A NEW CONCEPTION OF THE FUNCTION OF THE GENERAL VASODILATOR REFLEXES

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by

R.J.S. McDOWALL, D.Sc., M.B., Ch.B.

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ARRANGEMENT OF THESIS

1. A short introduction outlining the essential facts regarding the general vaso-depressor reflexes.

2. An annotated account of the discovery of these reflexes.

   (a) The afferent pathways.

   From the cardio-aortic region.

   From the carotid sinus.

   From other regions.

   (b) The vasodilator centre.

   The effect of higher centres.

   (c) The efferent pathways.

   The regions innervated.

3. The Function of the Depressor Mechanisms.

   A critical statement of existing theories regarding these functions.

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   Discussion putting forward a new view regarding the function of the general depressor mechanisms.

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INTRODUCTORY

The cardio-depressor and vasodepressor reflexes

These are a number of reflexes which have afferent and efferent paths to and from the medulla and which bring about depression of the activity of the heart and dilatation of the blood vessels.

The chief afferent paths of both categories commence in the cardio-aortic region and at the carotid sinus at the bifurcation of the common carotid artery, from which impulses pass by way of the aortic nerve and the carotid nerve (a branch of the glossopharyngeal) respectively.

The efferent pathways are in the case of the heart the vagus nerves, and in the case of the blood vessels the spinal cord, the posterior roots and the sensory nerves. Whether, however, the actual fibres concerned are exactly the same as the sensory fibres is a subject of discussion, and in view of the recognition of sympathetic vasodilator fibres it may yet be shown that all the fibres concerned in vasodilatation do not all pass out by the posterior roots.

Much of the early literature was devoted to the study of the relation of blood pressure to the heart rate, to which attention was first drawn by

Marey (1857) who considered it to be due to a direct action on the heart, but Bernstein (1867) and Nawrocki (1874) and subsequently Marey himself (1888) agreed that the vagus nerve was concerned in the relationship. Ludwig (1865) considered that the blood pressure might stimulate the vagus centres, but Bernstein (1867) postulated a reflex action without defining the paths. The first definite contributions in the latter direction were those of Cyon (1866), and from this time a very large amount of work has been done. This is reviewed systematically below.

Note. Throughout it is to be understood that the thesis is limited to the reflexes referred to above which affect the circulation as a whole. It therefore does not include local dilator reflexes which are concerned with increasing the blood supply to localised regions. Nor does it include the vaso-dilator fibres which pass out by the sympathetic and which are believed to be concerned in dilating the blood supply of active muscles. Nor are included such vasodilator mechanisms as are concerned in the regulation of body temperature.

THE AFFERENT PATHWAY

The aortic nerve.

Historically the first part of the efferent pathway to be described was the aortic depressor nerve of the rabbit, the effect of stimulation of which was discovered by Cyon in Ludwig's laboratory in 1866. It had previously been described by Theile in 1825.

Wooldridge (1883) described a nerve in the dog arising from the arch of the aorta and the heart. He did not appreciate its similarity to the depressor of the rabbit and called it the aortic nerve, a name now generally preferred.

In the rabbit and the hare the nerve is usually separate, but in most animals it is bound up with the vagus or sympathetic trunk. In man it corresponds to a twig of the external branch of the superior laryngeal nerve.

A great deal of detailed anatomical study of the nerve has been made, but the results serve to emphasise great variability in different species and from animal to animal. These studies do not throw any light on the function and are therefore not included herein. Extensive reference to the anatomical literature is given in the monographs of Heymans and, especially, that of Koch. It is interesting/

interesting to note that even where a separate nerve is present stimulation of the central end of the vagus gives a similar depressor response, but no differentiation of function has been made out for these fibres within the vagus. In the cat and the monkey a similar state is present, (Langley, 1912; Bernhardt, 1868, see Koch; Aubert & Roever, 1868; Kowalewsky & Adamuk, 1868). In the frog also it is bound up in the vagus trunk and less active than in the mammal, (Nikiforowsky, 1912-1913). The aortic nerve itself is made up of different sizes of fibres, but no special function has been allotted to the different fibres. It may be that some are pressor. We may indeed suggest that the nerve supply of the aorta is analogous to that of the carotid sinus. They are corresponding structures developed from the second and fourth branchial arches.

CENTRAL CONNECTIONS OF THE AORTIC NERVE

According to Sharpey-Schafer & Walker (1923) and Koch (1931), the nerve does not belong to the autonomic system, as might be expected from its close association and even connection with the vagus and sympathetic. They considered it to be essentially a sensory nerve like the fibres of a posterior root. Sarkar (1922) has pointed out that although the nerve may pass to the ganglion nodusum of the vagus, it passes through in a separate bundle, while Fuchs (1897) made out that the fibres passed into the medulla with the inferior part of the trunk of the glossopharyngeal.

The left nerve is stated generally to be more active than the right, an observation that may be related to the fact that the aortic nerve is the nerve of the fourth aortic arch, which on the left side eventually becomes the aorta.

Some authors have claimed (Spallita and Consiglio, 1892) that the fibres concerned with cardiac centres are different from those subserving the vasomotor centres, for they have found that on dividing the internal branch of the accessory there is a fall of blood pressure without cardiac slowing. Mirto & Pusateri appear to have confirmed this by finding degenerated fibres in the aortic nerve after intra-

cranial section of the accessory. Koch, however, suggests from the work of Waller (1856) and others that the observation of Spallita and Consilio were the result of damage to the efferent pathway of the vagus. Danielopolu, Aslan & Marcu (1926) have described in the dog a nerve filament passing from the heart and aorta to the inferior cervical ganglion. Stimulation of its central end may sometimes produce cardio-inhibitory effects, but sometimes the reverse. Marmorstein (1929), also Karasék (1933) have emphasised the intimate connection between the aortic depressor and the sympathetic, but Marmorstein, Linkatscher & Tschernik (1934) have found that although there is a variable point of fusion the aortic depressor maintains its functional individuality as far as the inferior cervical ganglion.

THE ORIGIN OF THE AORTIC NERVE

In his original description of the nerve Wooldridge states that it arises from the left ventricle and the aorta. This was supported by the findings of Kazem Beck (1888) and Smirnow (1886) the latter on the basis of degeneration experiments; but it is agreed that the multiple anastomoses with many fibres of the aortic plexus in this region make dissections and even degeneration experiments in this region very difficult. Their results were supported by the later work of Mollard (1908) and Perman (1924).

In 1902, Koester & Tschermak by degeneration experiments shewed that the aortic nerve arose from fibrils which took origin from the aortic arch and the roots of its chief branches. No fibres could be found by these authors arising from the heart itself. This conclusion is strongly supported by Tello (1924) from embryological studies, who points out that the fourth aortic arch from which the aorta arises has no aortic nerve, but that the latter appears only when the aortic arch takes up its position in the thorax as a single arch. No fibres could be found reaching the heart which is of course in action at the branchial arch stage, and we have no information regarding the occurrence of nerves

corresponding to the aortic nerve in arches of fishes.

On the other hand it is shown from the work of Kochmann (1906), of Perman (1924), of Koch ('93'), and of Daly & Verney (1927) that if the aortic nerve is not itself distributed to the heart, the heart possesses afferent fibres with a similar function. It may be that the afferent fibres are those in the vagus as distinct from the aortic nerve. The evidence for these fibres is discussed below.

The histology of the nerve in the rabbit has been specially studied by O'Leary, Heinbecker & Bishop (1934), who compared the action currents and fibre counts with the responses to increase of stimulus. They concluded that there were afferent vagal fibres present both myelinated and non-myelinated and also that not all the afferents are depressor in effect. They found considerable variation from animal to animal, the number of myelinated fibres being from 150 to 600, but they claim there was some correspondence between the size of the nerve and the maximum depression obtainable. It is a little difficult to assess such results as the response is affected by many factors, especially the degree of anaesthesia, which may easily vary during the progress of an experiment.

The view that the aortic nerve of the rabbit is much more mixed than is generally supposed is supported by the work of Karasek (1933), who examined 125 rabbits and concluded that it contains sympathetic as well as vagal fibres.

EVIDENCE THAT THE AORTIC NERVE IS AFFERENT

It was the fact that stimulation of the central end of the aortic nerve in the rabbit caused slowing of the heart and a fall of blood pressure which led to the discovery of its function (Cyon & Ludwig 1866). Stimulation of the peripheral end of the nerve, on the other hand, is without effect (In the cat, Bernhardt 1868, Kowalewsky & Adamük 1868; in the dog, Koch ; in the rabbit, Stelling 1867, Tschirwinsky 1895, Schafer & Walker 1922, Danielopolu 1927, Cyon & Ludwig 1866, Bézold 1863, Dreschfeld 1867, Aubert & Roever 1868). In studying the central end of the vagus, F.Franck (1880) found that the slowing occurred if one vagus was intact, but not if cut, and concluded that the phenomenon is a reflex by the vagus. Lehndorff (1908) found that the vascular and cardiac effects sometimes showed as two stages.

The aortic nerve is very easily stimulated by almost any variety of stimulus. Its sensitivity to slight mechanical changes has been pointed out by Cyon (1898), Sewall & Steiner (1885), Sollman & Brown (1912), Sharpey-Schafer (1920). It must be admitted, however, that even pulling on the nerve, which has been a usual method of stimulation, is not very conclusive, since in small animals at least the adjacent carotid sinus, which is so sensitive to mechanical change, is liable to be stimulated.

ELECTRICAL CHANGES

At each cardiac impulse, impulses have been found to pass up the nerves (Köster & Tschermak, 1902, Einthoven, 1908). Later Adrian, in 1926, using valve amplifiers and a capillary electrometer, showed that impulses passed up not only at systole, but also at the occurrence of the dicrotic wave. He has shewn that there are bursts of impulses, but silence during diastole, and emphasises that it is the change of pressure which is the essential stimulus. Similar work was done by Verzár & Peter (1926), and by Bronk (1931). Rijlant also confirmed these results (1932) using a cathode ray oscillograph with a valve amplifier. Rijlant did not observe the silence during diastole, and suggests that this only occurs with low pressures, and this view has been independently supported by Partridge (1932). Bronk & Stella (1932), Karasek (1933), Verzár & Peter (1926), also obtained a continuance of impulses during diastole.

THE NORMAL METHOD OF STIMULATION

The first experiments since those of Bernstein (1867), referred to already, which suggested that the blood pressure in the aorta was concerned in the stimulation were those of Sewall & Steiner (1885), who found that the rise of blood pressure caused by

clipping the carotid arteries was increased if the aortic nerves were cut. Konow & Stenbeck (1889) later observed an increased irregularity of the blood pressure during asphyxia if the aortic nerves were cut. Complete proof was, however, afforded by Koester & Tschermak (1903) who shewed that distension of the isolated aorta with fluid caused an electrical variation in the aortic nerve. Closure of the aorta in the animal had a similar effect. In 1921 similar results were obtained by Osborne in the right vagus by means of the string galvanometer. Ligation of the aorta or injection of adrenaline caused marked electrical changes, but reduction of the internal pressure by bleeding caused the impulses to cease.

Using the rate of the heart as an indicator, Eyster & Hooker (1907-8) found that tying the descending aorta set up the cardioinhibitory reflex. Kochman (1906) obtained slowing on injection of Ringer's solution into the cardiac end of the innominate artery of a rabbit and obtained a fall of blood pressure.

There has been general agreement amongst most workers on the subject that the pressure in the aorta is a normal stimulus. Verworn (1903), Bayliss (1908), Hering (1907) and Heymans (1933) may be mentioned.

The last-named, with Ladon (1925) proved the matter still further with cross-circulation experiments. They cut through all structures connecting the body with the head except the vagus and sympathetic, but kept the head alive by blood from another animal. They were thus able to demonstrate conclusively that pressure changes in the aorta brought about changes in eardiac frequency by a nervous mechanism involving the vagus and aortic nerves.

Some discussion has taken place as to how far pressure changes in the heart play a part, in spite of the early anatomical work, and the work of Cyon (1866).

Eyster & Hooker (1908) in their experiment were unable to obtain cardiac slowing if they occluded the aorta close to the heart or if the heart was distended through a cannula independently of the aorta. Daly & Verney (1926), on the other hand, using another technique obtained positive results. They short-circuited the arch of the aorta by means of a tube from the beginning of the aorta to the descending aorta, and found that a cardiac slowing could still be produced by clipping the descending aorta, although changes in the arch of the aorta had thus been excluded. Koch suggests that these experiments do not exclude a dragging on the aortic

arch, but on the other hand Köster & Tschermak had in 1902 been unable to obtain any positive results from stretching of the aortic arch, except by internal pressure. Daly & Verney (1927) however, have supported their results further by finding a slowing of the heart by stretching it by means of a negative external pressure, keeping the internal pressure constant. It can therefore be concluded that the evidence is in favour of the pressure within the left ventricle itself being a contributory factor in the stimulation.

The subject has not been much studied in animals other than mammals, but Kuno & v. Brucke (1914) found that in the frog a rise in the pressure in the aorta caused a fall of blood pressure and a slowing of the heart.

THE CAUSE OF THE CARDIAC SLOWING

In those animals such as the cat, in which the aortic nerve may be inseparable from the vagus, stimulation of the central end of one vagus causes a slowing of the heart. This is best seen if the

other vagus is intact (Frank, 1880), but, as pointed out by v.Brucke (1917), if both vagi are cut in a suitable animal a slowing of the heart accompanies the fall of blood pressure. This I have confirmed in chloralosed cats, and it is presumably due to an inhibition of the cardio-accelerator mechanism. See also Bronk, Fergusson and Solandt (1934) in relation to the carotid sinus. Bainbridge (1914) was apparently unable to obtain any slowing attributable to a reduction of sympathetic drive. It would seem that the conditions of his experiments negatived his results, or it may be that he did not wait sufficiently long to allow the heart to settle down after section of the vagi. Or possibly the morphine and ether used interfered with his results.

THE CAROTID SINUS

The carotid sinus is a bilateral dilatation of the common carotid artery where it divides into its external and internal branches. The existence of the dilatation had been noted by the older anatomists and was mentioned by Meyer (1876), Schafer (1878) and Binswanger (1879). Anatomists generally had also remarked upon the adjacent carotid body and its close nervous connection, e.g. Cunningham. The somewhat remarkable nervous supply to the region had been studied and it had been noted that the sinus is small or absent in children.

That the afferent stimuli arose from the carotid was noted by a number of investigators, but it was not, however, until the work of H.E. Hering published in 1923 that the importance of the sinus as a regulator of the circulation was appreciated, and since that time our knowledge of its physiology has been greatly extended, especially by Heymans, by Koch and their co-workers.

The sinus is present in all the usual laboratory animals, but in the ox it is at the origin of the occipital artery (de Castro 1928, van Damme 1933) which in such animals really corresponds with the carotid artery. Montane & Bourdelle (1917), Chauveau & Arloing (1915).

It has been shewn by de Castro (1926) that the wall of the sinus is particularly rich in fibres and nerve endings which are not to be seen in any other region apart from the aorta, in which are the endings of the aortic nerve.

Some discussion has taken place with regard to the function of the carotid body which is so close against the sinus that it cannot be satisfactorily separated. It has generally been regarded as a ductless gland, since it contains clumps of cells which stain with chromic acid like the medulla of the suprarenal gland. De Castro suggests, however, that the yellow coloration produced is due to lipoid. It has been shewn by de Castro to contain sinusoidal capillaries and to have a very rich nerve supply (1928), and it is suggested that it is essentially a sensory organ, possibly concerned with the quality of the blood. Fibres pass from the body to the glosso-pharyngeal and vagus, and it apparently receives an efferent sympathetic supply from the superior cervical ganglion. Although the very extensive nerve supply is suggestive of an important function, no definite evidence is available. The cells are somewhat glandular in appearance and the general structure reminiscent of the suprarenal medulla. No active substance has, however, been extracted from the body.

THE NERVE SUPPLY OF THE SINUS CAROTICUS.

The nerves of the region of the sinus were studies by Braencker (1922) and by Gerrard & Billingsley (1923), who traced to it branches of the glosso-pharyngeal.

In 1926, the minute anatomy of the part was extensively studied by de Castro, and his observations have since been extended by Heymans (1928), Daniel-opulu & Manescu (1928), Kahn, (1929) and Hovelaque, Maes, Binet & Gayet (1930), Cordier and Coulouma (1932). The latter, with all the literature at their disposal, have studied the innervation of the sinus in the dog, the cat and man.

It has now been amply shown that the glosso-pharyngeal is the chief nerve of supply, and there is evidence that one twig, sometimes called the sinus nerve of Hering and de Castro, is the most important. In this connection it is interesting to note that even in 1885 Knoll pointed out that stimulation of the central end of the glosso-pharyngeal near the head had the same effect as stimulation of the central end of the aortic nerve.

According to de Castro (1926), Heymans (1928) and Kahn (1929), fibres also pass to the vagus and

sympathetic, while in 1926 Moissejeff and in 1929 Tournade also pointed out that the sinus nerve was not the only important nerve of the part. The minute size of the nerves renders it very difficult to be dogmatic on this point, and the physiological proof that nerves other than the glosso-pharyngeal are concerned is not very strong. Terni (1931) and also Muratori (1931-2) describe the corresponding structure in the bird as innervated by the vagus and sympathetic, as well as the glosso-pharyngeal. It may be that the different fibres subserve different functions.

The carotid gland of birds appears to have a similar function and the nerve fibres in the gland have been found by Muratori (1932) to be wholly afferent. The carotid body in hens does not lie at the bifurcation but half way along the artery, the reflexes therefore can only be elicited by constriction of the artery behind the body and not between the body and the bifurcation. Thus the carotid body of birds corresponds to both the sinus and the body of mammals (Ara, 1934).

METHODS BY WHICH THE RECEPTORS IN THE SINUS ARE STIMULATED

The first clear proof that a rise of blood pressure in the carotid sinus causes cardiac inhibition and a fall of blood pressure we owe to H. E. Hering. But before his time a number of observers (Czermak, 1866; Thanhoffer, 1875; Concato, 1870; Malerba, 1875; Pagano, 1900; Siciliano, 1900; Wasilewsky, 1876; Carvelli, ; Sollman & Brown, 1912; Erben, 1921; Winterberg, 1923; Scherf, 1924; and others), andeven Hering (1923), had carried out experiments, the results of which we now know were in whole or in part, due to stimulation of the sinus. Some of these concerned the clamping of the carotid, but the results obtained were attributed solely to cerebral anaemia. Marey (1887) had also observed that a rise of arterial pressure caused slowing, and François-Franck (1880) actually recorded that the injection of fluid into the peripheral end of the carotid artery caused slowing.

In 1866, Czermak described the fact that pressure in the neck in men and animals caused cardiac slowing. It was until recently generally assumed that his results were due to stimulation of the vagus nerve, but there seems little doubt that the sinus was stimulated. Concato (1870) alone differentiated

between the vagus nerve and the bifurcation of the carotid. In 1885, Sewall and Steiner observed that after the aortic nerves were cut in rabbits, occlusion of the innominate artery caused a greater rise of arterial pressure with cardiac acceleration and removal of the clip a slowing. They did not apparently pursue the problem further, but like others presumed the changes were centrally produced. Later, Pagano(1900) noted that the region of the bifurcation of the carotid was particularly sensitive to chemical agents, which, if applied, caused cardiac slowing, which nervous section shewed to be due to nervous influences. He also obtained cardiac slowing when he injected defibrinated blood into the carotid, but he did not consider his results specially important. He obtained similar results with injections into the vertebrals, and apparently considered it to be a property of all arteries. The work was continued by Siciliano (1900), who saw the connection of this experiment with clipping the carotids, and emphasised the difference between cutting off the blood supply to the brain by the internal carotid and the effect of clipping the common carotid. Kaufmann (1912) however, who had been working on the effect of occlusion of the

cerebral circulation, described negative results with distension, but actually he hadoverlooked the point that Pagano had referred to the bifurcation of the carotid.

