A Lecture
ON
RECENT WORK ON THE AFFERENT CONTROL OF THE CIRCULATION IN HEALTH AND DISEASE*
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In recent years renewed attention has been paid by many investigators to the part played by the nervous system in the control of the circulation under various conditions, and as a consequence of this work discoveries of great importance have been made which are not only of physiological interest, but promise to throw light on a number of imperfectly understood clinical states. I will attempt in this lecture to summarize very briefly the outstanding results of these researches.

Afferent Nerves from the Heart and Aorta

The best known of the vascular afferent nerves is the so-called depressor nerve, discovered by Ludwig and Cyon in 1866. It is for various reasons, however, preferable to use a purely morphological expression, such as "aortic nerve" or "cardio-aortic nerve." The exact site of peripheral termination of the nerve has been the subject of considerable controversy, and the matter is still unsettled. It is quite certain from embryological (Tello, 1924) and degeneration studies that the fibres end in the adventitia of the arch of the aorta and the beginning of its main branches in a complex ramification leading to sense organs which resemble the Golgi organs of tendon. What is undecided is whether any of the fibres reach the wall of the ventricles. These aortic fibres reach the medulla oblongata by various paths: they may run for a considerable distance as a separate nerve (rabbit), or form an early junction with the vagus or sympathetic. Their route in man is unknown, but probably they do not restrict themselves to any special branch of the vagus. We shall see later that the receptors in the aortic wall are sensitive to changes in pressure, and send up impulses which reflexly regulate blood pressure, heart rate, and adrenaline secretion.

It must be borne in mind that another group of afferents arise from the *venous* side of the heart (right and left auricles and the roots of the great veins), and pass in the vagus nerve to the medulla. These fibres reflexly adjust the rate of the heart so that it may deal effectively with variations in the venous return.

Sympathetic Nerves and Angina

There is good anatomical evidence that large sensory medullated fibres leave the heart in the inferior and middle cervical branches of the sympathetic to join the corresponding ganglia, and thence in the ansa to the first thoracic ganglion or the fused upper two thoracic ganglia (stellate ganglion); other fibres go direct to the upper thoracic ganglia. These afferents travel in the white rami to the upper four (or more) thoracic posterior nerve roots, and thus into the spinal cord. No sensory medullated afferents have yet been demonstrated in man above the level of the middle cervival ganglion. The afferents in the sympathetic appear especially to subserve *pain* sensibility. The referred pain in angina pectoris and coronary disease is felt in the arm and chest, chiefly in the distribution of the eighth cervical to the fourth thoracic posterior roots. There is thus agreement with the anatomical findings given previously. In this connexion it is worth recalling that according to Leriche (1925) the anginal syndrome may be reproduced in man by stimulation of the stellate ganglion, injection of novocain into which may arrest a spontaneous attack of angina.

Various operations have been devised for angina pectoris with the object of dividing the path subserving the distressing pain sensibility. Jonnesco (1920), with this end in view, has removed the cervical sympathetic and first thoracic ganglion on the left side or on both sides, and claims to have obtained relief. Other workers (Cutler, 1927) have carried out similar though less extensive procedures. Although the published results are on the whole favourable, there can be little doubt that such drastic intervention is fraught with real danger in patients with heart disease. Operations limited to the *upper* part of the cervical sympathetic have been recently carried out. According to Coffey and Brown (1923) and Levene and Newton (1925), relief of pain has been effectively obtained by these measures, although the main afferents in the sympathetic have undoubtedly been left intact. It is very difficult in the present state of our knowledge to account for these results.

Structure and Innervation of the Carotid Sinus

The physiological and morphological studies of Hering (1927), Heymans (1929), de Castro (1928), Koch (1931), and others have clearly shown the great importance of the sinus caroticus in the control of the circulation, and have opened up a field of study rich in application to many practical problems. The term "carotid sinus" (sinus caroticus) is applied to a dilatation normally present at the bifurcation of the common carotid artery, and well known to anatomists for over fifty years. The exact situation of the dilatation varies slightly in different species, and in different individuals of the same species. In man it is most commonly restricted to the first part of the internal carotid, but it may chiefly involve the common carotid, or commence in the common and extend to the internal carotid. It is seen not only in healthy young adults, but also in young infants; it is absent in the foetus. There is no doubt that it is a perfectly normal structure. The wall of the sinus is thinner than that of adjacent parts of the artery, owing to a decrease in the number of muscle fibres in the media.

