going paragraph the stimulus to the heart is constant while the response is intermittent and rhythmic. This kind of relation between a continuous stimulus and an intermittent reaction is not peculiar to the heart, although it is perhaps most conveniently demonstrated upon strips of ventricular muscle. When these are suspended under a certain tension, the mechanical stretching of the fibres, acting as a constant stimulus, causes them to give a series of rhythmical contractions. The reason for this is found in the peculiar alterations in irritability which accompany the beat of the heart. When the contraction of the whole heart or of an isolated strip of heart muscle is recorded by means of a lever, the curve of contraction, after a relatively long latent period, rises slowly to a maximum and as slowly declines again. The entire duration of it varies in different animals; but the curve shows an unmistakable resemblance to the simple contraction curve of skeletal muscle. The electrical changes in the heart accompanying its beat corroborate the view that the beat corresponds to a single twitch, and the dictum that "the heart knows no tetanus" has long been current in physiology. Recently Walther[17] showed that under certain abnormal conditions a limited amount of fusion and summation of contractions, and hence incomplete tetanus, could be obtained in the case of the frog's heart; but normally this is never supposed to occur. The reason why heart muscle never gives tetanic contractions but responds rhythmically to rapidly repeated or constant stimuli is found in the so-called "refractory period" (Kronecker, 1874; Marey, 1876), which prevents fusion of contractions, and in the "law of maximal contraction" (Bowditch, 1871) which prevents summation.

When one stimulates a skeletal muscle with a strong stimulus, a large contraction follows; when a weak stimulus is applied, the contraction is small; within limits the contraction is proportional to the stimulus. Not so with the heart. The beat is always the best which the ventricle can accomplish at the time being, be the stimulus weak or strong, provided only it is efficient to provoke a response at all. With the heart it is "all or nothing." Moreover, the effect of a stimulus applied to the ventricle, when it is beating rhythmically either spontaneously or as the result of rhythmic stimulation, will depend upon the exact phase of the cycle of the beat at which it is thrown in. If it is thrown in just as a relaxation is taking place, a beat follows prematurely before the next beat would naturally follow, this premature beat being obviously produced by the stimulus. But if it be thrown in while a contraction is going on, no premature beat follows: the ventricle does not seem to feel the stimulus at all. This period, during which the ventricle is insensible to stimuli, is called the "refractory" period. From this it results that, when a succes-

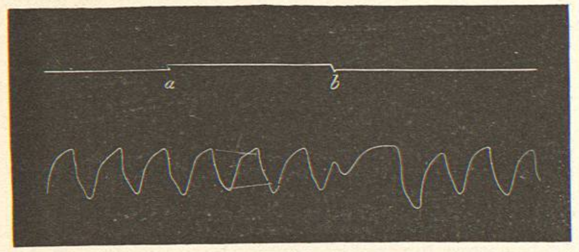

FIG. 1352.—Direct Stimulation of the Isolated Heart of the Cat. (According to Langendorff.) To be read from left to right; systole is represented by the down-stroke. The stimulus thrown in at a, beginning of systole, remains ineffective; stimulation at b, middle of diastole, causes an extra contraction. The compensatory pause and the increased contraction following it are also shown.

sion of stimuli repeated at a certain rate are sent into the ventricle, the number of beats does not correspond to the number of stimuli; some of the stimuli falling into refractory periods are ineffective and produce no beat. Hence the impossibility of producing tetanus of the heart by means of rapidly repeated stimuli, the usual effect of which is to throw the heart into the condition of incoordinated contraction known as fibrillary contraction or heart delirium. When a premature extra-contraction is induced by sending an intercurrent stimulus in during the diastole, this contraction will be larger the later the stimulus is thrown in. After this contraction a longer pause than usual follows, the *compensatory* pause, and the succeeding systole will be correspondingly increased, so that both the rate of beat and the work done are regulated by this compensation.