It must, however, in fairness be stated that Kaufmann had also before him the results of many workers which supported his view. The best known are probably those of Francois-Franck (1877), who shewed that in a head isolated from the trunk except for the vagi, but supplied with blood, a rise of cerebral pressure caused cardiac slowing. He concluded that the centres in the brain were sensitive. This was supported by Biedl & Reiner (1898), Filehne & Bi∉berfeld (1909), Eyster & Hooker (1907), and Lecrenier (1908). Porter & Pratt (1908) and later Hedon (1910), using the cross-circulation method of Frédéricq (1889), also Tournade, Chabrol & Marchand (1921) with the same technique, confirmed the view of Francois-Franck. Similar conclusions were published by Anrep & Starling (1925) and by Kisch & Sakai (1923), working in Hering's laboratory.

It may indeed be said that all the recognised authorities on the subject were agreed that the centres in the brain were sensitive. It should, however, be added that even since the appreciation

of the activity of the sinus McDowall (1933) has shewn that the centres are also sensitive to anaemia and asphyxia. It may, however, be shown that the response of the centres to anaemia or asphyxia is much less immediate than their response to nervous impulses arising in the carotid sinuses or aorta. This is seen in the effects of occluding the common carotid artery. At the beginning of an experiment when the blood pressure is good there is an immediate rise of arterial pressure. Later, as shock from bleeding or other procedures occurs, there is a reduction in the response from occlusion. Later still there is a greater reaction, but this is delayed and is due to cerebral asphyxia.

It is interesting to remark that when in man the region of the sinus is stimulated with a faradic current, the carotid gland response gives a much better response than the sinus, which gives negative results. The experiments were done on five men in whom the region had been exposed for other reasons, and the glandular tissue identified microscopically. (Jacobovici, Nitzescu & Pop, 1928). Such experiments show that the excitability of the nerves in the sinus and gland are different, and that the gland may be involved in the normal reflex. Sollman & Brown in 1912 came near to the complete truth when they found that in

the dog pulling on the central end of the carotid caused a fall of blood pressure amounting sometimes to 50 millimetres of mercury. Previous ligation of the vessel did not affect the result, but they obtained no result from other mechanical or electrical stimulation. The only branch which gave the result was the internal carotid, and they assumed that the effect was due to traction on nerves passing to the brain on that vessel. Traction on other nerves produced no results.

Hering's experiments by which he shewed the activity of the sinus were very simple and can easily be repeated. He applied a clip peripherally to the sinus, but not sufficiently tightly to stop the blood flow, and found that there was a vagal slowing of the heart and a fall of bloodpressure. The latter persisted after section of the vagi. The same effect occurred if the carotid had been previously ligatured to prevent any effect due to cerebral anaemia. Application of the clip at other places was without effect. Mere mechanical pressure on the sinus, dragging on it or faradic stimulation all produced a similar result.

The activity of the sinus may be considered to have been finally accepted at the International Congress of Physiology at Boston, 1929, when

Herin g demonstrated that the injection of fluid into the isolated sinus produced cardiac slowing, and Heymans, 1929, shewed that changes in pressure caused changes in the heart rate, in a sinus perfused from another animal.

In 1926, Moissejeff, by tying off the exit of blood from the sinus, showed that an increase of pressure in the blind end brought about cardiac changes, and by similar methods the essential facts have been abundantly confirmed. Koch (1929), Kahn (1929), Tournade (1930), Heymans & Bouckaert (1930), Vercauteren (1932). Kahn (1930) got similar results from mechanical stretching.

The most convenient demonstration of the action of the carotid sinus is occlusion of the common carotid artery before and after the application of cocaine to the sinus region. The effect of the rise of pressure may show itself in the first experiment when the clip on the carotid has been removed, but if there is not sufficient/a rise of pressure can be easily produced in the sinus by inserting a cannula below the region and occluding the vessels above. Ringer's solution may be injected through the cannula at a temperature of 40° - 42°. In small animals in which dissection of the nerves and vessels is difficult without damage, the

vessels in this region may be occluded by lycopodium (Heymans & Bouckaert, 1933) or by a clip not strong enough to damage the carotid nerves.

Generally, for more prolonged experiments, it is not found best to study the reactions of the isolated sinus and to perfuse it with defibrinated blood by means of a pump or from another animal.

Apparently a number of drugs, such as the nitrites, may slow the heart by acting upon the sensitive endings in the sinus (Heymans, 1931) A rise of blood pressure is produced if nicotine, lobeline, hydrocyanic acid, sodium sulphide, carbon dioxide, are applied to the sinus (Heymans, Bouckaert, Euler and Dautrebande, 1932).

A very large volume of work has been done, especially by Koch, on the effects produced by different pressures on the sinus. These do not, however, appear to have much bearing in the control of the circulation as a whole, the more so as McDowall (Part 2) has shown that the reactions of the sinus are affected by the height of the venous pressure. According to Heymans & Bouckaert (1931), the sensibility of the sinus is greatest at about the normal pressure of

the animals, and in the dog is absent above 200 and below 50 m.m. Hg. If the blood pressure is caused to fall by haemorrhage the responses may be caused to return if saline is injected.

The carotid sinus may also be stimulated by increasing its temperature, the most effective temperature being 40 - 42.5 degrees, Zbyszewsky (1928). It may also, as the experiments of Sollman and Brown indicate, be stimulated mechanically , but the response is rapidly lost if such stimulation is repeated.

Stimulation of the nerves is also possible, but not easy in the smaller animals, (Inaba 1931). Occasionally cardiac acceleration is produced. This is best seen if the vagi are cut and suggests the presence in the sinus of ordinary sensory nerves.

The currents of action in the carotid nerve have been studied by Heymans & Rijlant (1933), and by Bronk & Stella (1932). The frequency of the waves in one fibre is about 100 per second during systole, and 50-60 during diastole. A few vibrations at 20-30 have been found to persist, even when the carotid artery is occluded. They found that changes in the chemical composition of the blood also produced nervous activity.

THE CAUSE OF THE CARDIAC SLOWING

As in the case of stimulation of the central end of the aortic depressor, stimulation of the carotid sinus brings about slowing not only by vagus stimulation but also by inhibition of accelerator drive. Bronk, Ferguson & Solandt (1934) succeeded in finding a reduction of the impluses in the cardiac nerves from the stillate ganglion. They found complete disappearance of the impulses if the sinus pressure was raised from 125-150 mm. Hg. This reciprocal activity is of interest in view of the fact that Bayliss (see below) found a similar reciprocity between the general vasodilator and vasoconstrictor mechanisms.

OTHER AFFERENT PATHS

The obvious question arises as to whether or not there are any other areas of the circulation which, like the carotid sinus and aorta, are sensitive to changes in pressure. So far there is no good evidence of the existence of other such regions, but there is abundant evidence that a large variety of afferent stimuli reach the cardio-inhibitory centre. These may have no functional significance. On the other hand, they may represent some of the mechanism by which is produced the increased vagus restraint which is known to be associated with habitual exercise. Whether or not they have all a counterpart in the vessels through the vasodilator mechanism does not appear to have been investigated except in regard to the stimulation of the central end of the sciatic nerve (Scott, 1924).

It was first shown by Francois-Franck (1876, 1880) that stimulation of the mucous membrane of the lungs and the upper part of the larynx, also excitation of the nasal branch of the fifth nerve, caused cardiac slowing. Dogiel (1866) considered that the slowing action of chloroform was olfactory, but he later concluded that it was due to the stimulating action on the lung. Actually, it is

probably due to neither, but to depression of the opposing sympathetic.

The slowing effect of stimulation of the respiratory tract has, however, been amply confirmed, and the terminals of the superior laryngeal and trigeminal nerves have been shewn to be concerned. Holmgren (1867), Kratschmer (1870), Hunt (1899), Lombroso (1913), Brodie & Russell (1914), Magne, Mayer & Plautefol (1926).* The trigeminal nerves have also been shown to be concerned in the slowing produced by CO_2 (Berencsy 1934). It has, however, been pointed out by Saalfeld (1933) that a slight pulmonary distension may cause acceleration, and this, no doubt, accounts for the fact that it is not always possible to repeat successfully the experiment of Brodie & Russell. Probably the exact anaesthetic also makes a difference.

Tugging in the tongue of a dog is also stated to cause a fall of blood pressure in which reflexes from the carotid sinus, lingual, glossopharyngeal and other nerves are concerned, (Baltaceano & Vasiliu, 1934).

* Brodie & Russell found that the pulmonary branches of the vagus were more effective in producing slowing than the cardiac branches. Hering, 1871, also obtained acceleration from inflation of the lung, but it may be that his results were caused by the rise of venous pressure caused at the same time.

It is well known that tapping the intestines of a frog will bring about cardiac inhibition which depends on the vagus; Bernstein (1864), Goltz (1863). The afferent path appears to be the pancreatic branch of the splanchnic, Bachrach, Bonnet & Richard (1932). A similar result is obtained even by distension of the stomach, Mayer & Primbram (1872), Tournade & Rocchisani (1934), or irritation of the gastric vagus, Nitiforowsky (1913), Miller (1915). In vomiting the heart may be slowed, Brooks & Luckhardt (1915), but this is not constant, Kedroff (1915). Cardiac slowing may also be caused by stimulation of the lumbar cord, Merklin (1926), of the gall bladder or renal pelvis, Symanowsky (1881), of the centripedal nerves to muscles, Asp (1867), Tengwall (1895), of the proximal end of the cervical sympathetic in the rabbit, Bernstein (1864).

Central stimulation of the splanchnic, Asp. (1867), or of the sciatic or of the posterior roots may also cause cardiac slowing, C.Bernard (1858), Roy & Adami (1892), Hunt (1899), but almost any sensory nerve from the dorsalis pedis to the auricular may have a similar action. Asp (1867) emphasised that mechanical stimulation of the sciatic was more likely to cause slowing than electrical stimulation.

Usually there is a cardiac acceleration which masks the inhibition. The latter, however, comes on after the acceleration and may persist for some time after the stimulation has passed off. This inhibition has been analysed by McDowall (1931) who has put forward evidence that such stimulation sets up an after-discharge of the vagus centre and that if an appropriate dose of ergotamine is injected to paralyse the sympathetic, slowing only occurs when the central end of the sciatic is stimulated. The possible physiological significance of this inhibitory reflex makes interesting speculation. It may be suggested that during exercise the vagus centre is stimulated, but that its action is somehow prevented during the actual exercise.

The remarkable fact was brought to light by McWilliam (1883) that the heart of an eel could be slowed by strong stimulation of almost any part, even by tapping its tail. Such an experiment emphasises the dependence of vagal activity on a wide range of stimulation. Similar results may be obtained in the dog-fish, Scyllium canicula, in which mechanical and electrical stimulation of various parts of the body (even the starting and

stopping of water flow through the gills) causes slowing. Lutz (1930), Lutz & Wyman (1932). In fishes the heart may be slowed by stimulating many visceral nerves. Bonnet & Richard (1932).

It may be that the observations made by Byrne (1924) is related to the fact that such muscular nerves may, if stimulated, cause slowing. He found that a small dose of pilocarpine produces a greatly increased cardiac slowing, if proprioceptive paths from muscles and tendons are cut. He therefore suggests that these paths are normally concerned in vagus activity.

The nerves of the special senses appear to be remarkable in the degree of slowing produced when they are stimulated, Couty & Charpentier (1877), Hering (1894).

In 1885, Knoll described a slowing of the heart through stimulation of the infra-orbital nerve, but as he obtained also a rise of blood pressure his results now appear confused. The observation has been confirmed by Petzetakis and Vlachlis (1930). Since the discovery by Aschner (1908), that pressure on the eyeball also caused slowing, a very large amount of work has been done on the so-called oculo-cardiac reflex, especially with a view to

relating it clinically to abnormal states, particularly of the autonomic nervous system. Dagnini (1908), Cluzet & Petzetakis (1914-15), Gunson (1915), Achard & Binet (1918), Stewart (1918), Naccarati (1921), Gillespie, Ritcher & Wang (1926). The reflex may be obtained in domestic animals, Arloing, Jung & Lesbats (1925), and is, according to radovici, Sager & Kreindler (1926), apparently increased in vagotonia and by hyperpnoea. There does not, however, appear to have been any real advance in our knowledge of this reflex or of its physiological significance. If we may judge by the fall of venous pressure, Villaret, Saint-Girons & Bosviel (1922), there appears to be an increase in the general capacity of the circulation. This brings it into the category of the ordinary somatic depressor reflexes.

In the rabbit, acoustic stimulation may also cause slowing. The slowing with a continuous sound is temporary, but with intermittent sounds the slowing may be kept up indefinitely, Corbeille (1929). In man it is possible to stimulate the auricular (external ear) nerve. In 23 patients, Scheminzky (1922) obtained a decrease of pulse rate in 12 cases. In some persons, leaning forward produces a cardiac

slowing, and it has been suggested that there is a labyrinthine reflex comparable to the oculo-cardiac, Olmer & Jacques (1928). It may be that cardiac slowing in the duck when it puts its head down is of a similar nature, but in this instance purely vascular reflexes may be concerned and the asphyxia produced, Koppanyi & Dooley (1928). In man a slowing of the heart has been described as a result of rapid turning of the body from a horizontal position on the back to a vertical position with the head down. A turn in the opposite direction had the opposite effect (Enghoff, 1919). Either labyrinthine or direct sinus and aortic effects may be concerned. The reflex effects which are obtainable when the ear is irrigated and which are well seen in disseminated sclerosis are presumably of a similar nature. Vaso-constrictor effects (not due to abdominal dilatation) have also been described (Draganesco, Kreindler & Bruch, 1932), A general investigation as to whether all these procedures cause a fall of blood pressure if the vagi are cut is most desirable.

THE VASODILATOR CENTRES

The first experiments which suggested the existence of a vaso-dilator centre are those of Laffont (1880) who found that destruction of the floor of the fourth ventricle interfered with the dilatation of the liver which he obtained when stimulating the first and second thoracic nerves. In the process of stabbing he also obtained a dilatation on puncturing this region. It had also been observed that the depressor nerve is active after removal of all the brain above the medulla but not if the medulla is removed (Cyon and Ludwig, 1866). The existence of a centre had been suggested by Ostroumov (1876) and by Tschirwinsky (1896) from the study of vaso-motor reflexes.

The centre was more accurately localised by Ranson and Billingsley (1916) when exploring the floor of the fourth ventricle of the cat by the unipolar method. In the extreme posterior part of the fourth ventricle, just lateral to the obex, they found a point which, if stimulated, always gave a fall of blood pressure. This point is only 3 mm. from the vaso-constrictor centre.

The subject was re-investigated by Scott and Roberts (1923-24) who confirmed the essential points.

Scott (1924) subsequently demonstrated that the fall of blood pressure usually produced by slow stimulation of the central end of the sciatic was unobtainable if the depressor point was cauterised or was painted with strychnine.

It has also been suggested that there is a vaso-dilator centre in the substantia reticularis grisea in the upper part of the medulla, since marked degeneration of the region has been found post-mortem in a patient in whom the blood pressure rose from 165 to 209 mm. Hg (Nordman and Müller, 1932). How far the rise might have been due to other causes is difficult to decide.

It must also be assumed that the centres concerned especially with the control of the skin vessels are in close connection with the heat regulating centre. Section through the pons is stated to cause a rise of blood pressure presumably the result of cutting off a higher dilatation centre (Porter and Storey, 1907).

Petroff (1931) has put forward evidence that the dilator centre like the constrictor centre is stimulated by carbon dioxide.

THE EFFECT OF HIGHER CENTRES.

The phenomena of blushing and of erection indicate that the higher centres influence the vaso-dilator local mechanisms and many attempts have been made to demonstrate the effect of stimulation of the cerebrum.

A fall of blood pressure has been described by Bochefontaine (1876), by Stricker (1886), and by Bechterew and Mislawsky (1885). In some instances a remarkable fall of pressure was obtained on stimulating the sigmoid gyrus in the cerebrum adjoining the second primary convolution.

By far the most dramatic effect of the higher centres in causing dilatation is the phenomenon of fainting which is still a problem which is little understood. It is characterised by a profound fall of the arterial blood pressure which may be preceded by and is accompanied by intense pallor. Giddiness or complete loss of consciousness may occur. Typically the fainting occurs when the subject sees a disagreeable sight. The vessels affected are those of the muscles and it may be thoseof the splanchnic regions. The pallor of the skin indicates thatthese vessels are not concerned except

in a compensation constriction. That the skin pallor is not merely due to draining of blood from the skin is seen from the fact that even when the fall of blood pressure has been recovered from the pallor persists. This I have observed in students who have witnessed animal experiments for the first time. In this connection, however, it is interesting to note that Dastre and Morat (1884) and also Langley (1925) observed constriction of the vessels of the ear of the rabbit occasionally when the aortic depressor nerve was stimulated.

The classical observation of John Hunter (quoted by Lauder Brunton) when bleeding a patient from the median basilic vein that the venous blood turned arterial in colour immediately prior to a faint indicates that limb vessels other than those of the skin are concerned.

The subject has been made a subject of study by Lewis (1932) who points out that the condition affects both the heart and the vessels. The heart is slowed and although atropine causes a recovery in rate, the blood pressure remains below normal and consciousness is incomplete.

Many psychological explanations of fainting

have been given. Probably the best is that it represents biologically a psychological escape from distressing surroundings.

The phenomenon is of interest in relation to the present thesis in that there appears to take place a temporary gross exaggeration of the reflexes under consideration. Lewis (1932) refers to it therefore as a vaso-vagal syndrome. It is doubtful, however, if this completely describes the condition, which may rather be considered one of generalised sympathetic inhibition, for we know that any method of reducing sympathetic activity causes an apparent increase in vagus activity. Other forms of sympathetic paralysis or excessive parasympathetic action under conditions of extreme emotion are also common.

The faint is then the complete reverse of the circulatory response to exercise.

THE EFFERENT PATHWAYS

The pathway of the vasodilator fibres down the cord appears to be by the antero-lateral columns (Ranson & Billingsley, 1916). Such fibres have been found to emerge from the cord in several ways by special nerves, by the posterior roots and by the sympathetic. It seems reasonable to believe, however, that they are not all concerned with the same function, for vasodilator nerves are concerned, for example, in the control of body temperature as well as in control of circulatory capacity and resistance. It is therefore proposed to confine this review at this point to those fibres which have been definitely shown to be concerned in the depressor reflexes arising from the cardio-aortic region and carotid sinus, and which are known to pass out by the posterior roots.

Stricker (1876) showed that mechanical or electrical stimulation of posterior nerve roots of the 6th and 7th lumbar nerves brought about vaso-dilatation of the hind limbs, but a number of well-known workers (Cossy, 1876; Vulpian, 1878, and Kuchsweller, 1885) failed to confirm the observations which has, however, been amply confirmed since, by Morat (1892), Bayliss (1900), Ranson and Wightmann (1922), Langley (1923), Dennig (1924), Hinsey and Gasser (1930).

Hasterlik and Biedl (1893), Bonuzzi (1885), Laffont (1882), Bornezzi (1887) and Werziloff (1896) found that stimulation of the 4th to the 7th lumbar and 1st sacral nerves caused a rise of temperature in the hind limb of the dog, while the venous pressure increased.

