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THE ANTAGONISTIC CARDIAC NERVES AND HEART RATE[1].

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It is well known that section of the vagi nerves in the neck is followed by an intense cardiac acceleration which is mostly due to the unopposed influence of the cardio-accelerator nerves [Einbrodt, 1859; Boehm, 1875; Anrep, 1880; MacWilliam, 1893; Nolf and Plumier, 1904; Stewart, 1907; Petioky, 1913]. It may be likewise expected that the extirpation of the cardio-accelerator nerves in normal animals would be followed by a marked bradycardia; this, however, is not the case [Samaan, 1935] and the aim of the present communication is to study the relative effects of the antagonistic cardiac nerves on the heart rate.

Methods.

Thirty-one experiments were performed on dogs weighing from 7–23 kg.; chloralosane anæsthesia (0·08 g. per kg., intravenously) was employed, but in a few cases the use of the anæsthetic was omitted and observations were made on decerebrated animals 3–4 hours after the operation. Six experiments were performed on cats which were anæsthetized with numal (0·5 c.c. per kg., intraperitoneally). The heart rate, respiration and blood-pressure were recorded. The rectal temperature was maintained nearly constant (37·4°–37·8° C.) with the aid of an electric warming pad. In all experiments the suprarenal glands were isolated either by "mass ligature" or by tying the suprarenal veins. Artificial ventilation was used in procedures involving the opening of the chest or the section of the spinal cord. In some experiments laminectomy was performed at the level of the second cervical vertebra and a fine silk thread was passed around the cord. Tight ligature of the thread made

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clean-cut transection without injuring the spinal artery. A steel wire fitted with a ball of cotton-wool served to destroy the cord by passing it down the spinal canal.

Adrenaline hydrochloride was injected intravenously in doses varying from 0·002–0·1 mg. per kg.

After denervation of the heart the peripheral ends of the cardiac nerves were prepared for electrical excitation with special non-polarizable shielded electrodes. Each set of nerves was stimulated with induction shocks from a separate inductorium; metronomes were employed in the primary circuits. In a few cases condenser discharges were used.

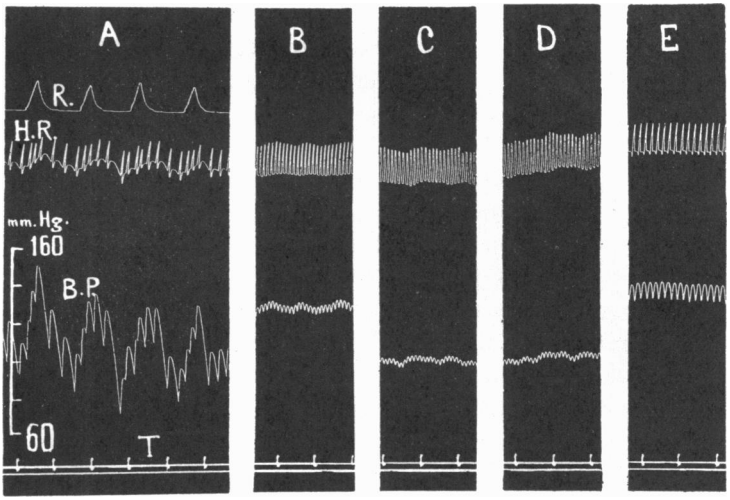

Fig. 1. The heart rate during the process of cardiac denervation. Dog: 14 kg.; chloralosane. A. Normal. B. After cutting the cervical vagi, artificial respiration on. C. After removal of the left thoracic sympathetic chain. D. After excision of the right thoracic chain excepting the stellate ganglion. E. After extirpating the right stellate ganglion. In this and in the following tracings R. denotes respiratory movements recorded with stethograph; H.R. is the heart rate taken with Hürthle's manometer; B.P. is blood-pressure record with mercury manometer; T. is time record in 3 sec. Details in text.

Results.

(i) The heart rate during the process of cardiac denervation.

Fig. 1 is obtained from a typical experiment. It may be noted that cutting one vagus in the neck is generally followed by a slight tachycardia. When, however, the other nerve is cut the heart suddenly exhibits an intense acceleration while the sinus arrhythmia disappears (Fig. 1 B).

It is also apparent that the excision of the right stellate ganglion interrupts the path of the majority of the cardio-accelerator tonic impulses (Fig. 1 E).