Numerous sensory receptors lie in the deeper part of the adventitia (de Castro). They are derived from large medullated fibres, which break up into an extensive and diffuse arborization. The terminal filaments wind spirally through the adventitia, or give off branches which, lying between the concentrically arranged fibrous lamellae, terminate in characteristic menisci. This sensory network is restricted to the wall of the sinus, and does not extend beyond it to the contiguous part of the artery. The sensory fibres are most numerous where the media is thinnest; their general arrangement closely resembles that found in the aortic wall, and the terminals appear well adapted to respond to changes in the internal pressure of the artery.

The nerve which leaves the sinus—n. intercarotidien (de Castro), r. caroticus glossopharyngei, sinus nerve (Hering)—joins the glossopharyngeal: connexions may also be made with the neighbouring structures, such as the vagus and, perhaps, the superior cervical ganglion and the hypoglossal nerve.

There is little doubt that the sinus nerves form the physiological complement of the aortic nerves, and function as pressure-receptors in the same manner. It seems strange at first sight that this special part of the arterial bed should be singled out. One might suppose that the rich sensory innervation of the internal carotid was associated with its relation to the cerebral circulation; but the sinus is equally well developed in animals like the rabbit or cat, in which the internal carotid is very minute, and supplies the brain only to a slight extent. Embryological considerations again help to make the position

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clearer (Koch, 1931). The first part of the internal carotid artery is derived from the third arch. It is found that all the arteries having a rich sensory innervation are those which represent the original arterial arches—namely, the aorta and its innominate branch, and the first part of the internal carotid.

AORTIC NERVES AND SINUS CAROTICUS: PHYSIOLOGY AND PATHOLOGY

The aortic and sinus nerves, through the connexions they establish with the bulbar centres, exert a most important controlling and stabilizing influence over the circulation. It is useful to have a single term to describe these four nerves: they have been called *Blutdruckzügler* (Hering), *Blutdruckregler, Pressorezeptorische Nerven* (Koch). Perhaps a convenient English equivalent may be the " buffer " nerves of the circulation.

AORTIC NERVES

It is well known that central stimulation of the separate aortic (depressor) nerve of the rabbit reflexly produces slowing and diminution in the force of the heart, vaso-dilatation, and a fall of blood pressure. The heart effect is due mainly to an increase in vagus activity, to a less extent to depression of accelerator tone, and perhaps also to decreased adrenaline secretion. The fall of blood pressure is partly cardiac in origin and partly the result of widespread vaso-dilatation in the splanchnic area, skin, mucous membranes, and glands. The cerebral vessels definitely share in the relaxation, but the effect on the kidney is doubtful. It is probable that the capillaries and the veins (Fleisch, 1930) may also be involved. The dilatation is caused by reflex inhibition of the vaso-constrictors and stimulation of the vaso-dilators, especially (Bayliss) the antidromic dilators in the posterior nerve roots. There is little doubt that, in the main, the aortic nerves in the normal resting animal exert a *tonic inhibitory* influence on the bulbar centres. Section of these nerves causes acceleration of the heart, a rise of blood pressure, and an increase in adrenaline secretion (*vide infra*).

It can be demonstrated, by means of capillary electrometer studies (Adrian, 1926), that nervous impulses do not flow continuously along these nerves. A series of large electrical oscillations is set up at the beginning of systole coincident with the onset of ventricular ejection, and a further small discharge coincides with the dicrotic wave ; there are no further action currents during the rest of diastole.

By means of cross-circulation experiments (Heymans, 1929) it can be readily shown that the sensory receptors of the aortic nerves are stimulated by changes in the cardio-aortic pressure, and that a rise of pressure increases their inhibitory activity. There is also evidence suggesting that the aortic nerves contain pressor fibres which come into action when the arterial blood pressure is low, and produce the reverse effects on the bulbar centres.

PHYSIOLOGY OF THE SINUS CAROTICUS

Czermak (1866) noted that pressure on the carotid artery at the level of the upper margin of the sterno-mastoid (where a definite round swelling of the vessel could be felt) brought about slowing of the heart. He believed that the swelling, which he attributed to dilatation and thickening of the artery, mechanically stimulated the inhibitory efferents in the vagus, and thus produced the effect. Doubt was first cast on this interpretation by Hering (1923), and soon Koch pointed out that the reaction could only be obtained from the region of the bifurcation of the carotid. Finally, Hering (1927) showed that pressure on the sinus caroticus, without any mechanical involvement of the vagus, gave identical results, and concluded that the *Druckversuch* of Czermak is a reflex phenomenon due to afferent inhibitory impulses arising in the sinus: later it was observed that vaso-dilatation formed part of the reflex response. The question of the sensitivity of the vagus nerve is of considerable importance. Direct experiment shows that the efferent cardiac fibres of the vagus are very insensitive to mechanical stimulation. The afferent fibres, under certain conditions of animal experimentation, may respond readily to both mechanical and thermal stimuli, with depressor, and sometimes pressor, effects. These afferents, judged by the results of direct stimulation at operations, are less sensitive in man, but it is possible that during carotid compression stimulation of the afferent fibres in the vagus may contribute somewhat to the total reaction.