In 1901 the problem was extensively studied by Bayliss. He was unable to distinguish between the efferent vaso-dilator fibres and the ordinary in-going afferent fibres. They degenerate when the posterior root ganglion is removed but do not degenerate if the roots are cut between the cord and the ganglion. Bayliss therefore gave to these dilator impulses the term antidromic because they pass in a direction opposite to that of the ordinary sensory impulses. Confirmation of such antidromic dilator fibres has been given by Hinsey and Gasser (1930) who showed that the fibres concerned in the posterior root were the same as those concerned in Sherrington's contracture, i.e. the contraction of a voluntary muscle sensitised by denervation, by Bonuzzi (1885) in relation to the supply of the fore-limbs, and by Langley (1923). It was later shown by Mosonyi (1927) that atropine did not prevent the action of the antidromic impulses even after ether, chloroform, and curare.

In the frog Doi (1920) found that stimulation of the posterior roots caused a dilatation of vessels in the web. This was confirmed by Krogh, Harrop and Rehberg (1922) and by Karlik (1929) who found that the dilatation so produced did not interfere with the effect of constrictor sympathetic stimulation. Krogh, Harrop and Rehberg (1922) consider that only a limited number of large capillaries respond. Bena (1930) could obtain confirmation in the guinea pig while Oinuma (1911) was unable to demonstrate dilator fibres in the 8th and 9th roots although he got a positive result with the sciatic. Hasama (1931), however, describes remarkable dilatation on stimulation of the 7th, 8th and 9th posterior roots in the toad. This he found was abolished by the application of nicotine to the posterior root ganglion.

Ranson and Wightman (1922) consider that the dilator nerves connect with the sensory cells in the spinal ganglion like sympathetic nerves and may either enter from the posterior roots or pass through the anterior roots and reach the ganglia by a detour through their respective thoracic and sacral nerves. It might then be considered that the fibres are not really antidromic except in part of the root. Mislawsky and Bistrenin (1905) on the other hand maintained that the dilator fibres pass out in the posterior roots and have no connection with the

cells of the spinal ganglion and do not degenerate centrally when the roots are cut. It is not possible, however, to obtain any inhibition of the crossed extension reflex by a stimulation of antidromic fibres as might be expected if the antidromic fibres were true sensory nerves (Forbes, Smith, Lambert, Caveness and Derbyshire, 1933). On the other hand, it was shown clearly by Feldberg (1926) that the dilators of the ear running in the auricularis ventralis and dorsalis correspond in distribution to the sensory distribution of these nerves.

The fibres which pass out by the posterior roots apparently join the ordinary mixed nerves and are distributed with them as is shown by the effect of slow galvanic stimulation. Bayliss (1901 and 1902) found that if the posterior roots are cut and time allowed for degeneration, stimulation of such a mixed nerve as the sciatic no longer gives dilatation, even when a suitable stimulus is used. In view of the evidence of dilator fibres in the sympathetic, this conclusion of Bayliss is doubtful. It probably refers to the skin only.

Bayliss quotes an interesting experiment by himself and Head (1923). At a stage of regeneration

of the radial nerve of the cat at which only the so-called protopathic sensory fibres were present, stimulation of the peripheral end caused an obvious dilatation of the paw. The constrictor fibres do not recover till some weeks later. This nerve contains no motor fibres for voluntary muscle, and it sometimes happens, apparently, there are no vaso-constrictor fibres in the normal nerve. The absence of constrictor fibres can be assured by removal of the stellate ganglion and, after time is allowed for degeneration, a pure vascular dilatation was obtained on stimulation of the sensory nerves to the limbs. In the case of the hind limbs, 5th, 6th, 7th lumbar and 1st and 2nd sacral are concerned (Bayliss, 1900). The vessels concerned are, apparently, both those of the skin (Doi, 1920) and also those of the muscles (Metallinos, 1925).

It is interesting in the light of later research to remark that several old experiments had demonstrated that sensory nerves had a dilator effect. We have already referred to the lingual which contains sensory fibres to the tongue. The trigeminal also is a vaso-dilator to the face and interior of the nose, the eye (Vulpian, 1875; Schulten, 1884; Morat and Doyon, 1892; Tschalussow, 1913). The general

significance of these observations was not at the time appreciated.

Kibjakow (1931) working on the posterior roots has found that their stimulation causes a dilator substance to be liberated into the blood or Ringer's solution perfused through them. The work of Dale & Gaddum (1930) and of Bain (1933) suggests that the substance is acetyl-choline, but why atropine fails to abolish the action of the aortic depressor nerve is difficult to explain since atropine abolishes the action of acetyl choline injected intravenously. Dale and Gaddum have suggested that the acetyl-choline is is produced at a point in a more intimate relation to the vascular muscle than the atropine can succeed in reaching. A consideration of this aspect of the humoral transmission of nerve impulses is outside the scope of this thesis.

According to de Waele, van de Velde, and Braeye (1933) the dilatation of the paw which occurs on stimulating the peripheral end of the posterior roots between the cord and the ganglion really depends on afferent fibres and is dependent on the presence of the superior abdominal ganglion. Similarly Bacq, Brouha and Heymans (1933) found

that removal of the lumbo sacral sympathetic brought about complete loss of the vascular reflexes in the hind limb from the carotid sinus. Mere removal of the thoracico-lumbar outflow did not interfere with the reflexes, although the blood pressure had completely recovered from the operative procedure, (Bacq, Brouha, and Heymans, 1932).

We may then conclude that the dilator fibres which pass out by the posterior roots are somehow connected to the lower part of the ganglionic chain although how this attachment is made is as yet uncertain.

From the posterior roots the vasodilator fibres pass out to the periphery with the ordinary mixed nerves, but since these nerves contain also vasoconstrictor fibres the vasodilator fibres require special means for their demonstration such as show galvanic stimulation.

THE REGIONS INNERVATED IN THE DEPRESSOR REFLEXES.

When the action of the aortic depressor nerve was first discovered by Cyon and Ludwig (1866) they put forward the idea that the dilatation was wholly splanchnic but by clamping the aorta high up Heidenhain and Grützner (1878) soon showed that the dilatation was by no means confined to this region. This was confirmed by Sollman and Pilcher (1912) and supported by Porter and Beyer (1900) who cut the nerve supply to the splanchnic region and by Stelling(1867) who cut the spinal cord at the level of the third thoracic segment and still obtained a fall of blood pressure. Smirnow (1886) also showed that this did not abolish the reflex.

Anrep and Starling (1925) and Heymans and Bouckaert (1929) demonstrated that the arteries of the head were also concerned in the reaction to a general fall of blood pressure.

That the capillaries take part in the reaction has been suggested by McDowall (1922) on the grounds that the absolute and percentage fall of blood pressure due to histamine was reduced by stimulation of the aortic nerve. This has subsequently been confirmed microscopically on the mesentery of the rabbit by Koch and Nordmann (1928) although the

authors are inclined to look upon the dilatation as passive rather than active. In the frog the capillaries take part in the dilatation which occurs in stimulating the posterior roots (Doi, 1920; Krogh, Harrop and Rehberg, 1932).

Bayliss (1908), it will be recalled, considere d that the efferent pathway of the depressor reflex was antidromic while in the pads and toes of the cat also it was found by Langley (1923) that the capillaries rather than the arteries were concerned in antidromic dilatation.

It is stated also that the coronary arteries are dilated (Hochrein and Gros, 1932).

The fact that the splanchnic region is greatly concerned has been amply confirmed by Dreschfield (1867), Bayliss (1893), Francois Franck and Hallion (1896), Dastre and Morat (1884), Bunch (1889), Jarish and Ludwig (1926 a), Koch and Nordmann (1928). Bayliss (1893) who carried out a most extensive plethysmographic study of the question found dilatation in all regions which were examined and that in the limbs both the skin and the muscle were affected. This has been confirmed by Fofanow and Tschalussow (1913). The dilatation of the muscles was also noted by Gaskell (1878) and confirmed by Jarisch (1926) in the gastrocnemius of the rabbit. Francois Franck (1899) had already noted that an eviscerated

animal showed a fall of blood pressure; that the pulmonary vessels are also affected was also shown by Sharpey Schafer (1920) assisted by the author. The vessels of the submaxillary are also affected (Bayliss, 1893; Asher, 1909), and also of the tongue and mucous membrane of the nose (Bayliss, 1908; Fofanow and Tschalussow, 1913; Tschalussow, 1913; Martin and Mendenhall, 1915), but it has been found that the dilatation is best seen if the antagonistic cervical sympathetic has been previously cut. Incidentally this experiment shows all the more clearly that the dilatation is the result of dilator stimulation rather than of reduction of constrictor tone. A dilatation of the kidney is described by Roever (1869) who observed redness and swelling, by Bradford (1889) using the plethysmograph and by Sollmann and Pilcher (1912) using the innervated perfusion method. The latter applied the same method to the spleen with a similar result.

A dilatation of the ear of the rabbit has been described by Bayliss (1893, Simon (1929), and Weber (1908), but Dastre and Morat (1884) and also Langley (1925) have described instances in which the ear vessels constricted when the general blood pressure fell as a result of depressor stimulation. The vessels of the penis are also said to dilate in

stimulation of the aortic nerve (Tournade and Malmejac, 1933).

The only contrary results which have been obtained have been on the ear of the rabbit (Dastre and Morat, 1884; Cyon, 1899; Bayliss, 1893; Weber, 1908; Simon, 1929; Langley, 1925). But Bayliss (1893) points out that a short period of dilatation can be found if adequate means are taken; for example, an examination by thermopile, but this view is not supported by Langley (1925).

Much work has been done on the effect of stimulating the carotid sinus by raising the pressure within it or by stimulating its nerve and by cutting off the impulses from the sinus by reduction of its internal pressure, especially by Heymans (1933) and his collaborators.

The areas shown to be affected are conveniently shown in tabular form. Unless otherwise stated the vessels concerned are constricted by a loss of the impulses from the carotid sinus.

Intestine: Moissejeff (1926), Tournade (1930), Heymans, Bouckaert and Dautrebande (1931).

Extremities: Sollman and Brown (1912), Tournade (1930), Rein (1931), Heymans, Bouckaert and Dautrebande (1931-2).

Head: Heymans and Bouckaert (1929).

Skin: Holtmeier (1927), Gaisbock (1928), Koch and Simon (1928).

Nose: Binet and Gayet (1929).

Thyroid : Rein (1932).

Liver: Heymans, Bouckaert and Dautrebande (1930).

Cerebral vessels: Negative results, Heymans and Bouckaert (1932).

Coronary arteries: Hochrein and Keller (1932). These observers found a constriction of these vessels during a fall of pressure in the sinus. In view of our knowledge of the coronary control this result requires confirmation.

Retina: Gollwitzer-Meier and Schulte (1932).

Lungs: Tournade (1932). This author considered the results to be secondary to changes in the general circulation, but in view of the experiments of Sharpey-Schafer (1920) in relation to the depressor nerve this seems doubtful.

Veins (femoral): Heymans and Bouckaert (1930), Heymans, Bouckaert and Dautrebande (1931); (mesenteric): Fleisch (1931); (intestinal): Gollwitzer-Meier and Schulte (1931).

Muscles: Rein (1930). Vessels dilated by fall of carotid pressure.

Penis: Tournade and Malmejac (1933).

There is still a very large amount of work to be done on the effects produced by vaso-dilatation brought about by the stimulation of somatic nerves. In this respect the work of Rein (1930) which showed that different methods of stimulating the centres may produce different blood distributions is most suggestive.

PART II

INTRODUCTION TO PART II

The function of the vasodepressor and cardio-depressor reflexes.

It has generally been assumed that the function of the depressor reflexes is essentially to maintain the blood pressure at a constant mean level. That this acts as a safety mechanism to protect the heart is assumed in the monographs of Bayliss (1923), Hering (1932), Heymans (1933) and Koch (1931). Heymans particularly emphasised the effect upon the peripheral resistance.

It is not denied that the reflexes may exert some influence in maintaining the blood pressure at a constant mean level during rest, indeed good evidence is available in support of this view. But that this is necessary for the protection of the heart is open to considerable doubt, in view of the very large rises of blood pressure which occur in exercise. A constant level of blood pressure at rest would appear to be necessitated by the fixed anatomical structure of the capillary wall upon the permiability of which depends the constancy of the blood volume and blood concentration.

There is considerable evidence that but for these mechanisms the blood pressure might undergo at rest considerable fluctuations from spontaneous

contraction or relaxation of vascular areas. This is well seen in Fig. 1 .

The following investigation indicates, however, a further and possibly more important function of the vaso-depressor reflexes, which has hitherto not been described. It is that the reflexes primarily control the capacity of the circulation and maintain in reserve a volume of blood which may be thrown into the circulation to make up for the increased capacity of the muscles in exercise. The importance of the addition of relatively small quantities of blood to the circulation in increasing the cardiac output has been particularly emphasised by Daly (1925, 1926).

THE EFFECT OF THE VASODEPRESSOR MECHANISM UPON CIRCULATORY CAPACITY

When Bayliss (1893) made his classical studies on the aortic depressor nerve he was specially impressed by the effect of its stimulation upon the capacity of the circulation, since he found not only a fall of arterial pressure but also a fall of venous pressure. This, in his monograph (1923), he describes as probably being of value in the protection of the heart since a simple reduction of the peripheral resistance would otherwise lead to a rise of venous pressure and lead to cardiac embarrassment. This dilator action he showed to be produced in every organ of the body examined, and this has been extended and confirmed by others (see Part I). Bayliss, however, since he was unable to obtain any evidence that the impulses passing up the aortic depressor exerted any tonic dilator influence on the blood-vessels, could not consider the effect of loss of the dilator impulses upon the circulation. The appreciation of the activity of the carotid sinus has rendered necessary a complete revaluation of existing data. This has become all the more necessary since continental workers have particularly stressed the effect of the carotid sinus upon the

peripheral resistance. Heymans (1933), in his monograph, has particularly emphasised that the loss of the activity of the carotid sinus results in a banking up of blood in the arteries.

The present experiments were undertaken to enquire into the possibility of there being any evidence of a function of the vasodepressor mechanism than the normally accepted one of the protection of the circulation and the heart in particular upon the circulation, since studies of the blood pressure of man during exercise make it clear that a rise of blood pressure may take place without there being any damage to the healthy heart. Further it was found that animals deprived of their vasodepressor mechanism did not appear to have reduced their reaction to circumstances which would tend to cause a fall of blood pressure, such as posture and small degrees of haemorrhage, (Fig. 2).

METHODS

The experiments were carried out on cats and rabbits anaesthetised with chloralose administered intravenously during preliminary ether anaesthesia. The loss of the vasodepressor impulses were for the most part studied by clipping off a common carotid artery, the other being tied with or without previous section of the aortic depressor nerves. The results were checked by clipping of the two carotid arteries simultaneously blood pressure being recorded from a femoral artery, and by the application of local anaesthetic to the sinus which did not necessitate any interference with the central circulation. In no instance, however, were any significant differences obtained, (Fig.3). It may perhaps be added that the practice of recording blood pressure from a femoral artery, which has become usual in some continental laboratories, is liable to considerable objection unless steps are taken to prevent the absorption of toxic products from the asphyxiated leg. In all experiments it is considered essential to reduce surgical procedures to a minimum as any degree of shock pressure materially affects the results. If the shock is sufficient to affect blood pressure it may be assumed that the circulatory adaptation is already fully in use.

THE EFFECT OF STIMULATION OF THE AORTIC DEPRESSOR AND CAROTID SINUS UPON THE ARTERIAL AND VENOUS PRESSURE.

In each case the venous pressure was recorded by the method described by McDowall (1922) in which a long sound-like cannula is passed down the external jugular vein, the neck muscles being used as a splint to secure it in position.

The results of Bayliss (1923) in relation to the effects of stimulation of the aortic depressor are confirmed (Fig. 4). Stimulation of the carotid sinus produced a similar fall of arterial and venous pressures (Fig. 5). These results may be accepted as due to an increased capacity of the circulation.

The extent of the depression caused by stimulation of the aortic depressor is not materially affected by the presence of the carotid sinus.

THE EFFECT OF LOSS OF THE CAROTID IMPULSES UPON THE VENOUS PRESSURE

As seen in Fig.6 there is commonly a small but definite rise of venous pressure. This rise may be, however, of short duration since the heart rapidly deals with any such increases. To obtain this result it is essential that the animal should be in the best possible condition and have been rested for 15 minutes after all operative procedures have been carried out. Quite small degrees of shock insufficient to show in the arterial blood pressure (but indicated by a low venous pressure) are sufficient to reduce the capacity. The peripheral constriction which then results from loss of the impulses then causes a fall of venous pressure, such as described by Heymans. If also the venous pressure is high the increased cardiac action tends to lower it. Often therefore there is little or no change in the venous pressure due to a balancing of these factors (Fig.13).

On the other hand a very large rise of venous pressure may occur from cardiac embarrassment, which may occur if the rise of arterial pressure is very great (Fig.5), and is particularly liable to occur if the vagi have been cut previously. Before any result is considered valid, it is necessary by subsequent experiment to test the capability of the heart to withstand a high arterial pressure.

THE EFFECT OF LOSS OF THE CAROTID IMPULSES ON THE VENOUS OUTFLOW.

In these experiments the outflow from the femoral vein was recorded by signalling each drop, chlorasol fast pink being used as an anticoagulant. Fig.7 shows the marked increase in outflow which may occur. The increase may, however, be rapidly succeeded by a decrease, a result of the increased peripheral resistance. Haemorrhage or the previous reduction of the capacity of the circulation by section of the aortic depressors may cause the increase to be much reduced or completely abolished, (Figs. 8 & 9). In some animals in poor condition a reduction was the only one which could be obtained.

X This holding up of the blood on the arterial side by the arterial constriction is well seen if a still more intense arterial constriction is brought about by producing cerebral anaemia by compressing also the vertebral arteries (Fig.10) and thus stimulating more intensely the vasoconstrictor centre. The period of reduced flow is followed by a greatly increased flow when the constriction passes off, (Fig.10 ϕ).

Of interest too is the effect of the carotid sinus in the outflow caused by action of adrenaline. It may be presumed that provided the animal is in the

same state the flow of blood from the femoral vein ought to be the same for any given blood pressure. The state produced by reduction of the carotid impulses might, in the light of the thesis, be expected to reduce the increased femoral flow produced by adrenaline. This reduction does in fact occur (Fig. 11) - indeed the flow is less even with a higher arterial pressure - but it might well be argued that the reduction of the adrenaline effect is not the result of a diminution of capacity but of an increased peripheral resistance produced by the loss of the sinus impulses.

It is probably best to imagine that at the periphery the vessels constitute a sponge-like reservoir which when it contracts drives out its blood towards the large veins before it actually impedes the flow of blood from the arteries to the veins. This double effect is seen in a number of records.

THE EFFECT OF LOSS OF THE CAROTID IMPULSES ON THE CARDIAC OUTPUT.

The output was measured in the usual way by means of a cardiometer. If care is taken to adjust the apparatus so that the heart is not pressed upon unduly no difficulty was experienced in demonstrating an increased cardiac output, although the severity of the operation necessary to expose the heart is of itself very liable to produce shock. Previous section of the aortic depressor and the occurrence of an exaggerated rise of arterial pressure, however, readily led to the opposite result. This result is that described by Heymans, who associated it rather with a diminished return of blood to the heart than with direct cardiac failure. Heymans did not check his results by simultaneous records of venous pressures. In some cases, as seen in Figs.12 & 13, the loss of the impulses from the carotid sinus results in actual doubling of the rate of the circulation. This confirms the experiments of Lauter (1930) and of Riml (1929) by the method of Fick.