γ. Sequence of the beat. The beat of the heart normally begins at the venous end and sweeps over the organ to finish at the arterial end. The myogonic theory, therefore, must provide a plausible explanation for the origin of the beat at one point and its propagation in one direction over the heart. In cold-blooded animals as well as in mammals (Kent) there is direct muscular continuity between the several segments of the heart, so that anatomically there is no difficulty in assuming the propagation of the contraction wave from muscle fibre to muscle fibre through the entire length of the organ. Measurements of the rate at which the contraction wave advances have been made; in the frog's heart at 8° to 12° C. it is 30 to 90 mm. per second, in the excised mammalian heart about 8 m. per second (Waller and Reid). This would indicate that the above assumption is true, these rates being very much slower than the rate of conduction in nerves. It remains only to inquire why the beat begins at the venous end. It was shown above, in connection with the neurogenic theory, that the potentiality of beating was greater in the sinus of the frog's heart than in the other parts. The isolated ventricle, when it beats at all, does so with a slower rhythm than the sinus. Similarly it can be shown on the terrapin's heart that interference with the muscular substance of the auricle, when carried to a certain extent, prevents the beat of the auricle from passing over to the ventricle so that the sequence is broken after the auricle beat. If, for instance, the auricle be cut through until only a narrow bridge of muscle be left connecting the sinus end with the ventricular end of the heart, or if this part of the auricle be compressed with a clamp, a point may be reached in which every second or every third beat only of the sinus is followed by a beat of the ventricle. Then if the bridge be still further narrowed or the clamp tightened, the ventricle stops altogether, or it may after a while set up an independent rhythm of its own, slower than that of the sinus. Experiments upon isolated strips taken from the sinus, auricle, and ventricle respectively show that the concentration of salts in the blood is adjusted to the irritability of the venous end. Sinus strips begin to beat at once in solutions of that degree of concentration; ventricular strips remain quiescent until the concentration is altered to suit their peculiar state of irritability. The normal sequence, therefore, is merely the result of the fact that the normal stimulus of the heart is attuned, so to speak, to the physiological properties of the venous end; the beat once inaugurated travels along from fibre to fibre until the cycle is completed. And so the auricle, as has been stated before, becomes the pacemaker of the entire heart and an important regulator of its work.

2. The Extrinsic Nerves of the Heart. While the heart contains within itself all the conditions necessary to the development of a regular rhythmic beat, its activity is constantly controlled and modified by impulses coming to it through the extrinsic cardiac nerves. It has already been stated that these nerves are derived from two sources, and their anatomical course from the cardiac plexus to their central origins may, for the various mammals, be broadly represented by the diagram (Fig. 1353).

The vagus (inhibitory) fibres, shown by black lines, run in the upper (bulbar) roots of the spinal accessory, by the internal branch of the spinal accessory, past the ganglion trunci vagi, along the trunk of the vagus, and so by branches to the cardiac plexus. The sympathetic augmentor fibres, also shown by black lines, pass from

the spinal cord by the anterior roots of the second and third thoracic nerves (possibly also from the first, fourth, and fifth, as indicated by broken black lines), and reach the sympathetic chain in the corresponding white rami communicantes. They pass the stellate ganglion by the annulus of Vieussens to the lower cervical ganglion, from whence, as also from the annulus itself, they pass along the cardiac rami to the plexus.

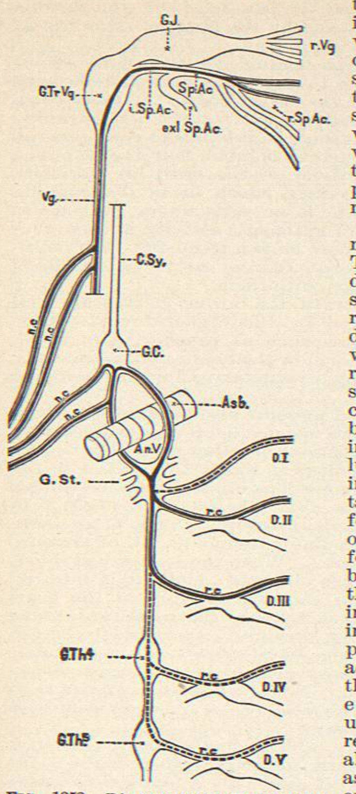

FIG. 1353.—Diagrammatic Representation of the Cardiac Inhibitory and Augmentor Fibres in the Dog. The upper portion of the figure represents the inhibitory, the lower the augmentor fibres.

