. sächs. Ges. (Akad.) Wiss.* **25**, 103–123.

LINDGREN, P. (1955). The mesencephalon and the vasomotor system. *Acta physiol. scand.* **35**, Suppl. 121, 1–189.

MCQUEEN, J. D., BROWNE, K. M. & WALKER, A. E. (1954). Role of the brain stem in blood pressure regulation in the dog. *Neurology*, **4**, 1–13.

MONNIER, M. (1939). Les centres végétatifs bulbaires. *Arch. int. Physiol.* **49**, 455–463.

OWSJANNIKOW, P. (1871). Die tonischen und reflectorischen Centren der Gefässnerven. *Ber. sächs. Ges. (Akad.) Wiss.* **23**, 21–33.

PEISS, C. N. (1956). An evaluation and extension of the concept of a medullary vasomotor center. *Abstr. XX int. physiol. Congr.* p. 715.

PEISS, C. N. (1957). Sympathetic cardioaccelerator center in the medulla. *Fed. Proc.* **16**, 100.

PEISS, C. N., MIDDO, R. T., RANDALL, W. C. & JONES, D. S. (1956). Cardiodynamic responses to electrical stimulation of the lower brain stem. *Fed. Proc.* **15**, 142.

PITTS, R. F., LARRABEE, M. G. & BRONK, D. W. (1941). An analysis of hypothalamic cardiovascular control. *Amer. J. Physiol.* **134**, 359–383.

RANDALL, W. C. & ROHSE, W. G. (1956). The augmentor action of the sympathetic cardiac nerves. *Circulation Res.* **4**, 470–475.

RANSON, S. W. & BILLINGSLEY, P. R. (1916). Vasomotor reactions from stimulation of the floor of the fourth ventricle. Studies in vasomotor reflex arcs. III. *Amer. J. Physiol.* **41**, 85–90.

SCHEIBEL, M. & SCHEIBEL, A. (1958). *International Symposium on the Reticular Formation*, Henry Ford Hospital. Detroit: Little, Brown and Co.

UVNÄS, B. (1954). Sympathetic vasodilator outflow. *Physiol. Rev.* **34**, 608–618.

WANG, S. C. & RANSON, S. W. (1939). Autonomic responses to electrical stimulation of the lower brain stem. *J. comp. Neurol.* **71**, 437–455.