So-called vagus compression has been employed as a therapeutic measure in a number of conditions. It is obviously desirable in the light of these facts that this form of treatment should be re-examined.

Compression of the freely exposed sinus caroticus in animals and man (Budde, 1926) is followed, as stated, by a fall of blood pressure and slowing of the heart ; the same is true of electrical stimulation. After injection of atropine to paralyse the vagal terminals, no slowing of the heart is produced, but the blood pressure is still lowered ; this proves that vaso-dilatation also occurs. The response can only be elicited from the sinus region, and not from adjacent parts of the artery ; it is abolished by section of the sinus nerves, and so is undoubtedly reflex in character. Interference with the cerebral circulation is not a factor, for the same result is obtained if the carotids are previously occluded. It must be borne in mind that the method of stimulation employed is not physiological, and can never come into operation in the normal body.

TRACTION ON THE CAROTID ARTERY

Sollmann and Brown (1912) observed that downward traction on the head end of the common carotid artery lowers the blood pressure and slows the heart ; the fall is greater when both arteries are pulled on simultaneously, and occurs equally well after ligation of the vessels. Traction on the central end of the common carotid artery headwards was found to be ineffective. By examining various structures in turn they found that the reaction was brought about by traction on the internal carotid artery alone, and was abolished by denervation of the vessel. After the discovery of the sinus caroticus it was easy to demonstrate that traction mechanically stimulated the sensory depressor-receptors in the sinus, and that the reflex—as it obviously is—was abolished by section of the sinus nerves. Budde (1926) showed that operative procedures in man involving traction on the neck similarly cause lowering of blood pressure (down to 80 mm.). Morphine, certain stages of chloroform anaesthesia, and digitalis all exaggerate the degree of cardiac slowing which may be obtained when the depressor-sinus reflex is set up. It may be sometimes worth while, in order to minimize the degree of surgical shock from operations on the neck, to paralyse the sinus nerve endings by means of the local application of cocaine.

PHYSIOLOGICAL STIMULATION OF THE SINUS CAROTICUS

The endings in the sinus caroticus can easily be stimulated by the introduction of a sound into the artery (Hering, 1927), but the more physiological procedure is to vary the pressure of fluid within the vessel. All the branches of the common carotid artery are tied, care being taken to ligate the internal carotid distal to the sinus, and not to damage the nerve filaments. A cannula is inserted into the common carotid and attached to a pressure reservoir, so that the internal pressure may be varied at will (Koch, 1929) ; or else the artery and sinus are perfused from a Dale-Schuster pump or from another animal, the fluid being led away by means of another

cannula in the central end of the lingual artery (Heymans, 1929). Under these conditions the sinuses are isolated from the circulation, and are only connected with the central nervous system by means of their afferent nerves. The type of stimulation employed closely resembles that which might come into operation in the body. It can thus be readily shown that the receptors in the wall of the sinus caroticus are very sensitive to changes of internal pressure, an increase of which reflexly produces vaso-dilatation and slowing of the heart, a fall reflexly giving rise to vaso-constriction and acceleration of the heart. The cardiac slowing (resulting from raised sinus pressure) is due mainly to reflex increase in vagus tone, but when the sinus pressure is very high some inhibition of accelerator tone also occurs. The vaso-dilatation involves the splanchnic area (spleen, intestine, kidney), and the cerebral vessels probably also share in the relaxation. A detailed report on these changes has recently been made by Heymans, Bouckaert, and Dautrebande (1931). The sinus reflexes just described are abolished on section of the nerves arising from the sinus.

Occlusion of the Carotid Arteries

It has been known since the earliest days of physiology that occlusion of the carotid arteries produces a rise of blood pressure and acceleration of the heart, and that on disocclusion the blood pressure falls and the heart slows (sometimes temporarily below the original level), and then gradually returns to normal. The rise of blood pressure is to some extent mechanical in origin (Magendie, 1837), and it is also possible that a certain degree of cerebral anaemia develops during the period of occlusion, and stimulates the bulbar centres (Couty, 1876). The principal factor, however, is the fall of pressure in the sinus caroticus, with its characteristic pressor reaction. If the occlusion is practised after denervation of the sinuses a far smaller rise of pressure is obtained. The reflex constriction involves the splanchnic area, but similar pressor effects are observed after previous section of the splanchnic nerves, so that doubtless other parts of the vascular bed are involved. There is a marked rise of pressure in the portal vein and evidence of increased venous tone (Heymans and Bouckaert, 1930).