In further support of the conclusion that the rise of venous pressure probably is not caused by cardiac failure is the fact that not infrequently it is found that the rise of venous pressure is associated with a fall of pulmonary arterial pressure (Fig.13 A) which indicates that the right ventricle has probably not had additional work to perform.

THE EFFECT OF LOSS OF CAROTID IMPULSES ON THE VOLUME OF ORGANS

This has been so extensively studied by others (see Heymans, 1933) that it is unnecessary to repeat all the experiments. Every organ examined has been shown to be constricted. No experiments, however, appear to have been carried out on the muscles.

The results of experiments carried out to study this point are shown in Figs 14, 15 & 16. Usually, and particularly in Spring time, there is a marked dilatation, but there may be no change whatever in circumstances in which the injection of small quantities of adrenaline cause a marked dilatation. It is possible that any central constriction that may occur is balanced by a secretion of adrenaline, which has been shown by Heymans (1933) to occur. This is suggested by the fact that occasionally a dilatation follows the release of the carotid, and the hormonal influence lasts longer than the nervous.

Moreover, in saline perfusion of the hind legs of an animal by the method described by McDowall, Fig. 17a, (1933) a loss of impulses from the sinus causes a marked constriction of the saline perfused limb, the reactions of which, as shown by Densham (1927), are due to muscle changes.

The view that adrenaline is secreted does not,

however, preclude the possibility that sympathetic dilator fibres may be stimulated. These, as has been suggested by Rosenblueth and Cannon (1934), are particularly supplied to muscles. At the same time this latter possibility seems unlikely because in studies of the venous outflow the increased flow is reduced if the experiment is repeated without return of the blood, although the arterial pressure is the same. In such circumstances a dilatation would show itself while an effect from diminished capacity would be affected by the continued loss of blood during the experiment. A number of experiments have been carried out after section of the splanchnic nerves and removal of the adrenal glands, but reactions then obtained from occluding the carotid artery are so small because of the attendant fall of blood pressure that the evidence has not been considered conclusive.

THE EFFECT OF THE VENOUS PRESSURE ON THE ACTIVITY OF THE CAROTID SINUS.

It has been shown by Bainbridge (1915) that a rise of venous pressure causes cardiac acceleration partly by a reduction of the vagus restraint of the heart, and the existence of a reflex from the right auricle has been amply confirmed, (Sassa and Meyakaki, 1920; Anrep and Segall, 1926). These facts, together with the observation of Hooker (1911) that the venous pressure rises in exercise, have led to the conclusion that probably the rise in venous pressure is in part responsible for the cardiac acceleration in exercise.

Since in exercise the arterial blood pressure rises in spite of the existence of mechanisms from the carotid sinuses and the sino-aortic region, the possibility has been considered that a rise in venous pressure might in part be responsible for a reduction in the activity of the vasodepressors, which, like vagus restraint, arises from the carotid sinus. Experiments were therefore carried out to investigate this possibility, the effect of loss of the impulses from the carotid sinus being taken as an indication of the degree to which the sinus is active.

The result of raising the venous pressure by the rapid injection of fluid after the manner used by Bainbridge is shown in Figs. 18, 19, 20. It is seen that such a procedure materially reduces the activity of

the carotid sinus. In carrying out this experiment it is necessary to emphasise that it is the absolute venous pressure which is concerned in the response, not the amount of the rise. For example, a rise from -20 to +10* is not effective, while a rise from +20 to +50 is,(Fig.21,21a). A possible criticism that the arterial pressure cannot rise higher because the heart is not capable of sustaining a higher pressure is negatived by control experiments on this point, in which the pressure is caused to rise much higher by acute cerebral anaemia.

The raising the venous pressures by placing the animal in the vertical head down position has a similar effect in most animals, (Fig.22). Some animals, however, gave negative results, possibly because in them the venous pressure was too low.

Quite by accident it was discovered in these experiments that in animals under chloralose, especially if chlorasol fast pink was used, were liable to acute pericardial oedema. Fig.23 shows an instance of this. It will be seen with the high venous pressure consequent in the cardiac impiarment the effect of the loss of sinus impulses was very small, but greatly increased after the pressure in the pericardium was relieved.

* This pressure is that actually measured in the superior vena cava, to which ought to be added the negative pressure in the chest.

In connection with these experiments it is of interest to note that Pilcher and Sollman (1914), using the reactions of an innervated perfused spleen as indication of the reactions of the vaso-motor centre, found that the injection of fluid into the general circulation caused splenic constriction and not dilatation, as might have been expected from the existence of the depressor reflexes.

How this rise of venous pressure is effective has not been studied in detail, nor does it appear possible without such operative procedures which are liable to upset the results as a result of shock.

It has, however, been suggested by McDowall (1934) that there exists on the venous side of the heart a vaso-pressor reflex corresponding to the cardio-accelerator reflex from the right auricle. The existence of such a reflex is suggested by the fact that in certain circumstances section of the vagi causes a fall of arterial pressure. This was originally remarked upon by Pavlov (1879), but has since been confirmed by Anrep and Starling (1925).

McDowall (1934) has subsequently described in the cat a branch of the vagus which arises from the heart and which produces a rise of arterial pressure when stimulated by a current which, if applied to central end of the vagus, would cause a fall. It seems reasonable to believe the presence of these

pressor fibres in the vagus which is responsible for the rise of arterial pressure which may occur in cats when the central end of the vagus is stimulated.

THE EFFECT OF ADRENALINE ON THE ACTIVITY OF THE CAROTID SINUS.

Since it is well known that the injection of adrenaline reduces vagus activity, and the belief that this substance is secreted in emotion, which of itself raises the arterial pressure and causes cardiac acceleration in spite of the depressor reflexes, the possibility of adrenaline reducing the activity of the carotid sinus was considered, the activity again being judged by the effect of loss of the sinus impulses. The results of such experiments are shown in Figures 24, & 25 & 15, in which it is seen that the activity of the sinus is materially reduced or even abolished by adrenaline. This is not to be confused with the well known vagus inhibition which is brought about by large and quite unphysiological doses of adrenaline. As is seen in Fig. 24 this cannot be explained that the blood pressure had already reached its maximum since acute cerebral anaemia caused a much larger rise.

DISCUSSION AND CONCLUSION

The results of study of stimulation and of loss of the impulses from the cardio-aortic region and the carotid sinuses indicate that the general capacity of the circulation is controlled from these regions. A stimulation causes an increased capacity as indicated by a fall of both arterial and venous pressures, and a loss the reverse. Since, however, a rise of venous pressure may be caused by cardiac failure, this possibility is studied by experiments in relation to the cardiac output and venous outflow, which supports the view that a loss of impulses from the carotid sinus brings about a reduction in the capacity of the circulation.

It has also been shown that a rise of venous pressure and adrenalaemia, both of which are believed to occur in exercise and in emotion respectively, bring about a reduction in the activity of the carotid sinus not accelerating the heart but constricting the blood vessels in regions other than the muscles (and probably the heart itself). It would seem, therefore, that the general vasodepressor reflexes have a parallel relationship to the cardio-depressor reflexes, which is activated from the carotid sinuses and cardio aortic regions, conditions which affect one affecting the other to the same extent.

It is now possible to obtain some idea as to the possible integration of the circulation in exercise in so far as it effects the operation of the vasodepressor reflexes which are activated from the cardio-aortic region and the carotid sinus.

Immediately before the onset of the exercise the effects of the higher centres, and as the exercise proceeds other factors, cause a reduction of parasympathetic and an increase ofgeneral sympathetic activity. These bring about cardiac acceleration. All the evidence available, e.g. McWilliam (1893), Hunt (1899), Hering (1895), Gasser and Meek (1914), Samaan (1935), suggests that the cardiac acceleration is brought about largely by a reduction of vagus restraint.

In exercise, however, the capacity of the muscles is greatly increased and the venous pressure would fall but for a closing down of the vessels of less active tissues, e.g. the hand (Mosso, 1923), the spleen (Hargis and Mann, 1924; Barcroft, Harris, Orahovats and Weiss, 1925; Barcroft and Stephens, 1927; Barcroft and Florey, 1929), and the colon (Drury, Florey and Florey, 1929). This, it is suggested, is brought about by a simultaneous reduction of the vasodepressor impulses controlling

circulatory capacity which, like the vagus restraint of the heart, is dependent on impulses from the carotid sinus and cardio-aortic region. It seems then the vagus restraint of the heart and the general depressor mechanisms are essentially parallel reflexes for the benefit of the body in physical exercise.

If this conclusion is correct we should anticipate that on the integrity of the vagus would depend the capability of the heart to deal with an increased venous pressure such as occurs in exercise (Hooker, 1911).

In 1926 it was pointed out by the author that but for the vagus restraint a rise of venous pressure might so increase the cardiac rate that the trained heart would not be able to benefit from its increased efficiency. Hence we see that normally training and vagus restraint go together.

At the same time also Anrep and Segall (1926), working on the coronary circulation, found that the increased coronary flow which normally accompanies an increased cardiac output did not occur if the vagi were previously cut.

The reduction of efficiency of the heart when the vagus is thrown out of action may be shown experimentally by the rapid injection of gum saline, and to render the effect of the vagus mechanism more

clear cut the sympathetic may be thrown out of action by the previous administration of ergotamine (Fig. 26).

As might be anticipated the heart takes appreciably longer to deal with a given rise of venous pressure if it is so denervated.

This result is in accordance with the findings of Samaan (1935), who found that the maximum endurance of dogs working until exhausted on a treadmill was reduced very greatly if the vagi were cut.

It would be expected then that the degree of normal activity of the vasodilator reflexes would be parallel to the degree of normal vagus restraint. Since the latter is well known to be increased in training it would be expected that the vasodilator reflexes might be increased also. There are already some suggestions referred to in the literature such as the finding in a trained person that the normal increase of red blood corpuscles which takes place in exercise was greatly increased.

SOME INDICATIONS OF CLINICAL SIGNIFICANCE OF THE THESIS

In relation to the effect of the higher centres the phenomenon of fainting has already been referred to in which there is a temporary fall of arterial pressure associated with an exaggeration of the cardio-inhibitory and presumably of the vasodilator reflexes, but the evidence put forward opens up many new points.

It is evident that the effect of a high venous pressure such as occurs in cardiac failure must, by throwing out of action the cardio-inhibitory vaso-dilator reflexes, throw an increased strain on the heart by the still further increased venous pressure and the increased peripheral resistance which it tends to produce. It would, therefore, seem that there is a strong therapeutic indication to break the vicious circle by the use of vasodilators and by blood letting as once was fashionable.

How far some cases of high blood pressure may in part be due to reduction of the activity of the vaso-dilator reflexes requires to be considered, and with this in view the value of graduated exercises and of thermal treatments to increase the activity of such reflexes require consideration.

That there may occur cases of gross exaggeration of the reflexes which may be insufficient to cause fainting is also possible. This may occur from sympathetic underaction or exhaustion which is known to follow periods of intense mental and physical activity.

It will be evident too that the capability of the body to respond to the absorption of toxic dilator substances must in part depend on the reserve of blood available, and therefore on the activity of the vasodilator reflexes. This consideration is relevant in regard to many infections and also to surgical shock. It may well be that the special liability of some persons to shock is related to the previous activity of the dilator reflexes and the reserve of blood available for emergencies. At the same time the possibility that some cases of shock associated with a small amount of injury may be due to exaggeration of the vasodilator reflexes and of an increased capacity of the general vascular bed becomes evident.

Where there has been actual loss of blood the importance of the reserve of blood is obvious. These indications of clinical implications of the conclusions are by no means exhaustive, but they go to indicate that the view of the function of the reflexes now put forward may not be without value in the realm of practical medicine and surgery.

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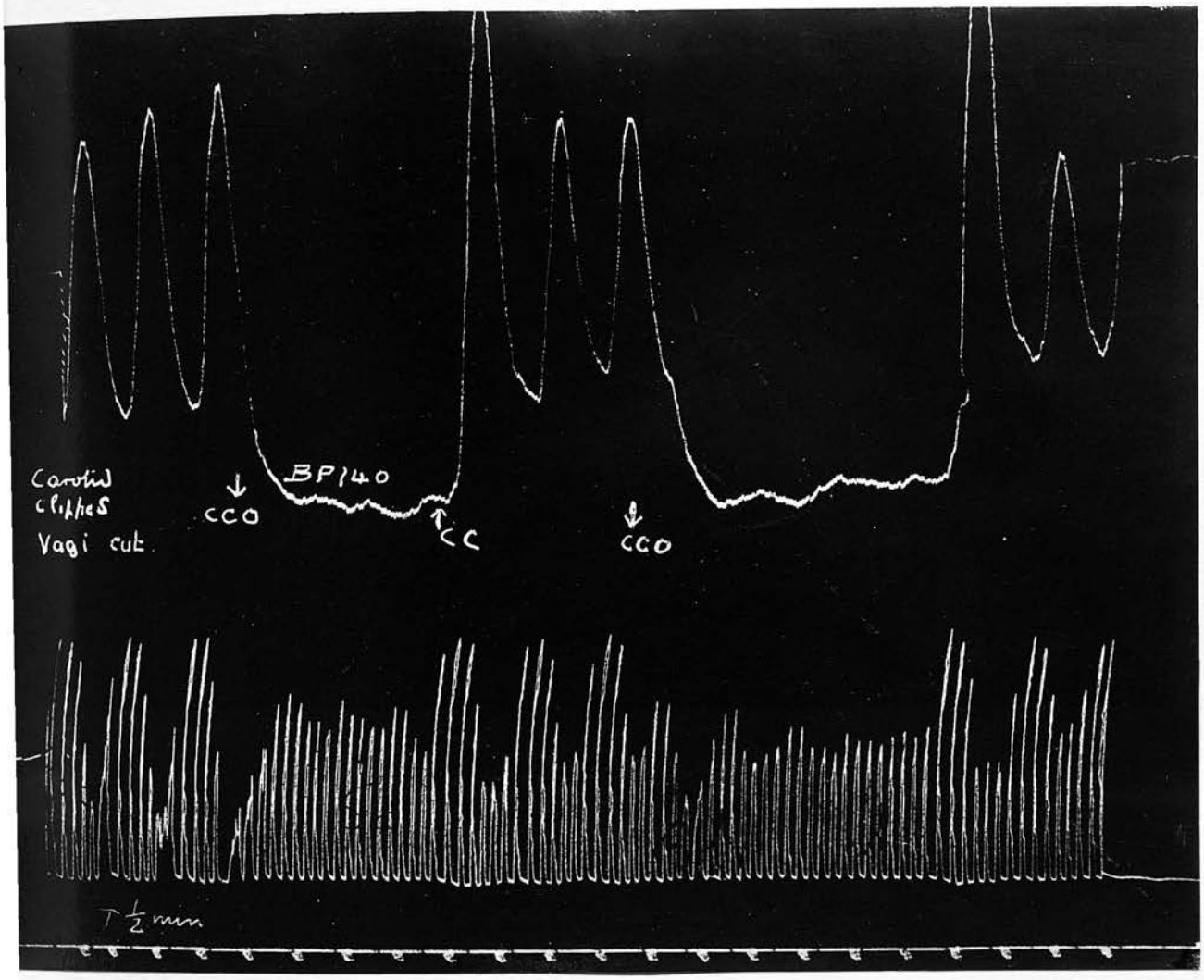
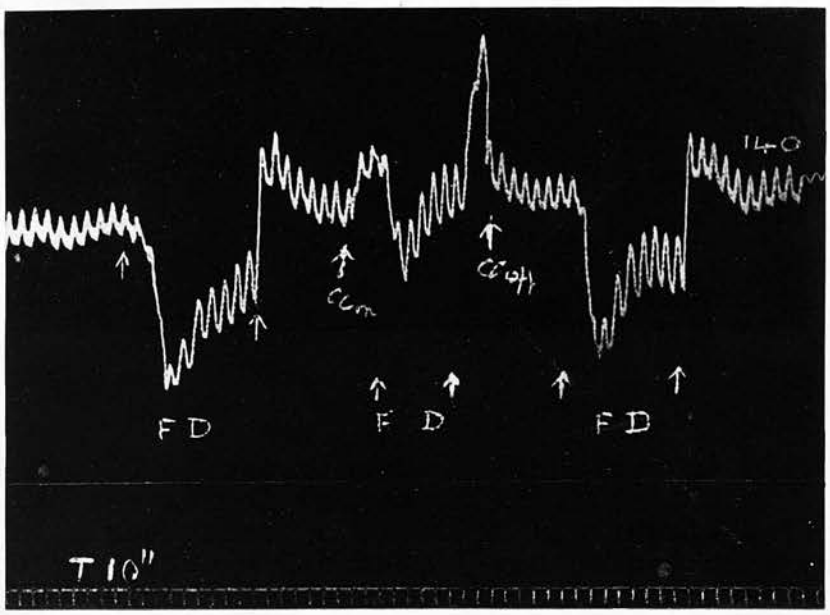
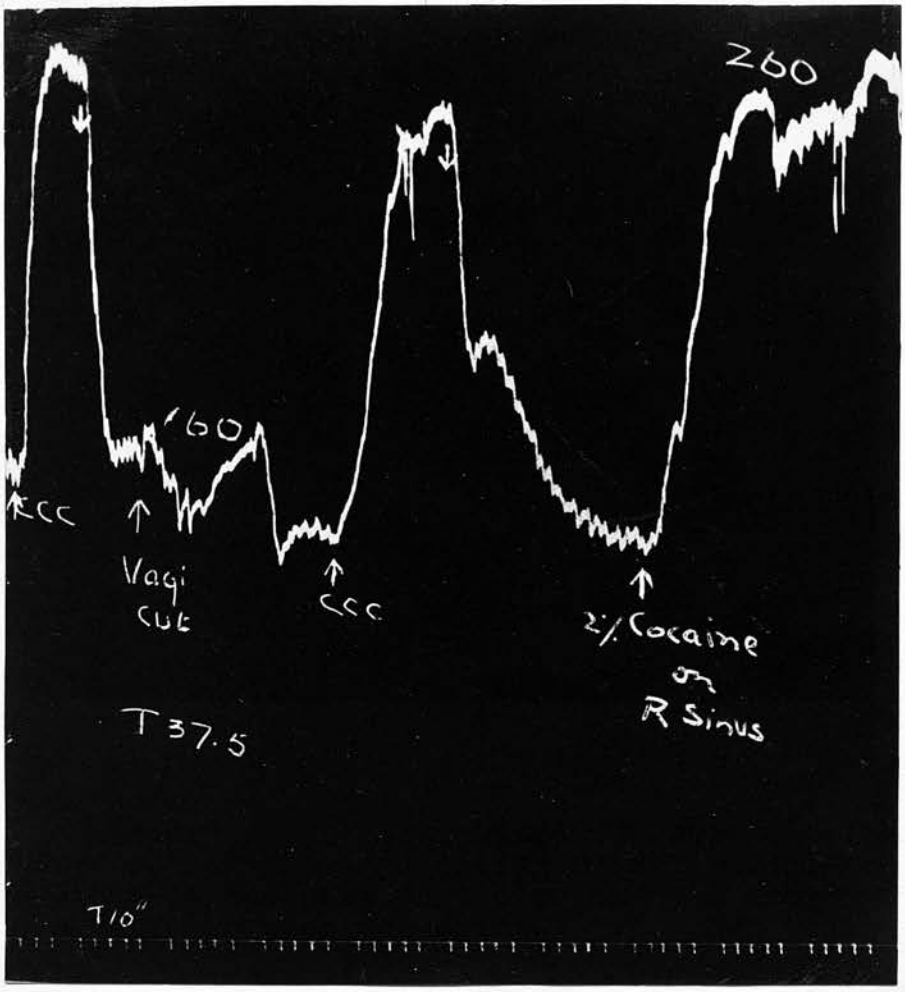


A record of blood pressure and respiration showing the effect of loss of the sinus impulses at CC. At CCO the carotid sinus was released. Such gross undulations of blood pressure are common if the vagi are cut and the carotid sinus occluded or anaesthetised.