Section of the cord in vagotomized animals, whether decerebrated or under numal anæsthesia, is followed by a definite slowing of the heart from 210 beats per min. down to 120–130. Further destruction of the cord is associated with a transient tachycardia which passes away in a few minutes, leaving the heart rate unchanged (about 120 per min.). Under chloralosane anæsthesia, however, transection of the cord in vagotomized dogs is not associated, in many cases, by any appreciable change of the heart rate (about 220 per min.), while destruction of the cord in such cases is followed by a permanent slowing down to 120. Further extirpation of the cardio-sympathetic nerves in the chest is without effect; thus suggesting that under chloralosane the cardio-accelerator neurones in the cord exert a tonic influence.

(ii) EFFECT OF SEPARATE AND OF SIMULTANEOUS STIMULATION OF THE ANTAGONISTIC CARDIAC NERVES.

(*a*) *Vagal stimulation.* The cardiac slowing in animals with denervated hearts appears at the first beat which follows the onset of the stimulation and persists at a practically constant rate throughout the period of excitation (Fig. 2 A). The degree of the bradycardia is dependent on the strength and on the frequency of the individual stimuli. It is also observed that the repetition of a given stimulation is associated with identical effects. As soon as the excitation is removed the heart returns to its automatic rate within 1–3 sec. In some cases, however, it shows a definite acceleration for a few seconds, and then returns gradually to its resting rate.

(*b*) *Sympathetic stimulation.* The onset of the cardiac acceleration appears $2\frac{1}{2}$–8 sec. after the commencement of the excitation, and the maximal rate is reached in 7–12 sec. (Fig. 2 B). Later, however, it slows down slightly and is then maintained at a nearly constant rate. Excitation of the branches derived from the right stellate ganglion provokes a stronger effect than that of any other cardio-sympathetic fibres. When the stimulation is discontinued the heart maintains the fast rate for a few seconds and then gradually slows down to reach the automatic rate in 15–63 sec. It may be noted that the frequent repetition of a given stimulus within short intervals of time is accompanied with progressively diminishing effects. If, however, a period of a few minutes is allowed for recovery, the responses of the heart are practically identical.

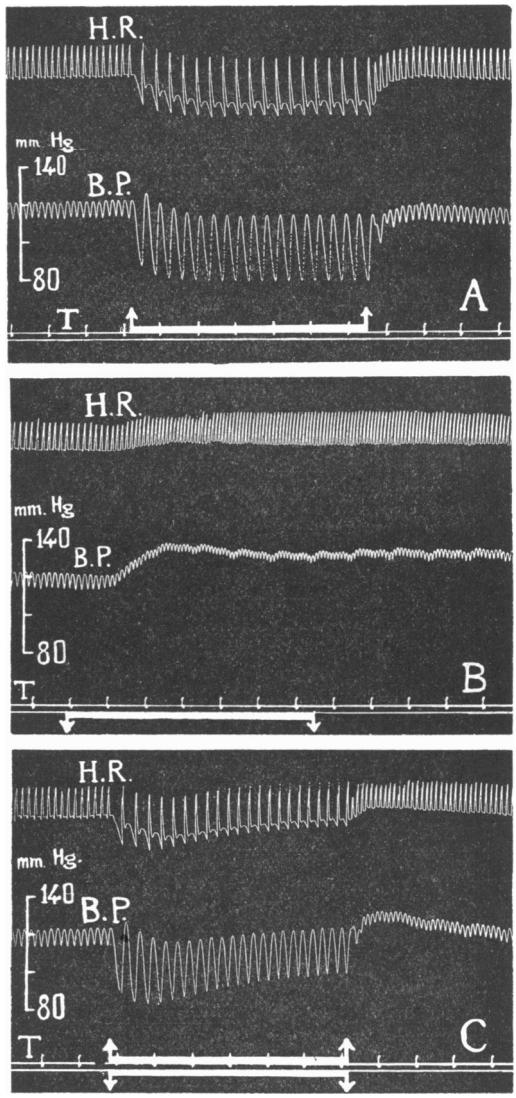

Fig. 2. Dog: 15 kg.; decerebrated; suprarenal glands isolated. All the cardiac nerves are cut. A. Between the two arrows ↑ ↑, stimulation of the peripheral end of the left vagus nerve (coils 12·3 cm. apart). Slowing of 61 beats per min. below the rate of the denervated heart. B. Between the two arrows ↓ ↓, stimulation of the cardiac nerves arising from the right stellate ganglion (coils 7·4 cm. apart). Acceleration of 93 beats per min. above the rate of the denervated heart. C. Between the two pairs of arrows ↑ ↑ and ↓ ↓, the same stimuli which were used in A and in B are applied simultaneously. Slowing of 44–57 beats per min. below the rate of the denervated heart. The tracings are to be read from left to right. Further details in text.