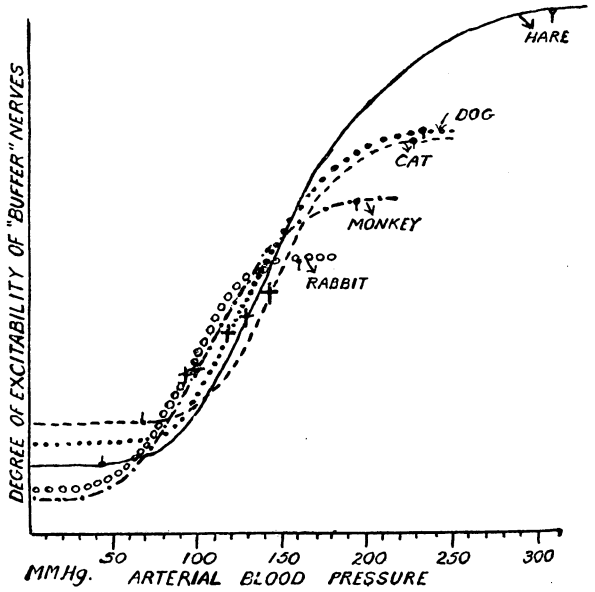
The effects following the re-establishment of the carotid blood flow are due mainly to distension of the sinuses and to a minor degree to the removal of the anaemia and of the mechanical resistance.

Tonic Influence of the Sinus Nerves

Hering (1927) and Koch (1931) consider that the sinus nerves exercise solely a tonic *inhibitory* influence on the circulation, and that the afferent discharge in them is dependent on an adequate degree of distension of the sinus caroticus by the blood pressure. They regard the rise of pressure and acceleration on carotid occlusion as due to a decrease or abolition of sinus inhibitory action owing to a fall of the sinus pressure below threshold value ; they suppose that afferent impulses cease to pass up to the bulbar centres, which consequently overact. In support of this view is the fact that section of the sinus nerves or cocainization of the sinuses produces similar pressor effects. But it does not seem possible as yet to exclude conclusively the existence in the wall of the sinus of pressor fibres which are stimulated by the fall of pressure.

Sinus Pressure, Blood Pressure, and Heart Rate

The sensitivity of the sinus to internal pressure change is remarkable ; a deviation of 10 mm. is sufficient to cause a reflex response. Koch (1929) studied the reflex effect on blood pressure of raising the pressure from zero to various levels in the isolated innervated carotid sinus. The other buffer nerves (that is, the other sinus nerve and the two aortic nerves) were severed to prevent them setting up compensatory reactions, and the vagi were cut to exclude cardiac effects. The results were plotted, with the pressure in the sinus along the abscissa and the percentage fall of blood pressure on the ordinate (see Fig.). The curve is S-shaped in all the species examined (cat, dog, rabbit, hare, monkey), though with important differences of detail. The smoothness of the curve is noteworthy in view of the complexity of the reflex path involved and the extensive effector organ



Blood pressure " characteristics " in different species (after Koch).

employed. The main features are these: there is a threshold value for the sinus pressure below which no reflex is set up (this varies from 30 to 70 mm. Hg) ; at the other extreme there is a maximum effective pressure beyond which there is no additional response (this varies between 150 and 300 mm.). The curve is steepest in the normal blood pressure range, and it is interesting to note that the actual turning-point (*Wendepunkt*) marked with + on the tracings, agrees very closely with the normal average level of blood pressure in the particular species studied—the figure for the monkey is 85 to 95, the rabbit 90 to 95, the dog 110 to 135, and for the cat 145 mm. Hg. This finding is probably related to some extent to the elastic properties of the wall of the artery. Inspection of the curve shows that variations in sinus pressure on either side of the *Wendepunkt* cause the greatest reactions. In the intact animal, therefore, when the blood pressure tends to deviate from the normal, the receptors in the sinuses will respond in a very sensitive manner, will affect the bulbar centres appropriately, and will rapidly restore the blood pressure to its usual level.

These results have been substantially confirmed by Heymans and Bouckaert (1929) for the dog, except that they find that when the pressure in the sinus was raised from 0 to 50 mm., instead of getting no response (as claimed by Koch), they obtained a reflex rise of pressure. This surprising reaction, which is difficult to explain, may, I have found, also be seen in the cat.