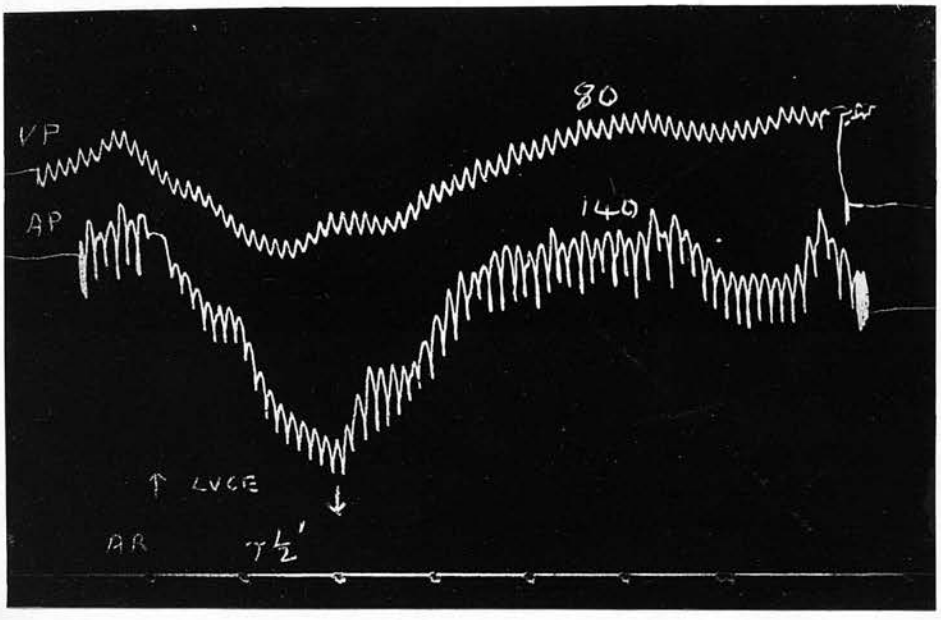
Record of blood pressure showing the effect of placing the animal in the vertical feet up position on the effect of loss of the impulses from the carotid sinus. The animal was placed on a special tilting table.



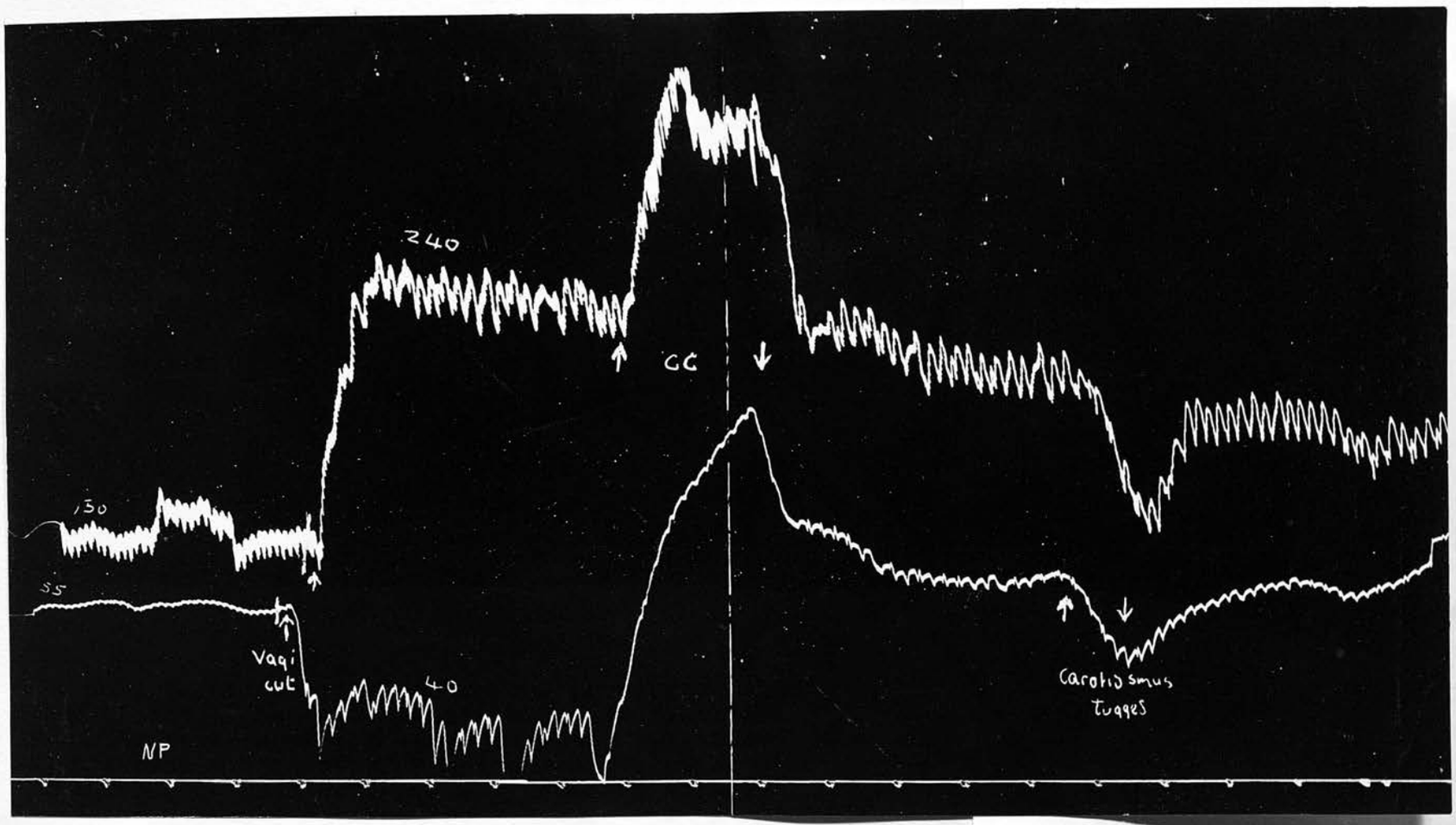
Record of arterial blood pressure showing that the effect of the application of 2% cocaine to the carotid sinus is the same as occlusion of a common carotid artery (between the arrows) the other being tied.

There are 5 arrows!

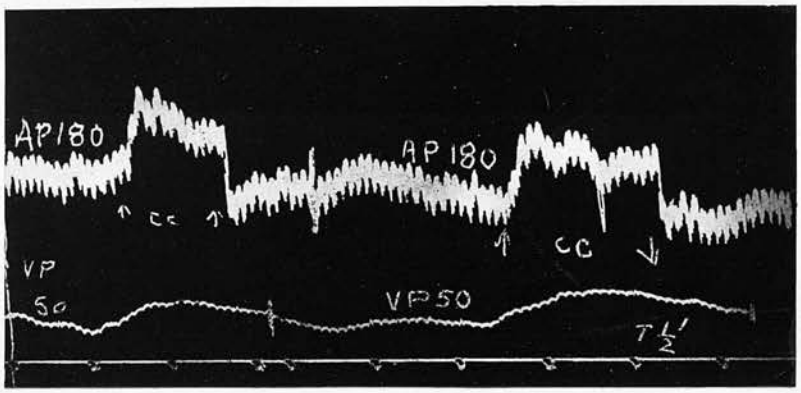
Not sufficient explanation in legend.



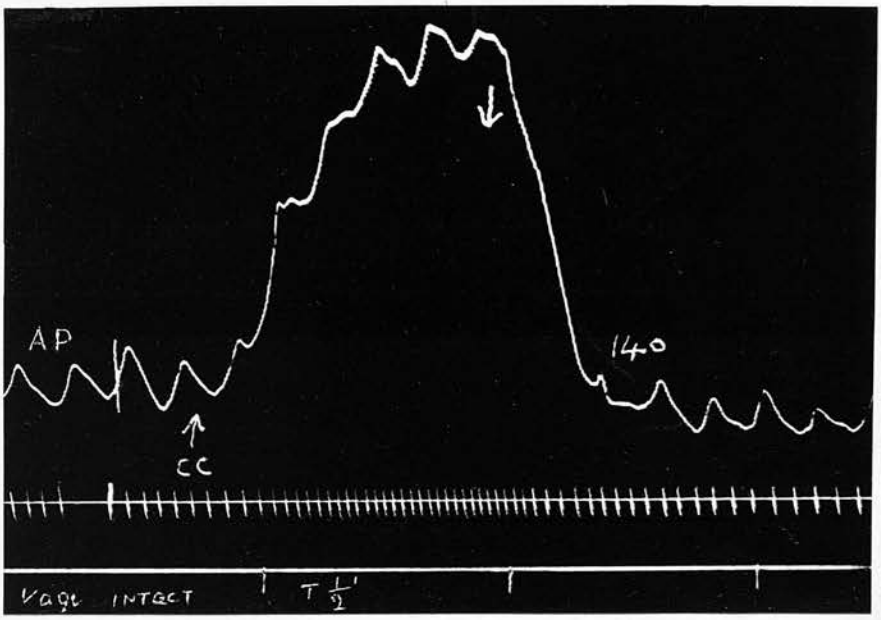
Records of arterial and venous pressures showing the effect of stimulation of the central end of the left vagus upon the arterial and venous pressures.



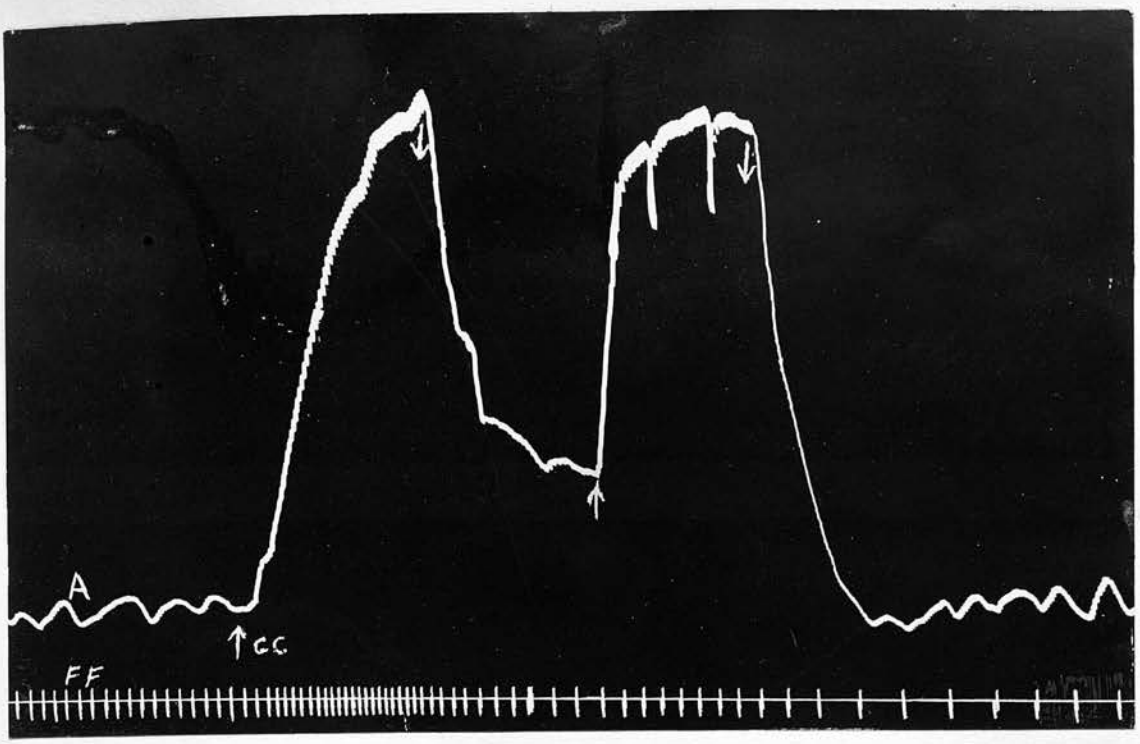
Records of arterial and venous pressures (lower) showing the effect of the carotid sinus on circulation capacity. The section of the vagi caused a fall of venous pressure, presumably because of the increased cardiac activity, which more than balanced any capacity effect. The loss of sinus impulses then caused a rise and an increase of sinus impulses a fall. The sinus was stimulated mechanically.

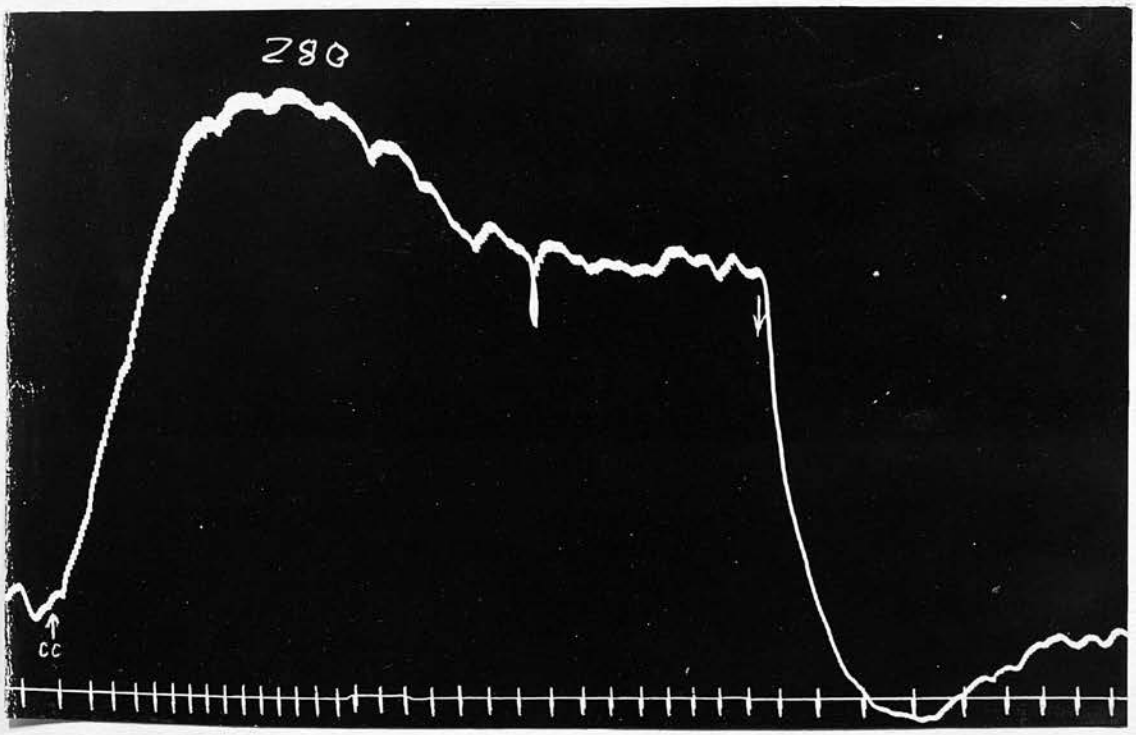


Records of arterial and venous pressures showing the effect on the venous pressure of loss of carotid sinus impulses, the vagi being intact. The change of arterial pressure is so small that it could scarcely be held that it produced cardiac failure. The vagi were intact.

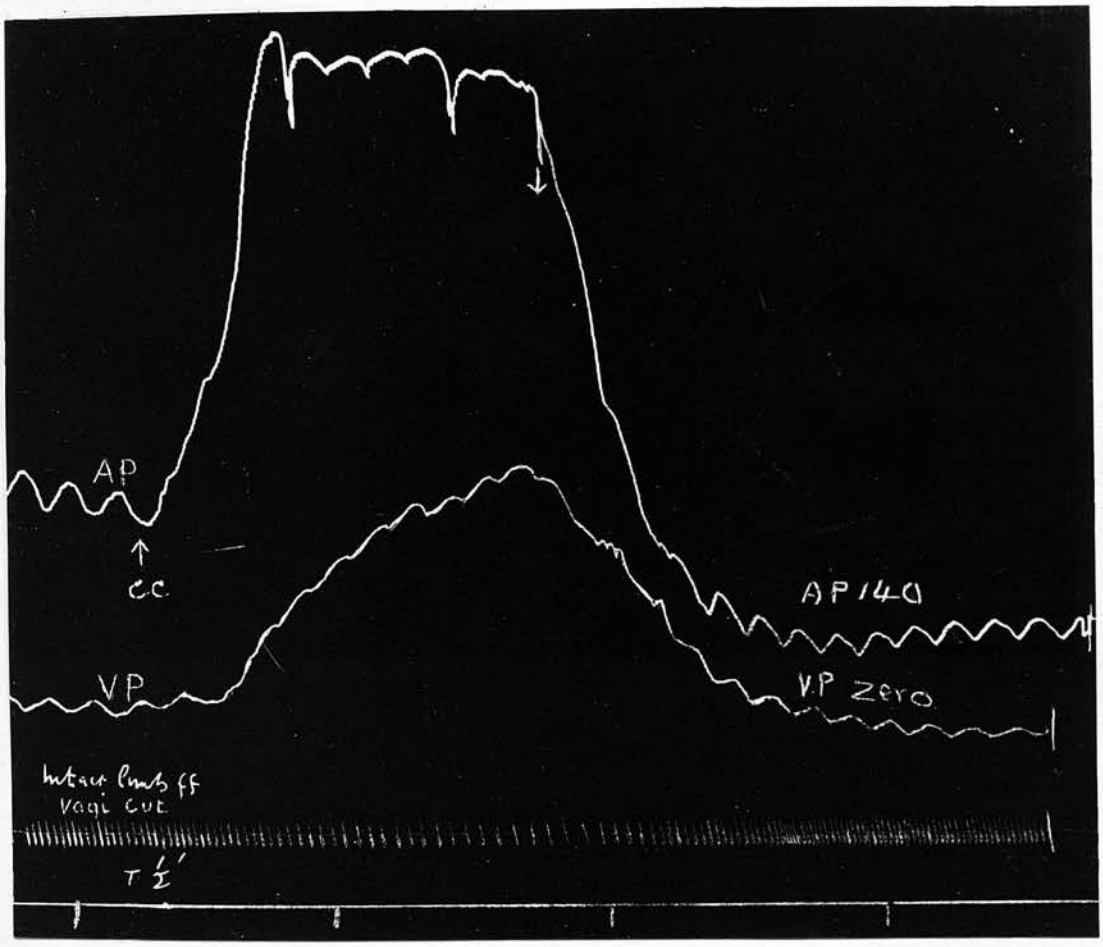


Records of arterial blood pressure and out-flow from the femoral vein showing the increased flow produced by loss of the impulses from the carotid sinus at CC.