α. The inhibitory nerves of the heart. The brothers Weber discovered in 1845 that stimulation of the peripheral stump of the divided vagus nerve with the faradic current caused either a slowing or complete cessation of the heart beat, according to the intensity of the stimulus; that the vagus, in other words, contains inhibitory fibres for the heart. Section of both nerves they found to be followed by an acceleration of the pulse, the effect being more pronounced in animals of slow pulse. The inhibitory action of the vagus on the heart is conveniently demonstrated upon a blood-pressure record, in which the altered heart rhythm as well as its influence on the height of arterial pressure is immediately apparent.

The slowing of the beat is, however, not the only effect of vagus stimulation on the heart. The force and extent of the individual beats are also diminished, and the effects upon the rate and force are to a certain extent independent of one another, so that in a given case the rate may remain entirely unchanged while the contractions go on diminishing in extent and force until complete rest results. The contrary effect of a slowing in rate without simultaneous diminution in size is not known to occur. Finally stimulation of the vagus produces a partial or complete loss of tone, thus allowing more complete relaxation and giving rise to the characteristic over-distended and engorged appearance of the completely inhibited heart.

The inhibition from vagus stimulation tells much more on the auricles than on the ventricles, the extent of the auricular contraction being especially affected. The auricles may be brought to a complete standstill while the ventricles continue to beat, the latter then exhibiting that independent rhythm spoken of above. In a somewhat similar manner the stimulation of the vagus, by affecting the rhythm of the auricles more than that of the ventricles, may lead to a lack of coordination between the two, the specially slowed auricles beating at one rate, the ventricles at another. The question as to whether the vagus acts directly on the ventricles, as it does on the auricles, or whether the effect on them is of a secondary nature caused by the changes in the auricles, must for the present be left undecided.

β. Accelerator nerves. Diametrically opposite changes are set up in the heart on stimulating the peripheral end of one of the accelerator nerves. These nerves are characterized by their lesser irritability, a longer latent period of stimulation, and a more lasting after-effect when compared with the pneumogastrics. With a suitable stimulus an acceleration of the heart amounting to from five to one hundred per cent. may be obtained according to the initial rate on which the maximum acceleration that can be obtained seems to be independent. As in the case of the inhibitory fibres, the effect is of a dual nature, the increase in rate being generally accompanied by an increase in the size and force of both auricular and ventricular contractions. Either effect may moreover appear alone, so that the name "augmentor" has come to be used side by side with that of "accelerator" for these nerves. In fact, the suggestion has been offered that the heart really receives four distinct varieties of nerve fibres through its extrinsic nerves instead of two, corresponding to the various results obtained by artificial stimulation—namely, accelerating, retarding, augmenting, and depressing fibres.

It is interesting to note the effect of simultaneous stimulation of both inhibitory and accelerator nerves. It was long believed that even feeble stimulation of the vagi was able to overcome comparatively strong stimulation of the accelerators, so that when both nerves were stimulated together the inhibitory effect predominated so long as the stimulus lasted. Upon the cessation of the latter, however, the characteristic accelerator after-effect showed itself in a secondary quickening of the heart, indicating that the effect of the stimulus on the accelerator nerves was only temporarily superseded.

The recent work on this subject has shown that these two sets of nerves are true antagonists, and that the effect of simultaneous stimulation is determined entirely by the relative strength of the stimuli applied to them. Hunt[18] concludes that in all cases the result is approximately the algebraic sum of the results of stimulating them separately.

The mechanism through which these nerves produce their characteristic effects upon the heart and the nature

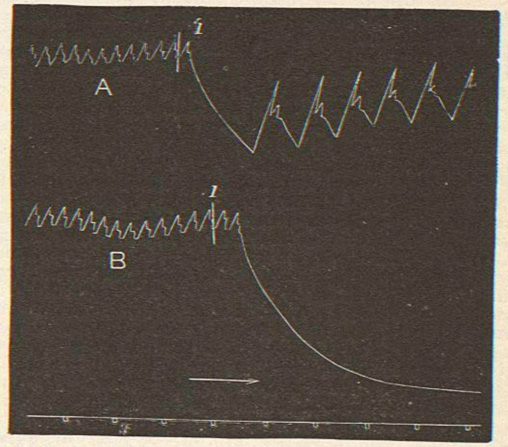

FIG. 1354.—Blood-Pressure Tracing (Rabbit). Vagus stimulated at I. Stimulus stronger in B than in A (Hürthle's spring manometer).

of the ultimate changes underlying the inhibition and acceleration are also points of fundamental theoretical importance.