Further studies have been made in animals with intact vagi to determine the relation beween sinus pressure and heart rate ; the results are plotted in the same way, except that the ordinate represents the duration of the cardiac cycle (Koch, 1929). The type of curve is very similar, and again the turning-point of the curve and the region of most sensitive reactions is at about the normal resting heart rate. The sinus caroticus can thus efficiently

maintain reflexly the normal resting heart rate as well as the resting blood pressure.

Like the tension receptors in skeletal muscle and tendon, the sensory endings in the wall of the sinus do not show "adaptation" (in Adrian's sense) to any degree: in other words, if the pressure in the isolated sinus is raised to a certain height for some time, the reflex fall of blood pressure and the cardiac slowing persist throughout this period at a fairly steady level.

Relation of Sinus Caroticus to Heart Rhythm

Occlusion of the carotids is very apt to set up various kinds of cardiac irregularities, especially in the rabbit (Kisch, 1921, Kisch and Sakai, 1923), less commonly in the cat or dog. The disturbance of rhythm is facilitated by certain concentrations of morphine and by previous section of the aortic nerves. It cannot be attributed to the rise of blood pressure adversely affecting the heart, because it may occur without rise of blood pressure. Further, hypertension produced in other ways does not produce this arrhythmia. Nor can it be said to be due to cerebral anaemia, for the arrhythmia is abolished by central stimulation of the aortic nerve or of the sinus nerves—procedures which lower the blood pressure and further decrease the cerebral blood supply. A similar arrhythmia is set up by denervation of the sinuses. The arrhythmia persists after section of the vagi, but is abolished by section of the cardiac sympathetics or by paralysing them with ergotamine (Regniers, 1930). These results strongly suggest that the sinus nerves exert a tonic inhibitory influence over the cardiac sympathetic, and thus help to maintain the normal cardiac rhythm.

The irregularity most commonly observed during carotid occlusion is the onset of extrasystoles; they may be solitary or form runs of varying length, and may arise from the right or left ventricle or from both. They do not necessarily persist throughout the period of occlusion, and may be less marked, or absent, during subsequent occlusion. Occasionally fibrillation sets in and proves fatal.

There is much evidence (that cannot be quoted here) that the sympathetic increases cardiac irritability. Carotid occlusion probably removes the normal afferent inhibitory influences which are exerted on the cardiac sympathetic, and may also set up pressor impulses which reflexly stimulate the sympathetic, and thus the arrhythmia noted above is produced.

Carotid Sinus, Aortic Nerves, and Adrenaline Secretion

It has hitherto been generally believed that adrenaline is not secreted in the resting condition of the body, but is only poured out in states of stress and emergency. It is becoming difficult, however, to maintain this position in the face of the recent evidence. When both adrenals are removed in an acute experiment the blood pressure usually tends to fall gradually—for a time, at any rate—though recovery may later set in. If the nerves to the heart have been previously divided (and the hepatic nerves cut to prevent the formation of an unknown accelerator substance made in the liver), adrenalectomy is also followed by a definite decrease in the pulse rate. By means of the technique of Tournade and his co-workers it is possible to drain the blood from the suprarenal vein of one animal—the donor (A)—into the jugular vein, and thus into the general circulation, of an adrenalectomized animal—the recipient (B)—(suprarenal-jugular anastomosis). It is found that the entrance of the suprarenal blood into B causes the blood pressure to rise, the arterioles to constrict (the volume of the spleen decreases), and the rate of the denervated heart to go up. These observations prove clearly that a resting secretion of adrenaline goes on in A which can compensate for the loss of the adrenals in B. Cannon and Rapport (1921) found that the rate of the denervated heart in the adrenalectomized animal may be restored by perfusing 0.00007 mg. adrenaline per kg. per minute, and this is probably a rough measure of the amount of the resting secretion.

It has been shown by Tournade and his co-workers that adrenaline secretion is adjusted in such a manner as to assist in steadily maintaining the normal resting blood pressure. Thus, if the blood pressure of the donor (A) is lowered by haemorrhage or by stimulation of the peripheral end of the vagus, adrenaline secretion is increased; if the blood pressure is raised (for example, by injection of a large volume of blood) the secretion is arrested. Even very slight changes in the blood pressure may appropriately modify adrenaline secretion.