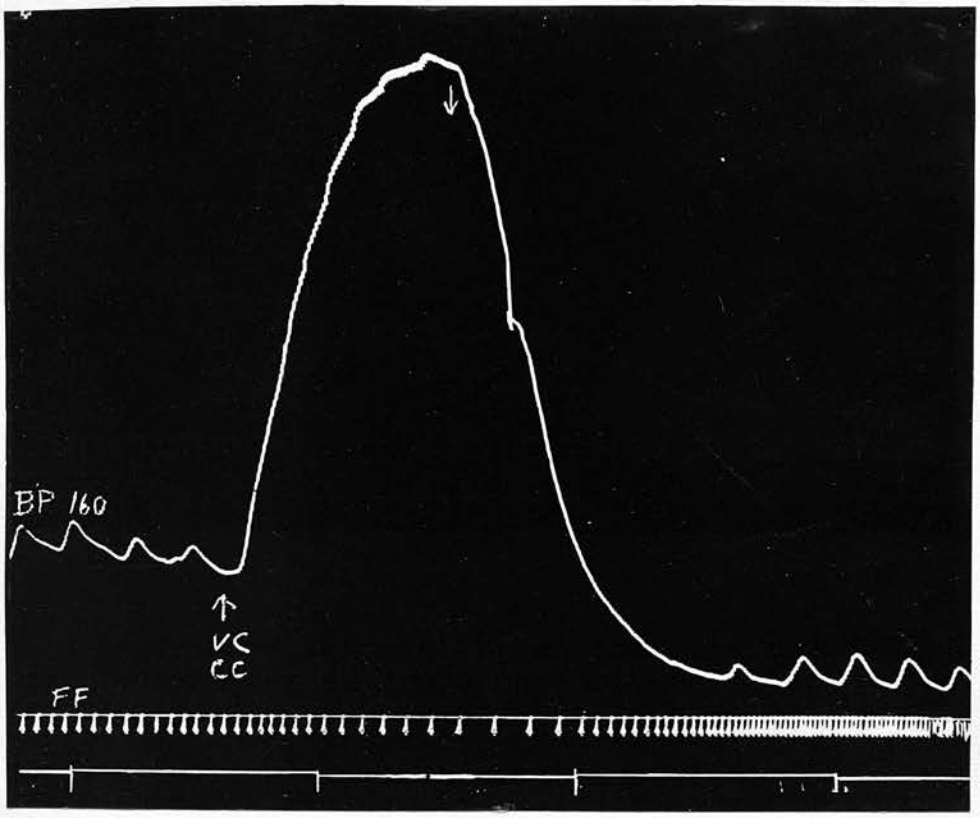




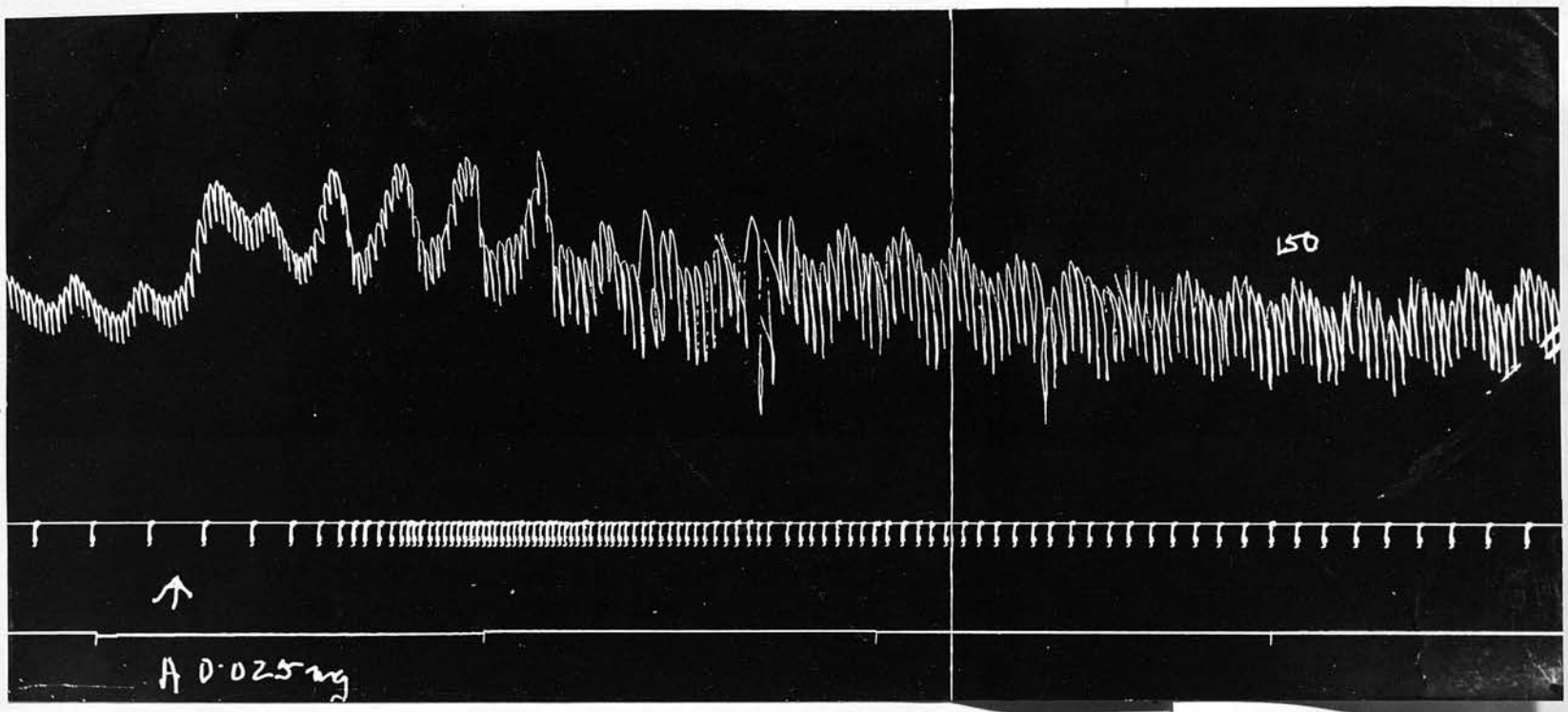
Record of arterial pressure and femoral venous flow recorded in drops showing the effect on the femoral venous flow of repeated application of the carotid clip without returning the blood to the animal. Note that the marked acceleration is absent, although the arterial pressure rises practically to the same height in each instance.



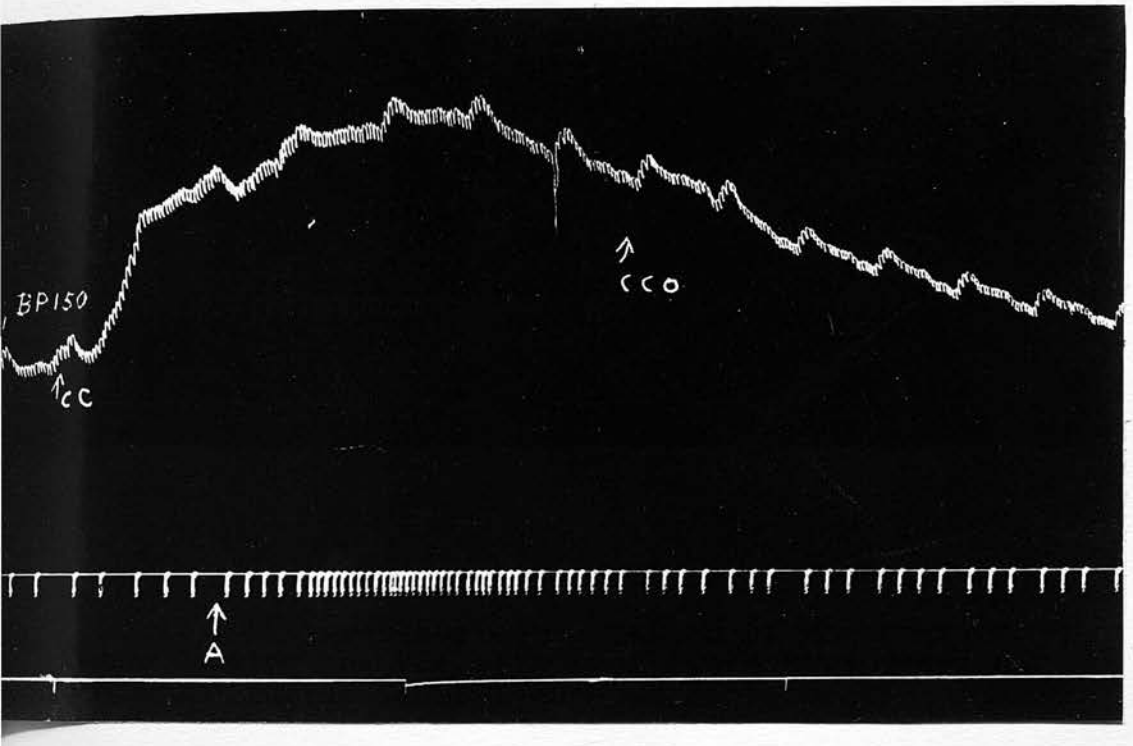
Records of arterial and venous pressures together with the output from the femoral vein in drops. The effect of loss of the carotid sinus impulses after the vagi have been cut. A slight initial acceleration of flow is seen, followed by a marked slowing, presumably the result of the increased peripheral resistance. The rise of venous pressure may have been due to cardiac failure, which is suggested by the extra systoles at the height of the blood pressure.



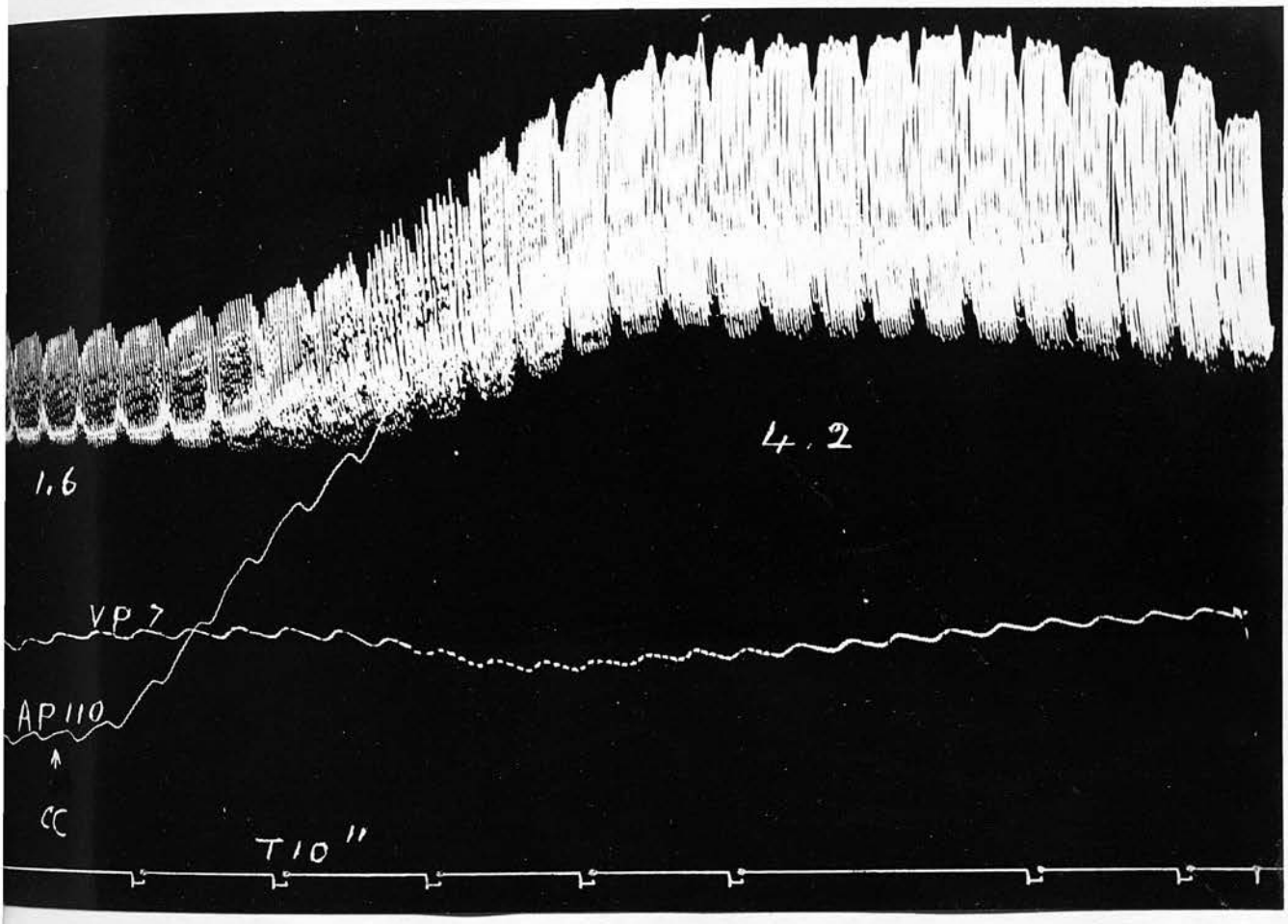
Records of arterial blood pressure and of
e femoral venous flow in drops showing the effect of
ute cerebral anaemia. Note (1) the initial acceleration
flow due to a capacity effect, (2) the diminution in part
e to cardiac failure of the heart to overcome the intense
ripheral resistance and (3) the increased flow when the
rebral circulation is restored. The latter half of the
cord corresponds to the findings of Heymans in relation to the
rdiac out-put.



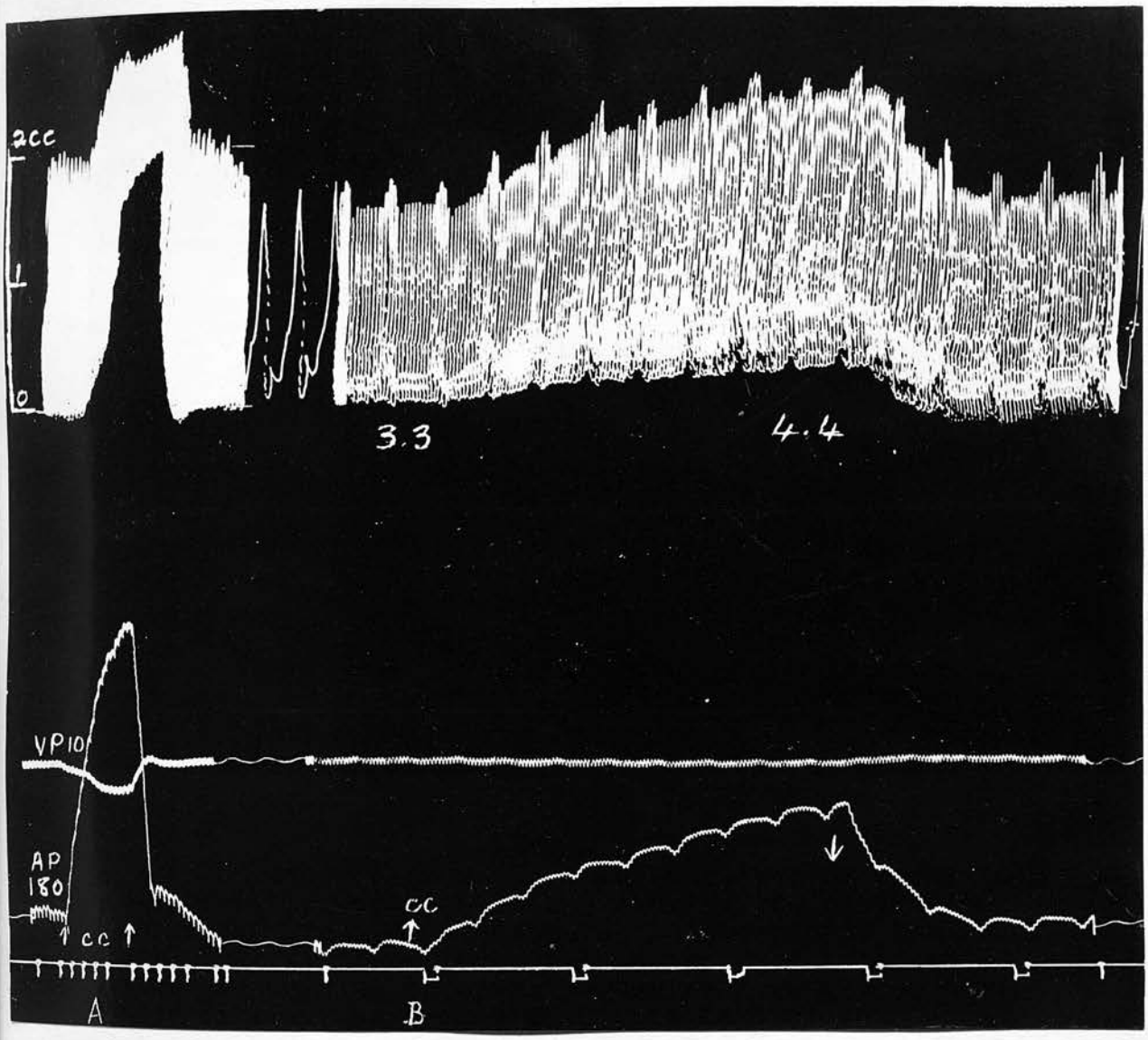
Records of blood pressure and out-flow from femoral vein in drops showing the effect of injecting a small dose of adrenaline 0.025 mg.



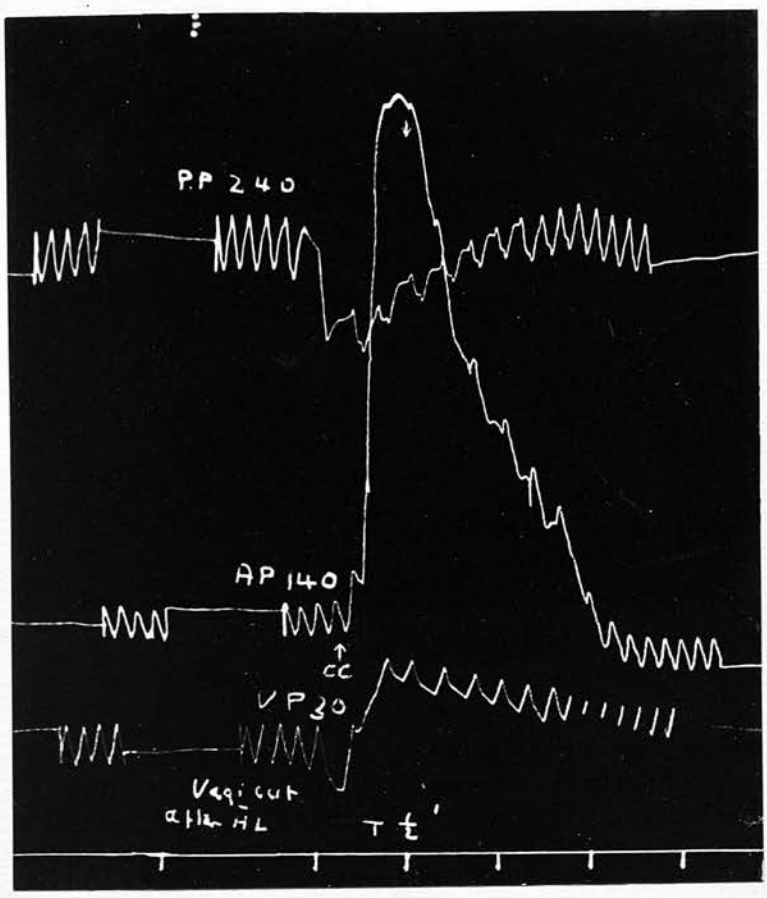
An immediate continuation of the previous figure showing how the effect of successive doses of adrenaline in the femoral out-put is reduced.