As to the first part, it has been supposed that some of the intrinsic ganglia of the heart constitute peripheral nervous mechanisms which mediate between the extrinsic nerves and the heart muscle. Reasons have already been given for denying to these ganglia any share in the maintenance of the normal beat, and hence the suggestion that they may act as local inhibitory and local augmentor centres. The evidence adduced in support of this view is based on the action of certain heart drugs like nicotine, atropine, and muscarine, and on the interesting classical experiment known as the "ligatures of Stannius." Since neither of these series of experiments is thoroughly understood and both admit of various equally plausible explanations, they have furnished no crucial test or definitive solution of the problem. In fact, it may be said that the alternative view is gaining in favor, according to which the cells on the course of the fibres in the heart are rather stations where the fibres lose their medulla and where possibly other anatomical changes and rearrangements occur, than important intermediate mechanisms which essentially modify the physiological impulses falling into them and which shape the visible results that follow these impulses.

In this case the effect of both inhibitory and accelerator fibres would be upon the muscular tissue direct, and this leads to the second part of the question as to the ultimate nature of these effects. On this point our information is a little more definite, although far from satisfactory. The most plausible theory as to the action of the inhibitory nerves is the trophic theory of Gaskell. While the augmentor nerves are compared to ordinary motor nerves which increase katabolic and destructive changes, the vagus is supposed to have a contrary influence on the chemical changes going on in the heart so as to give them a trophic or anabolic or constructive turn, and thus to lessen for the time being the destructive changes underlying the muscular contraction. According to Gaskell the natural consequence of inhibition should be a stage of increased efficiency and working power when the inhibition has passed away, and the natural consequence of augmentation should be temporary exhaustion. Experiment shows that this is exactly what occurs. The activity of a weak heart has frequently been heightened by vagus stimulation, while a fairly vigorous heart, especially a bloodless one, may by repeated stimulation of the accelerator fibres be reduced to a very feeble condition. In support of the view that the changes set up in the heart by vagus stimulation are of a constructive anabolic kind must be mentioned the positive variation of the demarcation current which accompanies such stimulation. If the ordinary conception that the negative variation accompanying functional activity in various tissues is an indication of increased katabolism be accepted, it is fair to infer from a positive variation that changes of an opposite character are going on.

But the clearest proof of the trophic nutritive influence of the vagus on the heart is obtained from the study of the pathological changes appearing in that organ as a result of unilateral vagotomy in animals. All other organs remain normal while the heart alone presents an area of atrophic degeneration (not fatty degeneration), varying in position according to which nerve was cut (Fantino).

As to the normal mode of functioning of these two sets of antagonistic nerves, it is to be noted in the first place that both are in a state of tonic activity; section of both vagi causes a marked acceleration while subsequent destruction of the accelerators distinctly slows the rate again. These facts point to centres of origin which are in a state of constant activity either automatically or reflexly, and a change in the rate of the heart in either direction may evidently be brought about in two ways, by increasing or diminishing the activity of either of these centres. Nature seems to provide here an excess of regulating mechanism with unwonted and superfluous extravagance, but the general occurrence of this double mechanism throughout the series of vertebrated animals, and even among certain invertebrates,[19] indicates that some useful end must be gained by this arrangement; possibly the great mobility and power of adaptation so necessary in this central organ may be one of the advantages derived thereby.

It is by no means a unique arrangement in the living organization as we find it paralleled by the double mechanism of the iris and by the familiar structure of joints with antagonistic muscles.

The inhibitory and accelerator nerves can be stimulated along their course to the heart only under exceptional circumstances in the intact body. A tumor or an aneurism may occasionally press upon the nerve trunks, or it may be possible in some individuals to compress the vagus against the vertebral column, but the impulses which regulate the activity of the heart are normally discharged from the centres which lie in the medulla oblongata. While there is no satisfactory evidence to indicate the existence of automatic activity in these centres, various conditions are known to modify their activity, and practically every afferent nerve of the body comes into reflex relation with them.

The medullary centres of the cardiac nerves are well known to be influenced by the higher brain centres. Various psychical states, such as pleasure, pain, hope, and fear, may quicken or slow the heart, and occasionally individuals are able by a voluntary effort markedly to accelerate the pulse.