Developing this work, Heymans (1929) found that the regulation of adrenaline secretion to blood pressure needs is reflexly controlled by the aortic and sinus nerves. Richards and Wood (1915), and Cannon and Rapport (1921), had found that central depressor or central vagus stimulation could arrest adrenaline secretion; while Houssay and Molinelli (1924) were able to show that the vagus nerve also contains afferents which can increase the secretion. Heymans perfused the isolated sinus caroticus (connected only by its nerve supply to the central nervous system) of an animal (A), connected by means of a suprarenal-jugular anastomosis with an adrenalectomized recipient (B). He was able to demonstrate that a rise of pressure in the sinus inhibited, and a fall of pressure in the sinus stimulated, adrenaline secretion in A. Using Tournade's technique, he further showed that occlusion of the carotids when the sinuses were innervated stimulated adrenaline secretion, but not when the experiment was repeated with the sinus nerves destroyed—in other words, pressure changes in the circle of Willis do not directly affect the centres regulating adrenaline secretion. If the sinuses are denervated changes in the general blood pressure can still reflexly modify adrenaline secretion when the vagi are intact, but produce no effect when the vagi are cut. These experiments prove convincingly that adrenaline secretion is reflexly adjusted by means of the aortic and sinus nerves, and that neither the glands nor the bulbar centres controlling them are acted on directly by the level of the blood pressure.

At rest, the aortic and sinus nerves seem to exert in the main a tonic inhibitory influence over adrenal activity; it is found that denervation of the sinuses stimulates adrenaline secretion. Goormantigh and Elaut (1929) have made confirmatory histological observations.

Sinus Caroticus Reflexes in Man

Pressure applied to the sinus region in normal man is succeeded by reflex depressor effects consisting of slowing of the heart and a fall of blood pressure (Koch, 1923, Mandelstamm and others, 1929). When sinus compression (sinus reflex) and pressure on the eyeballs (oculo-cardiac reflex) are carried out on a large series, it is found that the latter is most easily elicited in young healthy subjects, while the former is especially observed in old people with arterio-sclerosis, in whom the neck vessels are thick, and can be readily rolled under the finger.

The marked reflexes which are obtained in arterio-sclerotic cases may be due to the fact that the sensory nerve endings in the adventitia of the sinus are pressed against the hardened media, and so are vigorously stimulated; possibly, too, the thickened sinus may excite the afferent fibres in the subjacent vagus nerve.

Electrocardiographic studies (Mandelstamm, 1929) show that pressure on the sinus may reflexly arrest the heart completely, in some cases for as long as eleven seconds; the heart may not resume beating for some seconds after stimulation is discontinued, and syncopal symptoms may develop. Auriculo-ventricular conduction may be interfered with, and the heart-block may be partial or com-

plete. The effect on ectopic beats is inconstant—they may be decreased (as is found experimentally), but sometimes they are unaffected or even increased in number. Attack of paroxysmal tachycardia may be arrested (Danielopolu, 1929), though as a rule only for a short time ; sinus tachycardia is, however, little affected.

Sometimes the sinus region appears to be hyperexcitable, and the reflex may be elicited with extraordinary ease. Thus in a case recorded by Roskam (1930) the slightest pressure on the skin over the sinus, or the introduction of the fingers between a stiff collar and the neck, was liable to produce complete stopping of the heart (sometimes for as long as fifteen seconds) and consequently epileptiform convulsions. When the heart resumed beating the rate was rapid, and numerous ectopic beats were present. This patient also suffered from numerous, apparently spontaneous, syncopal attacks. Careful investigation showed that the heart stopped only when there was contact with the sinus, but not from pressure on the common carotid artery or the adjacent structures. Roskam suggests that hypersensitivity of the sinus nerve endings may be a factor in certain types of syncope or epileptiform convulsions.

Chronic Effects of Extirpation of Aortic and Sinus Nerves

As has already been pointed out, if both aortic and sinus nerves are cut, the heart accelerates and may become irregular, the blood pressure rises, and adrenaline secretion is increased. If the operation is carried out at one sitting the animals do not, as a rule, survive long, and soon die from ventricular fibrillation or oedema of the lung.

Koch and Miss (1929) extirpated the aortic and sinus nerves, first on one side, and then, after an interval of about one week, on the other side. Most of the animals (usually rabbits) survived, and were kept under observation for long periods. The initial effect of the operation was often a fall of blood pressure. Following on this, however, the blood pressure gradually mounted up, and in animals examined at intervals varying from 14 to 511 days after the double denervation the blood pressure was found to range between 125 and 180 mm. Hg (the normal pressure for the rabbit is 95 to 100 mm. Hg). In 9 out of 16 animals the pressure exceeded 150 mm. Hg. A persistent hypertension had therefore been produced.