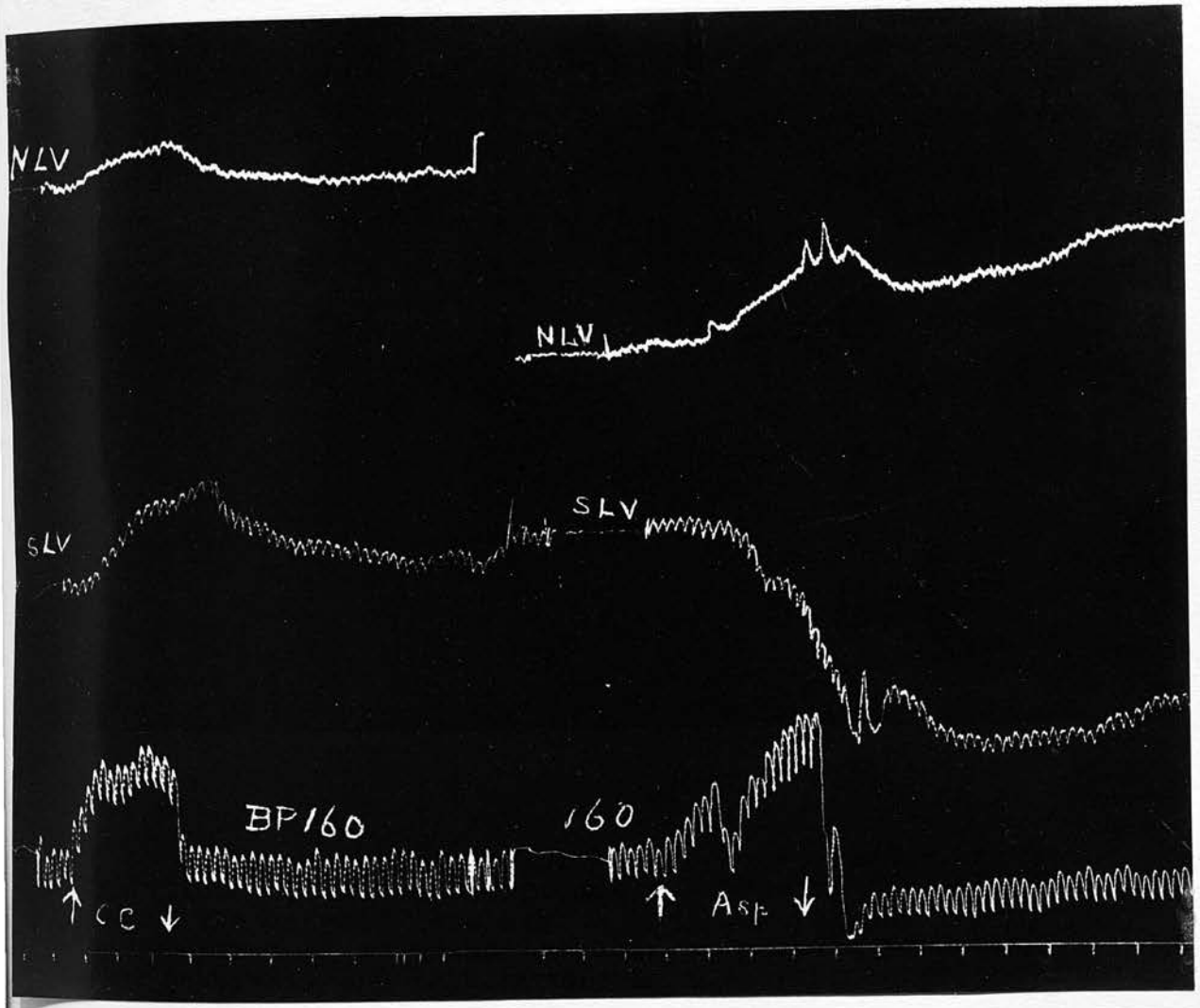
Records of cardiac out-put (upper) with arterial (middle) and venous pressures showing the effect of loss of the sinus impulses at CC on the cardiac out-put, venous and arterial pressures. Scale as in following figure. An increase of out-put from about 27 c.c. per minute to about 100 c.c. per minute has occurred. This result would be anticipated from other work of Heymans which showed that adrenaline is secreted in such circumstances.



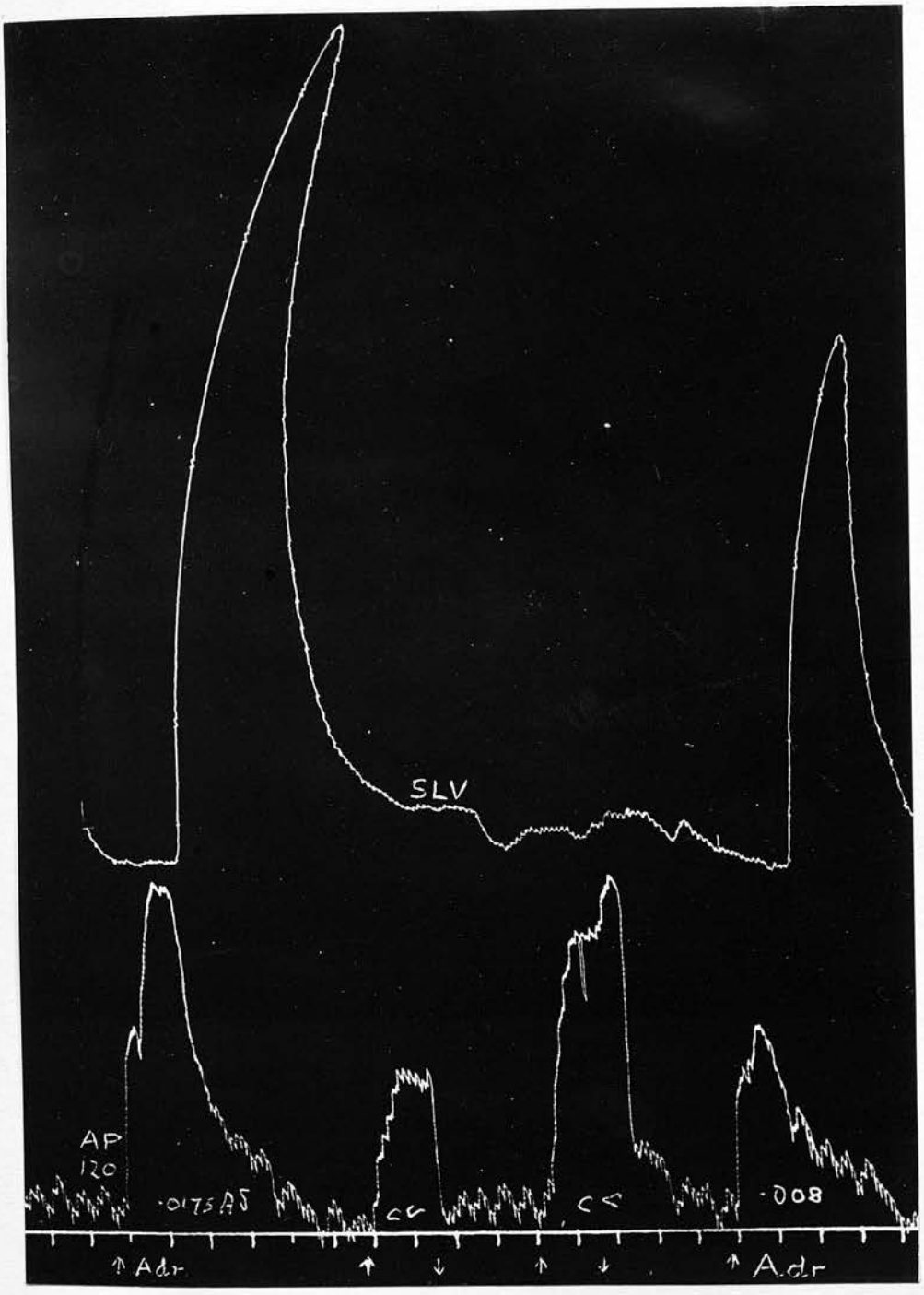
Records of cardiac out-put, venous pressure and arterial pressure (lowest) showing the effect of loss of the sinus impulses upon the out-put of the heart. At A. the effect of loss was associated with diminished cardiac out-put, partly as a result of the venous filling, as suggested by the fall of venous pressure (Heymans,). Immediate repetition of the experiment which gave less action on the arterial pressure show the increased cardiac out-put from about 67 c.c. per minute to about 90 c.c. per minute. The lessened effect of immediate repetition of the experiment is common and is presumed to be due to the secretion of adrenaline, see figures 15 & 24.



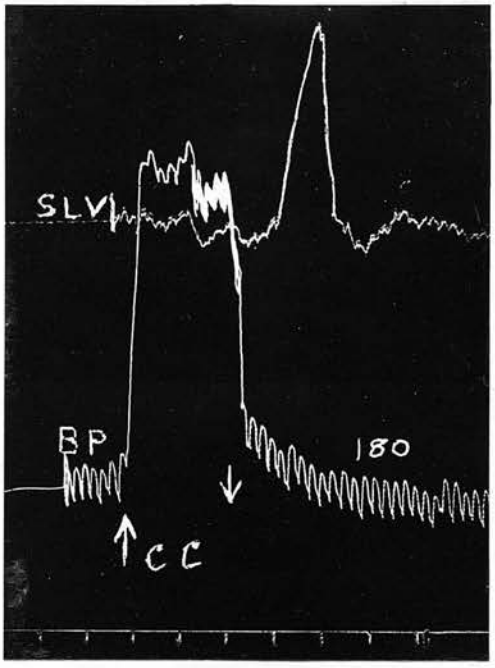
Records of pulmonary arterial (top) carotid (middle) and venous pressures (lowest) showing the effect of loss of the impulses from the carotid sinus at CC. Such a rise of venous pressure could not presumably be associated with right ventricular failure.



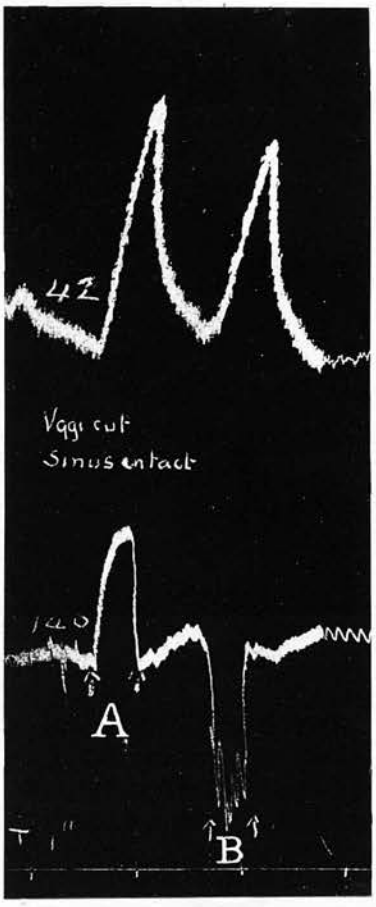
Upper record normal limb volume, middle skinned limb volume, lowest blood pressure. Showing the effect of loss of the carotid impulses on the limb volume. The upper record in which the skin is present probably moves passively and is common. In the second portion of the record is shown the effect of asphyxia.



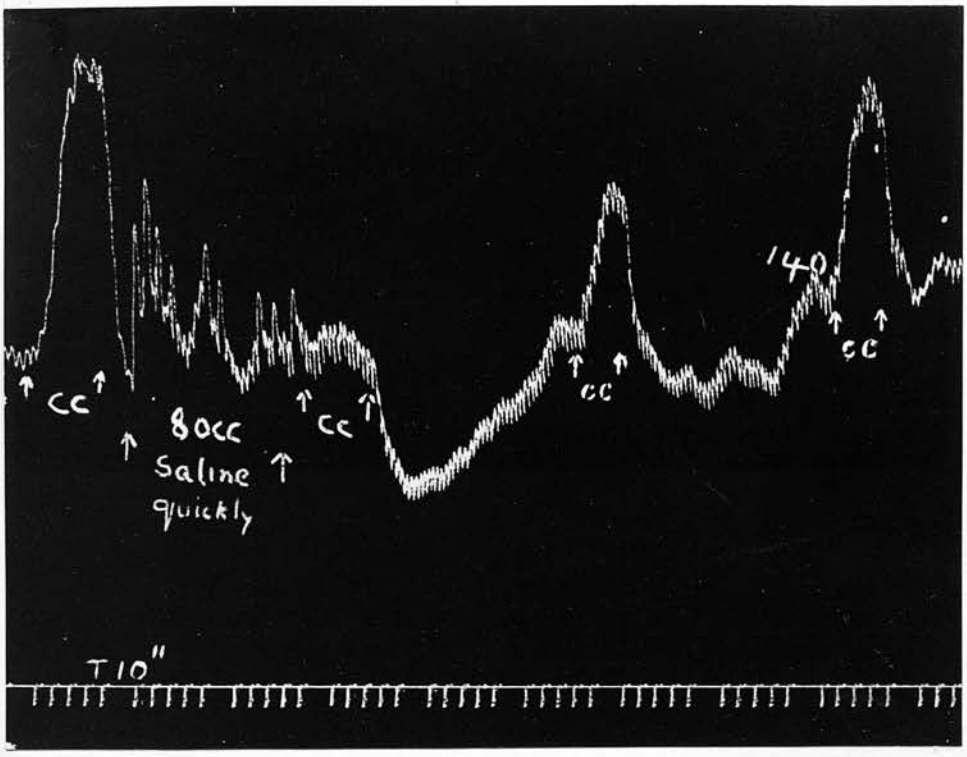
Records of skinned limb volume and of blood pressure showing the effect of loss of sinus impulses on the skinned limb volume. Controls were made by injecting adrenaline. The reduction of the effect of loss of the sinus impulses after the injection of adrenaline is well seen.



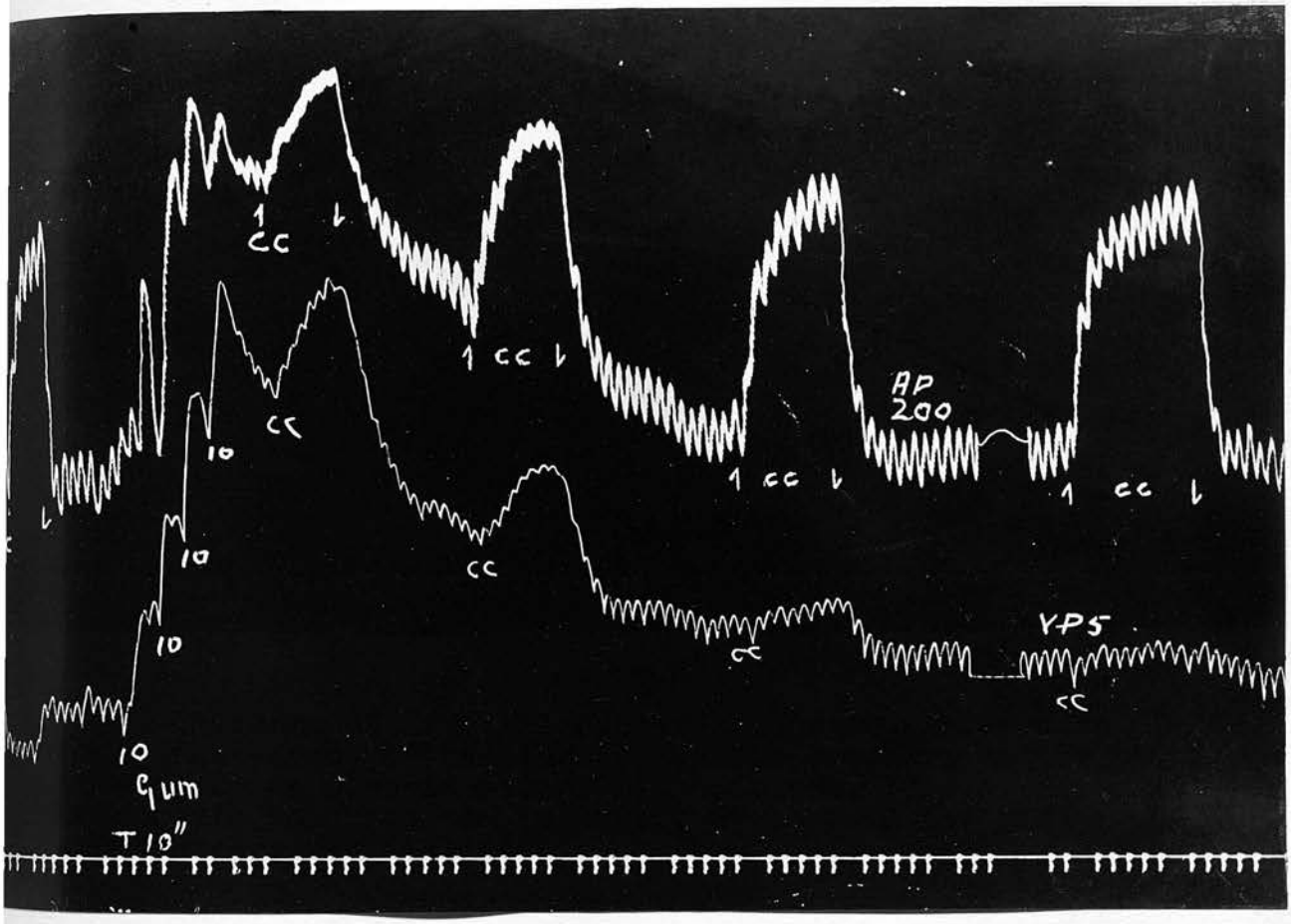
Records of skinned limb volume and arterial pressure showing the effect of the loss of sinus impulses upon the arterial pressure and skinned limb volume. Note the late dilatation.



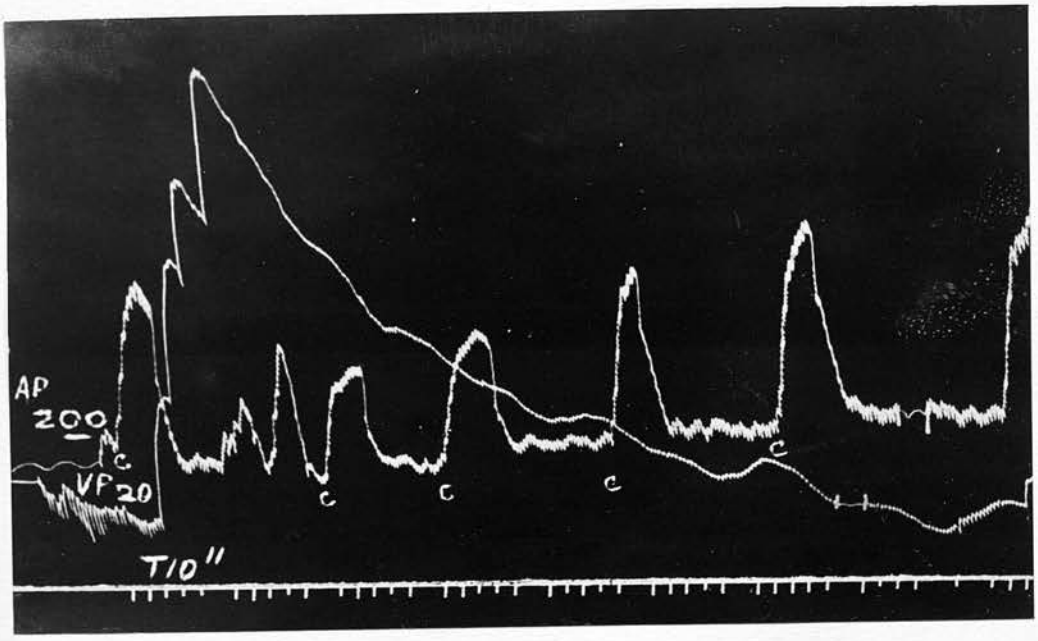
Records of perfusion resistance and of blood pressure (lower) showing the effect, between the arrows, of A. loss of sinus impulses, B. stimulation of peripheral end of vagus, and on the resistance of the vessels of a perfused hind limb with nerves intact.