(c) *Simultaneous stimulation of the vagal and of the sympathetic cardiac nerves.* Table I shows the effects of two simultaneous stimuli, each of which when applied alone has nearly the same relative influence upon the heart rate. It is evident that the vagal impulses predominate. Indeed, Fig. 2C shows that as soon as the stimuli are applied, the heart

TABLE I.

Experiment No.	Denervated heart rate per min.	Average change in rate with vagal stimulus beats	Average change in rate with sympathetic stimulus beats	Average change in rate with both stimuli simultaneously beats
3—Cat	128	−34	+ 41	−30
9—Dog	116	−45*	+ 44†	−44
	116	−45*	+ 62†	−40
	116	−45*	+ 78†	−38
	116	−45*	+102†	−31
22—Dog	124	−60	+ 92	−49
	124	−60	+ 66	−58
	124	−76	+ 48	−76

* Stimulus unchanged. † Stimulus augmented.

It may be noted in Exp. 22 quoted above that the stimuli are unaltered but are repeated quite frequently. The vagal stimulus becomes more effective while the sympathetic one becomes less effective.

slows down immediately to the vagal rate for a few seconds (4–7 sec.), then it accelerates a few beats and maintains it during the stimulations. On removal of the excitations the heart exhibits an intense tachycardia (an increase of 100 beats per min.) which gradually subsides to reach the automatic rate in about 25 sec.

(iii) THE RELATIVE EFFECTS OF THE ANTAGONISTIC CARDIAC NERVES.

It is evident from Fig. 3A that a sympathetic stimulus, which by itself would increase the heart rate from 115 to 170 beats per min., if applied during vagal stimulation increases it by 10–12 beats per min. only. Again, a vagal stimulus, capable of reducing the rate from 115 to 62 per min., if applied during a sympathetic stimulation will reduce the cardiac frequency from 165 to 70 per min. (Fig. 3B).

(iv) ADRENALINE AND VAGAL INHIBITION.

The changes in the heart rate in response to vagal stimulation are studied during the administration of adrenaline. Small doses of this drug, although provoking a marked increase in the rate of the denervated heart, yet sensitize it to vagal impulses (Fig. 4C). With larger doses,

however, the influence of the vagi is reduced or may even be abolished (Table II). Not uncommonly cardiac irregularities may be provoked with vagal stimulation.