As a variable number of aortic depressor fibres run in the vagus nerve, even in the rabbit, the operation which has been described cannot be regarded as always successfully destroying all the buffer afferents. In conformity with this, it is found that when the hypertension is not marked section of the vagi causes a further considerable rise of blood pressure, but when the blood pressure is already high the rise produced is small. In other words, the more complete the operation the greater is the resultant hypertension. Some acceleration of the heart is noted, but it must be borne in mind that vagus tone in the rabbit is normally slight. The venous pressure may rise up to 30 cm. H_2O (Mies, 1930). Histological examination of the heart revealed a diffuse connective-tissue proliferation or the presence of more discrete patches of fibrosis where the cardiac muscle fibres had disappeared ; the latter lesion was found in proximity to small arteries which had become narrowed from intimal thickening (Nordmann, 1929).

The pathological changes observed by these workers in the blood vessels are very interesting. The aorta down to the origin of the renals shows structural changes which are marked in proportion to the degree of arterial hypertension present. In the media there are thinned patches where the muscle and elastic fibres have been destroyed and replaced by a very hard cartilage-like tissue ; over these areas the intima is thickened from proliferation of cells and elastic fibres. It is claimed that sclerosis may be noted in the pulmonary arteries. The surface of the kidneys is often irregular. The glomeruli under the capsule, singly or in groups, may show various degrees of destructive change ; in addition, there is a certain amount of diffuse fibrosis. The renal vessels, however, are not altered (Nordmann, 1929).

It is impossible yet to say definitely whether the structural changes, thus said to be produced, in the arteries are secondary to the hypertension or whether both result from one common factor. Hering (1929) points out that the arterial changes closely resemble those occurring after injection of adrenaline, and is inclined to attribute them (and also the hypertension, in part) to the hyperadrenalaemia following the division of the buffer nerves. He also points out that the arterial changes have not yet been produced by prolonged injection of other pressor bodies like ephedrine. These results, though they await thorough confirmation,[1] are obviously of the greatest interest and importance, and arouse many stimulating questions. To what extent, for example, may hypertension or arterio-sclerosis in man be attributed to loss of afferent control of the bulbar centres? It is conceivable that if the aortic arch and the carotid sinuses were both markedly sclerosed the local sensory nerve endings might be put out of action, and in this way a primary change in the large arteries might lead secondarily to the development of hypertension. But it is not usual clinically for gross structural changes in the large arteries to be followed secondarily by hypertension. It has been suggested, on the other hand, that some temporarily acting cause may lead to arterial spasm, hypertension, and arterio-sclerosis ; the changes in the aorta and sinuses thus induced may throw the buffer nerves out of action, and so the hypertension becomes perpetuated. It is clearly not profitable to theorize further along these lines, but there is little doubt that a most promising field for future study has been opened up by these researches.

Reflex Regulation of Heart Rate and Blood Pressure

It is tolerably clear that the aortic and sinus nerves under resting conditions play an essential part in stabilizing the heart rate and blood pressure within normal limits, principally by means of the tonic inhibitory influence which they exert on the cardiac and vasomotor centres and on adrenaline secretion. A rise of blood pressure at rest increases their inhibitory activity, a fall of blood pressure lessens it, and may also bring into action pressor fibres which possibly arise from the aorta and carotid sinuses. It may be supposed, too, that the ventricular afferents which pass up in the vagi act in the same sense, but the evidence is slender, and their functional importance is perhaps not great. The cardiac afferents which return along the sympathetic do not appear to play a great part in the regulation of the circulation ; it has already been argued that their nerve ends may be pain-receptors rather than pressure-receptors. The receptors on the venous side of the heart are mainly concerned with the acceleration of the heart which occurs in exercise.

All four buffer nerves form a functioning entity: their role in the body can be illustrated from many observations. Occlusion of the carotids produces a greater rise of blood pressure after the aortic nerves have been cut and their restraining influence removed (Sewall and Steiner). When the carotids are successively occluded a greater rise of pressure is obtained from occlusion of the second than from the first, because the occlusion of the

[1] A considerable amount of unpublished work on this subject has been carried out in this laboratory (Kremer, Scarff, and Wright), and the results obtained are in substantial agreement with those reported by the German workers

first carotid abolishes its tonic inhibitory influence (Hering, 1927). The rise of blood pressure after stimulation of the peripheral end of the splanchnic nerves is greater after cutting all the buffer nerves, although the initial blood pressure is higher (Izquierdo, 1930). Stimulation of the central end of the aortic nerve in the rabbit brings about a bigger fall of blood pressure and a more sustained slowing of the heart when the other buffer nerves have been divided ; the same is true of stimulation or distension of the sinus caroticus (Koch, 1930). According to Izquierdo and Koch (1930), if the splanchnic nerves in the rabbit are cut, with the buffer nerves intact, the fall of blood pressure is slight, transient, and soon recovered from. If the buffer nerves have been previously divided splanchnic section produces a larger absolute and percentage fall of blood pressure (70 per cent.) ; and in chronic experiments there is little evidence of recovery. Similar observations have been made in the cat (Kremer and Wright, 1932). After haemorrhage it is found that section of the vagi may produce a further fall of blood pressure (McDowall), owing to removal of the compensatory afferent pressor influence of these nerves.