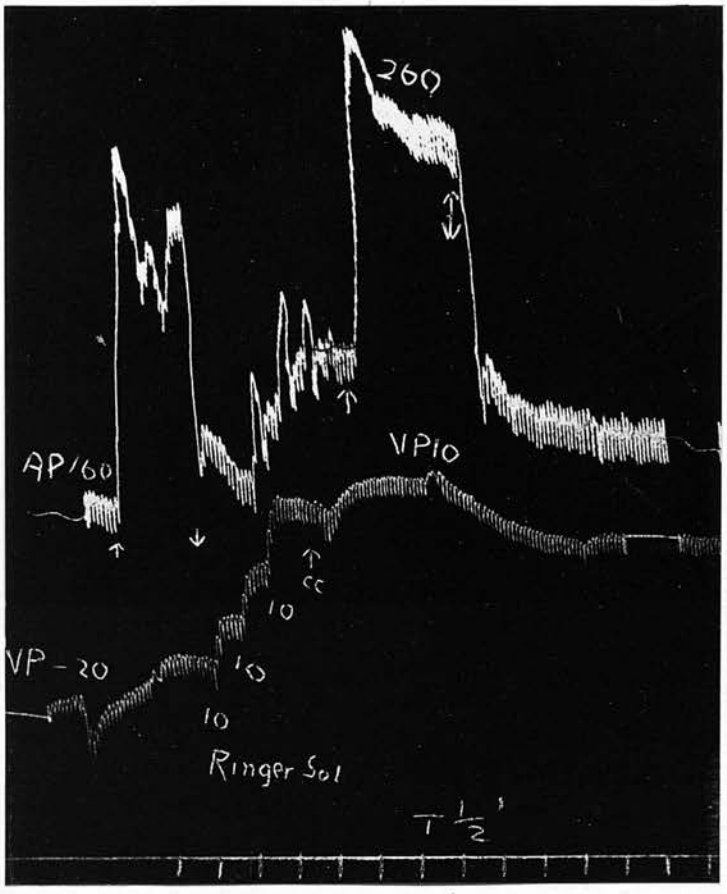
Record of arterial pressure showing complete disappearance of the effect of loss of carotid sinus impulses as the result of the rapid injection of fluid. 80 c.c. of saline were injected quickly.



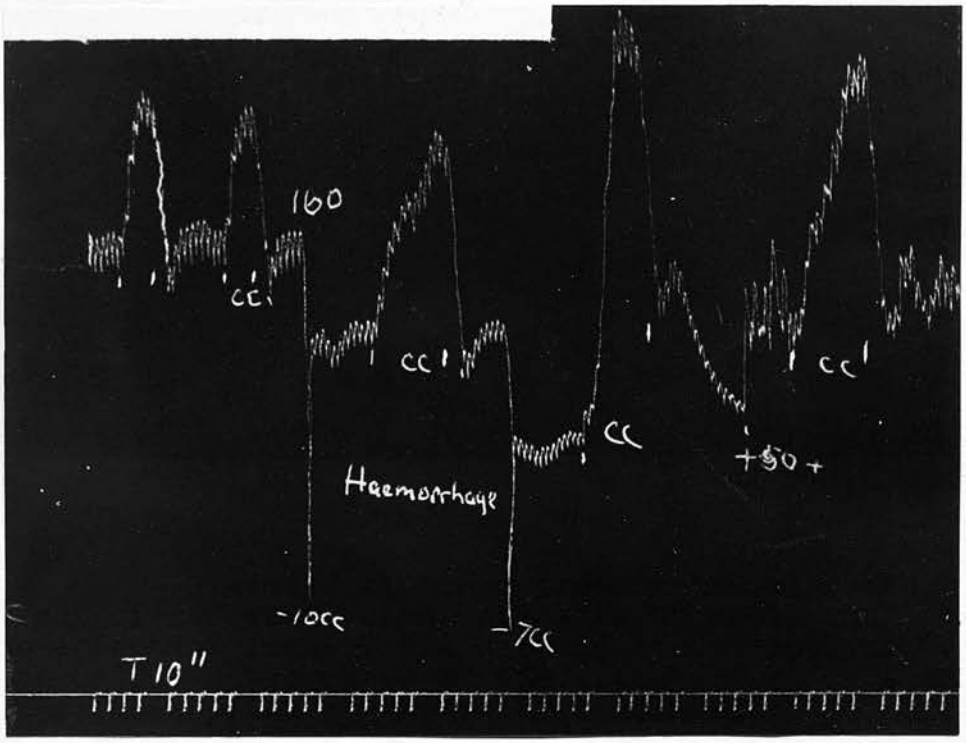
Records of arterial (upper) and venous pressures showing the effect of raising the venous pressure on the response of the carotid sinus. At each ten, 10 c.c. of Gum Ringer's solution was injected, at each CC the right carotid artery was occluded.



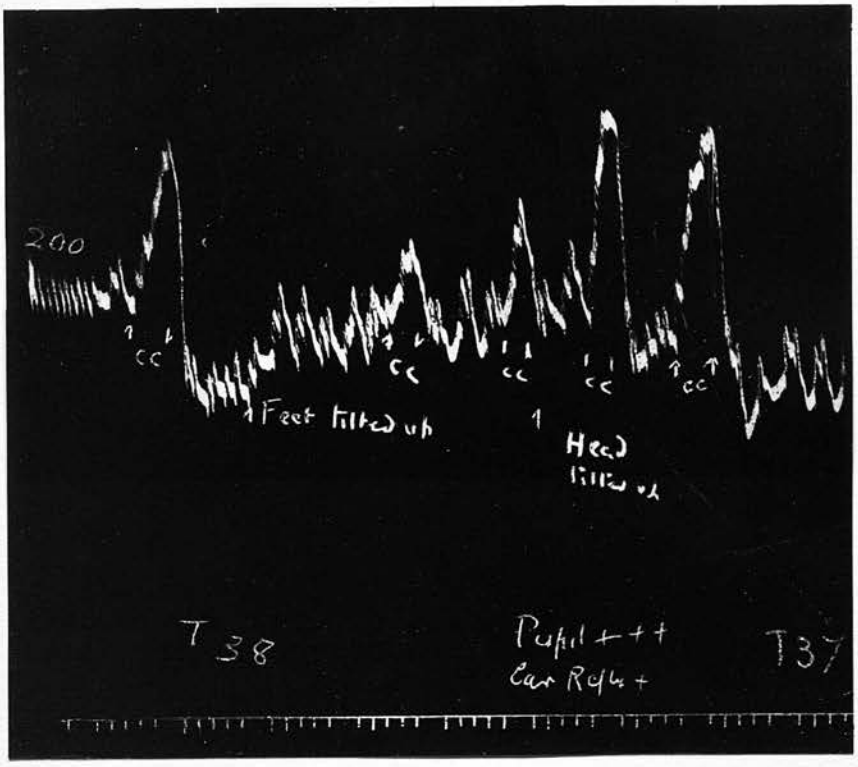
Records of arterial and venous pressures showing the effect of a rise of venous pressure on the effect of loss of impulses from the carotid sinus at C in each instance. In this instance there has been no rise of arterial pressure. 40 c.c. of saline were injected.



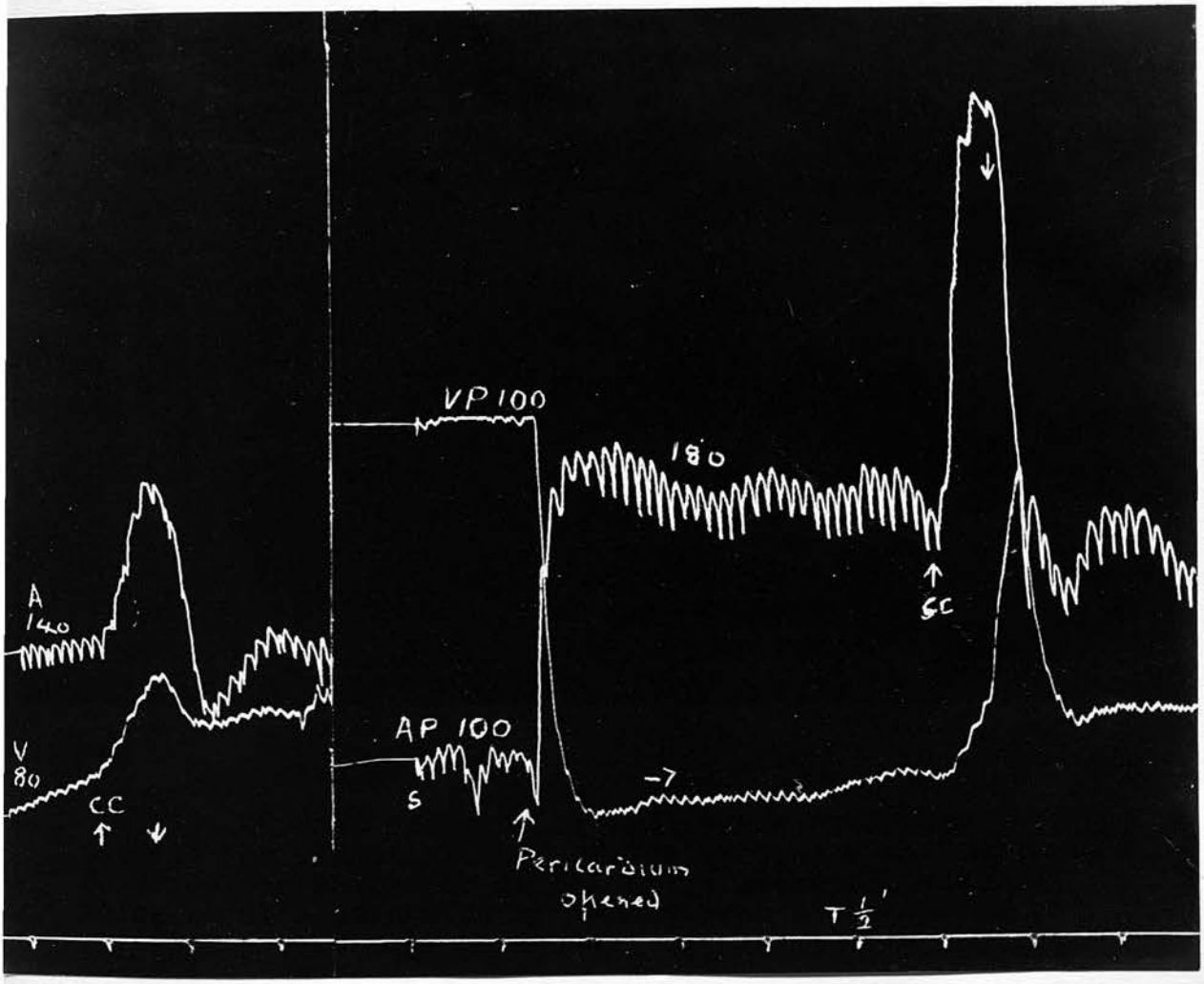
Records of arterial and venous pressures showing the effect of injecting fluid in an animal in shock in which the venous pressure is very low. No diminution in the carotid response is seen. At CC the carotid arteries were occluded in each instance.



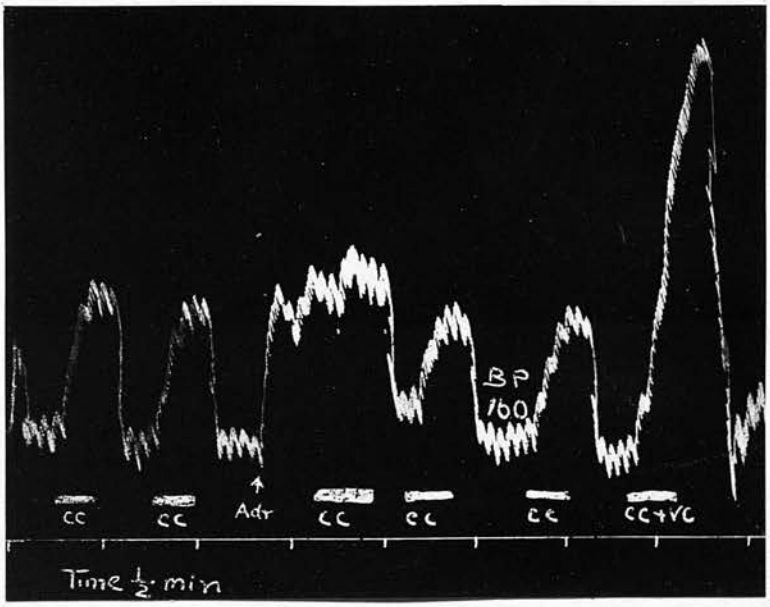
Record of blood pressure showing the effect of reducing venous pressure by haemorrhage on the effect of loss of the carotid sinus impulses (at each CC). Haemorrhage to the extent of 10 c.c. and 7 c.c. took place at the point indicated.



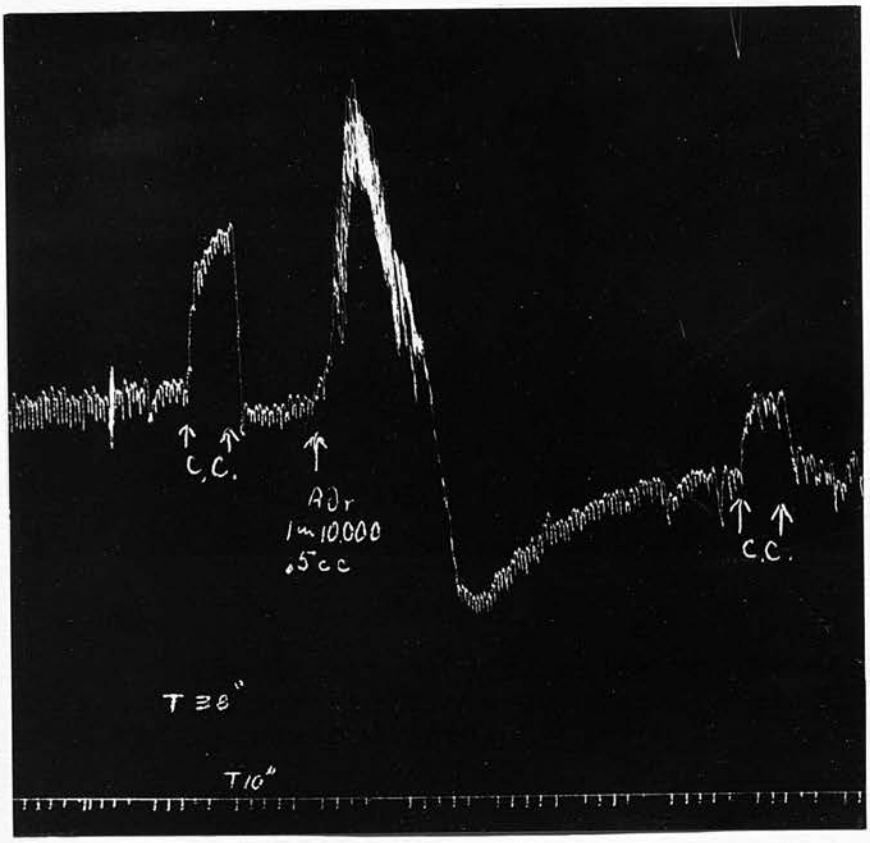
Showing the effect on the response to loss of the carotid sinus of placing the animal in the vertical feet up position.



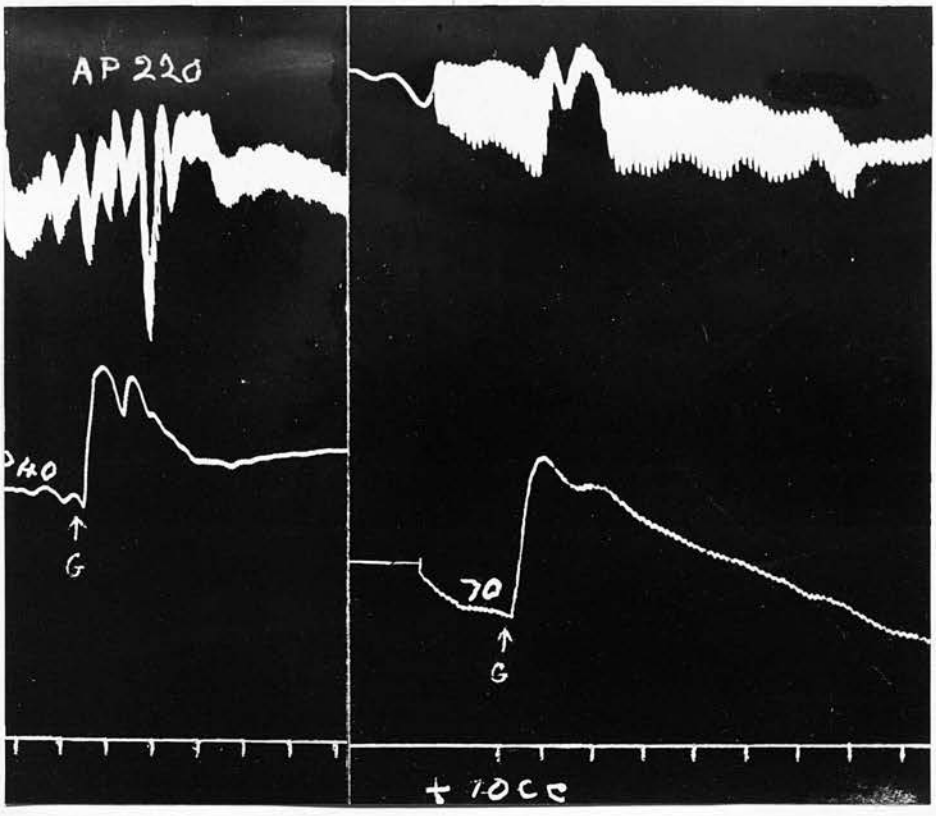
Records of arterial and venous pressures showing the effect of loss of the carotid sinus impulses at CC before and after relief of pericardial oedema, which results in a fall of venous pressure and rise of arterial pressure with recovery of the activity of the carotid sinus.



Record of arterial pressure showing the effect of adrenaline ½ c.c. 1-50,000 on the effect of loss of the impulses from the carotid sinus. That the effect is not due to the pressure having reached a maximum is shown by the effects of simultaneous compression of the carotid and vertebral arteries.



The effect of adrenaline on the effect of loss of the carotid sinus impulses. At CC the carotid artery was occluded.



Record of arterial and venous pressures showing the effect of the injection of gum saline before and after section of the vagi. Between the two injections, 10 c.c. of fluid were removed to make the two results comparable. Other experiments showed that similar results could be obtained whatever the effect of the vagal section had on the venous and arterial pressures. In this instance the venous pressure rose but the writing point was lowered.

SUMMARY OF THESIS

A survey of the literature regarding the vasodepressor and cardiodepressor reflexes is given.

Evidence is put forward that the impulses which arise from the cardioaortic and carotid sinus regions control not only the normal vagus restraint of the heart but also the capacity of the circulation. Loss of these impulses not only causes cardiac acceleration but results in an increased return of venous blood to the heart.

It is shown that conditions which are believed to be produced in exercise and which are known to reduce the vagus restraint of the heart at the same time reduce the effect of the carotid sinus impulses upon the vessels.

The view is therefore put forward that an important function of the vasodepressor reflexes is to control the capacity of the circulation in order to provide a reserve of blood for use in physical exercise, just as is provided a cardiac reserve to deal with such blood maintained by similar reflex mechanisms.

The possible clinical significance of the findings is indicated, and a bibliography of the literature referred to in the text is given.