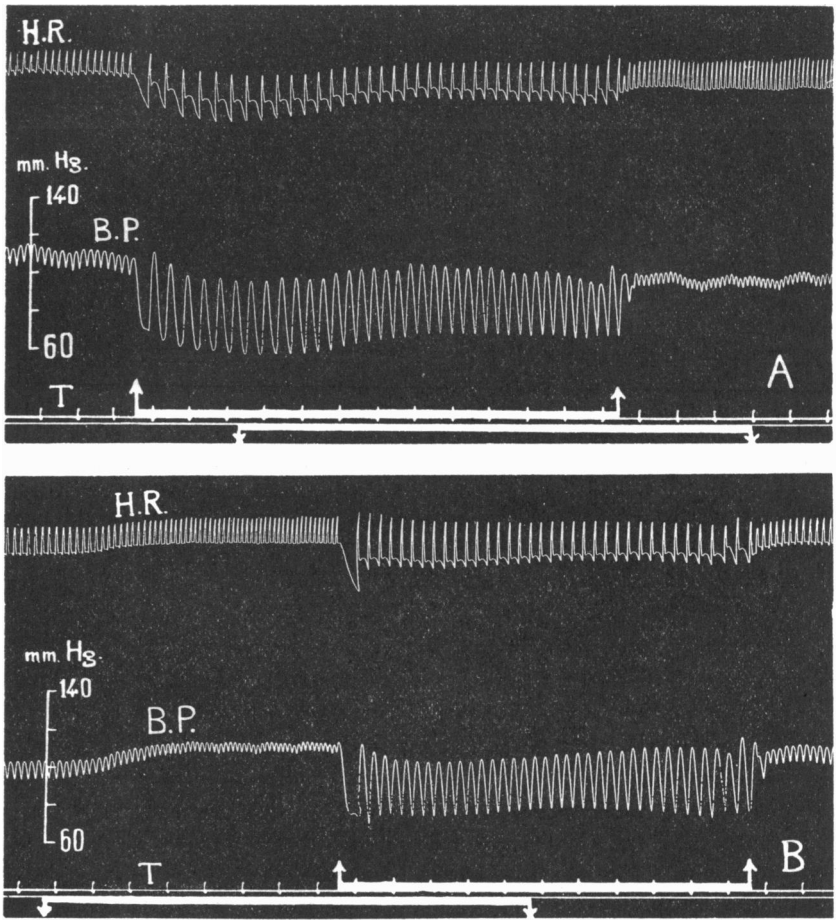

Fig. 3. The relative effects of the antagonistic cardiac nerves. Dog: 12 kg.; chloralosane; suprarenal glands are isolated. All the cardiac nerves are cut. A. The vagal stimulation (between the two arrows ↑ ↑) is applied before the onset of the cardio-sympathetic stimulation (which is indicated by the two arrows ↓ ↓) and is terminated during the application of the latter. B. The cardio-sympathetic stimulation (as indicated by the arrows ↓ ↓) is applied before the commencement of the vagal stimulation (which is shown by the arrows ↑ ↑) and is removed during the action of the latter. Note the predominating effect of the vagal inhibition. To be read from left to right. Details in text.

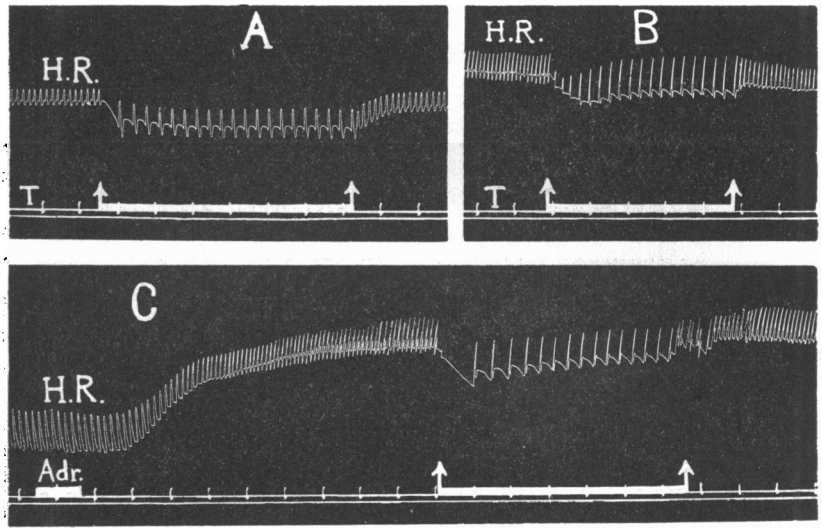

Fig. 4. Adrenaline and vagal inhibition. Dog: 12 kg.; chloralosane; suprarenal glands isolated. All cardiac nerves are cut. A. Stimulation of the peripheral end of the right vagus applied between the arrows ↑ ↑ (coils 14·2 cm. apart). B. The same vagal stimulation as used in A, applied 30 sec. after the administration of 0·20 mg. adrenaline. C. At Adr. 0·10 mg. adrenaline was injected intravenously, and between the arrows ↑ ↑ the same vagal stimulation as used in A was applied. Details in text.

Discussion.

The observations above recorded show that the antagonism between the cardio-accelerator and the cardio-inhibitory nerves on the rhythm of the ventricular muscle is not perfect; the vagal impulses always predominate in the sense that the final frequency at any moment is not the algebraic sum of the two components. Indeed Baxt [1875], Hunt [1899], Rothberger and Winterberg [1911], and Vaquez and Donzelot [1925] have shown that the vagi exercise a powerful restraining action upon the heart. It has also been observed that the repeated stimulation of the sympathetic fibres is attended not only by progressively diminishing responses but also by sensitization of the heart to vagal stimuli (Table I). Furthermore it is noted that small doses of adrenaline—a typical sympathico-mimetic drug—renders the cardiac muscle more susceptible to vagal impulses. This observation supports Mathieu [1904], Asher and Rodt [1912], Sollmann and Barlow [1926] and Beccari [1933]; and indeed the peripheral influence of adrenaline on vagal inhibition may have played a part in the observations of Stella [1932] on adrenaline bradycardia.