After section of all four buffer nerves, besides the hypertension which has been fully considered, there is cardiac acceleration to an extent which is dependent on the initial degree of vagal tone ; there is little increase in heart rate in the rabbit, but in the dog the increase may be from 50 to 220 per minute, in the monkey from 150 to 230, and in the cat from 190 to 220. Subsequent section of the vagi (when they contain no aortic afferents) may then produce no further acceleration, so that it would appear that vagus tone is normally exclusively reflex in origin. From some observations of Koch (1931) it would appear that the aortic afferents exert a great inhibitory influence on heart rate and a small effect on blood pressure, while for the sinus nerves the reverse is true.

Contrary to the belief of Anrep and Starling (1925) it has been shown apparently conclusively that the pressure in the cerebral vessels does not act directly on the cardiac or on the vasomotor centre.

The variation in heart rate which occurs with *respiration* —sinus arrhythmia—is still not quite adequately accounted for. There is no doubt that it depends on variations in vagus tone, and that it is abolished by vagal section. It has been attributed to afferent impulses from the lungs, to variations in pressure on the venous side of the heart (Bainbridge), or to some central influence. If the isolated head, connected with the trunk only by means of the vagi, is artificially perfused, it is found that the sinus arrhythmia does not follow the rate of the artificial respiration which is applied to the trunk, but it corresponds to the respiratory rate of the *head* ; this becomes even more evident if the respiratory movements in the head are stimulated. The arrhythmia also persists after denervation of the lungs. The arrhythmia is independent of the fluctuations in the cerebral-perfusion pressure. Heymans (1929) concludes from these observations that the arrhythmia is to an important degree due to direct *irradiation from the respiratory to the cardiac centre.*

In exercise, the greatly increased venous return raises the auricular pressure, and reflexly produces a quickening which enables the heart to cope effectively with a larger inflow. The consequent increased heart output mechanically raises the blood pressure, and this presumably tends to intensify the inhibitory tone of the buffer nerves, but to what extent it is impossible to say. During severe exercise the auricular reflex predominates, and the heart accelerates to its maximum extent ; whether the heart quickens or not in moderate exercise will presumably depend, to a considerable degree, on the relative potency of the two antagonistic reflex mechanisms. It is not known, too, to what extent the buffer nerves are a factor in preventing an excessive rise of blood pressure in exercise. When one remembers that the output of the heart may increase threefold or fourfold in exercise, the actual rise of blood pressure observed is comparatively trivial ; it is conceivable that the buffer nerves play a part in the necessary " damping " operations.

Finally, the influence which is exerted by the basal ganglia and the upper brain stem on the bulbar circulatory centres must not be ignored. A number of illustrative observations will be quoted. Stimulation of the hypothalamus may produce a rise of blood pressure (Karplus and Kreidl, 1927) and secretion of adrenaline (Houssay and Molinelli, 1925), with evidence of increased cardiac sympathetic activity, such as acceleration of the heart, shortening of the A-V conduction time, and extrasystoles. The liability to the occurrence of extrasystoles spontaneously or on afferent stimulation, which is so characteristic of the lightly chloroformed animal, is abolished by removal of the hypothalamus (Beattie, Brow, and Long, 1930). Penfield (1929) has described a case of thalamic tumour involving the mesial nuclei on the two sides, in which attacks occurred characterized by a great rise of blood pressure (from 110 to 210 mm. Hg), cutaneous vaso-dilatation in the distribution of the cervical sympathetic, and cardiac acceleration. In the acute decorticate animal there is widespread sympathetic activity—sweating, exophthalmos, a large rise of blood pressure, cardiac acceleration, and increased adrenaline secretion (Cannon and Briton) ; the centre for these reactions is in the ventral part of the thalamus and in the adjacent hypothalamus (Bard, 1930). Cannon has co-ordinated many of these observations, and has shown that the rage reaction, with its striking circulatory changes, is, in all probability, fundamentally dependent on a thalamic reflex. When the thalamus is cut off from cortical control this reaction occurs in an exaggerated form in response to quite trivial sensory stimuli. Normally, however, the activity of this thalamic centre is kept in check to a varying extent by means of impulses from the cerebral cortex. Future research may show that the higher level control of the circulatory centres is of especial importance in the human subject.

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