TABLE II.

Experiment No.	Denervated heart rate per min. before adrenaline	mg. adrenaline per kg. intravenously	Average heart rate with adrenaline before stimulation beats	Average heart rate with vagal stimulus applied during adrenaline action beats	Percentage inhibition
28—Dog	125	—	—	68	45·6
	125	0·003	141	51	63·8
	125	0·008	158	56	64·5
	125	0·050	190	77	59·5
	125	0·070	234	124	47·0
	125	0·100	278	240*	13·6
	125	0·100	284	280–284	0·0
	125	—	—	66–68	45·6–47·2

* Irregular.

These findings may also afford an explanation of why the elimination of the vagi in normal animals is followed by a very marked tachycardia, while the extirpation of the cardio-sympathetic nerves in normal dogs is only attended by a trivial slowing of the heart. The possibility, however, that the tonic impulses of one set of cardiac nerves may change in intensity after the elimination of the antagonistic set, cannot be excluded.

In the few cases in which the heart rate exhibited a definite acceleration after the conclusion of the vagal stimulation, it was possible to trace the tachycardia to the presence of accelerator fibres in the vagi. Thus stimulation of the same nerves after the administration of atropine is associated with delayed pure cardiac acceleration. Section of the vagi peripheral to the heart does not affect the result. The same phenomenon is observed in atropinized dogs deprived of the thoracic sympathetic chains a few weeks previously. This supports the observations of François-Franck [1884], Arloing [1896], Tulgan [1923] and Jourdan and Nowak [1934].

SUMMARY.

1. The relative effects of the antagonistic cardiac nerves upon the heart rate have been studied in anæsthetized and in decerebrate animals (cats and dogs). The vagus predominates over the cardio-sympathetic nerves in the sense that a moderate vagal stimulation may provoke a bradycardia which will mask the effect of a strong cardio-accelerator stimulation (Figs. 2, 3).

2. Repeated stimulation of the cardio-accelerator nerves, as well as small doses of adrenaline, sensitize the heart to vagal impulses.

3. Chloralosane excites the cardio-accelerator neurones in the spinal cord.

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REFERENCES.

Anrep, B. von (1880). *Pflügers Arch.* **21**, 78.
Arloing, S. (1896). *Arch. Physiol. norm. path.* **8**, 75.
Asher, L. and Rodt, W. E. von (1912). *Zbl. Physiol.* **26**, 223.
Baxt, N. (1875). *Ber. sächs. Ges. (Akad.) Wiss.* **27**, 323.
Beccari, E. (1933). *Arch. ital. Sci. farmacol.* **2**, 338.
Boehm, R. (1875). *Arch. exp. Path. Pharmak.* **4**, 255.
Einbrodt (1859). *Arch. Anat. Physiol.*, Lpz., p. 439.
François-Franck (1884). *Dict. encycloped. scien. med.*, Paris. Article "Grand sympathique."
Hunt, Reid (1899). *Amer. J. Physiol.* **2**, 395.
Jourdan, F. and Nowak, S. J. G. (1934). *C. R. Soc. Biol.*, Paris, **117**, 234.
MacWilliam, J. A. (1893). *Proc. Roy. Soc.* **53**, 464.
Mathieu, X. (1904). *J. Physiol. Path. gén.* **6**, 435.
Nolf, P. and Plumier, L. (1904). *Ibid.* **6**, 241.
Petioky, R. (1913). *Pflügers Arch.* **152**, 509.
Rothberger, C. J. and Winterberg, H. (1911). *Ibid.* **141**, 343.
Samaan, Adli (1935). *J. Physiol.* **83**, 313.
Sollmann, T. and Barlow, O. W. (1926). *J. Pharmacol.*, Baltimore, **28**, 159.
Stella, G. (1932). *J. Physiol.* **77**, 68.
Stewart, G. N. (1907). *Amer. J. Physiol.* **20**, 407.
Tulgan, J. (1923). *Ibid.* **65**, 174.
Vaquez, H. and Donzelot, E. (1925). *Les troubles du rythme cardiaque*, p. 36. Paris, J. B. Baillière et Fils.