The state of the blood pressure also modifies the activity of these centres. An isolated heart does not react by a change of rate to variations of either arterial or venous pressures within physiological limits[20 21 22]; but in the body with its nerve connections intact it may be almost put in the form of a law, that "the rate of the beat is in inverse ratio to the arterial pressure"; a rise of pressure being accompanied by a diminution and a fall of pressure by an increase of the rate. When the vagi are divided, this relation is no longer observed; hence it is inferred that increased pressure causes a slowing of the beat, when the vagi are intact, because the inhibitory centre is stimulated by the high pressure, either directly by the pressure obtaining in the blood-vessels of the medulla, or in some indirect manner, and the heart in consequence is more or less inhibited. Nothing definite is known as to the conduct of the accelerator centre over against these variations of blood pressure.

The afferent impulses, which reflexly modify the activity of the medullary centre, arise everywhere in the body, including the heart itself, and only a few special cases need be referred to here.

The heart is supplied with centripetal nerves which, while they are not known to mediate conscious sensations, may evoke muscular, vascular, and cardiac reflexes.

Wooldridge described fibres on the anterior and posterior surfaces of the ventricle, stimulation of whose central end gave either reflex acceleration or inhibition.

The depressor nerve of Cyon, which will be referred to in more detail later, also takes its origin in the heart and reflexly inhibits it when the central end is stimulated, the vagi being intact. Reflex inhibition results also from the stimulation of the following nerves: the central end of either vagus, the other being intact; the superior laryngeal nerve; the splanchnic, and the trigeminal.

Reflex acceleration is obtained by forcible inflation of the lungs, and in man whenever intrapulmonary pressure is increased, as in loud talking, singing, etc.

Sensory nerves proper and the nerves of special sense give either inhibition or acceleration, the result apparently depending, in part at least, on the intensity of the stimulus, feeble stimulation giving acceleration, strong stimulation inhibition. It is rarely possible to interpret the result in a given case and to state through the mediation of which centre it is obtained, or whether both centres cooperate, since, as we have seen, either centre may be utilized to obtain both slowing and quickening of the heart. The older physiologists attributed the main share of the reflex regulation to the cardio-inhibitory centre, assigning to the augmentor mechanism a subordinate and auxiliary rôle. At present there is a distinct tendency to magnify the importance of the accelerator mechanism

and to place the two halves of the heart-regulating apparatus on equal footing.

B. *Vaso-Motor Nerves.*—From what has been said about the influence of gravity and the respiratory movements on the blood flow in the veins, it may be inferred that these mechanical factors influence the distribution of the blood in the body, more especially that in the veins. Aside from such changes, however, the vascularity of the various organs undergoes incessant fluctuations, which are evidently correlated in part with changes in their functional activity and in part related to the heat regulation of the body. These changes in blood supply are not the passive effects of mechanical factors like those just mentioned, but are brought about by local changes in the walls of the vessels themselves, especially those of the small arteries, by which their calibre is increased or diminished; and these changes throughout the body are so coordinated that in general it may be said that the blood flow to each organ is constantly adapted to the existing state of its physiological activity.

By holding the ear of a rabbit up before the light or watching the web of a frog's foot under the microscope, such changes in the calibre of the arteries may be readily seen. It will be noticed that these vessels frequently expand and contract without any apparent cause, rarely remaining at rest for any great length of time. The size of the vessels thus oscillates about a mean state of moderate contraction, which is habitual though variable and which is spoken of as their tone or tonicity. The arteries owe this tone to the peculiar properties of the non-striated involuntary muscle tissue which enters so largely into the structure of their walls, forming as it does practically the whole thickness of the middle coat in the smaller arteries, where the changes in question are most marked. Histological examination shows, moreover, that these muscle fibres are richly supplied with nerves by which their activity is regulated and controlled, and to which therefore the name of vaso-motor nerves has been given.

The study of the vaso-motor nerves becomes of paramount importance in view of the intimate relations they bear to the activity of every organ and tissue of the body. The fact that the apparently spontaneous irregularly rhythmic changes in calibre of the arteries are under the control of special vaso-motor nerves was discovered by Cl. Bernard in 1851 when he divided the cervical sympathetic nerve in the rabbit. He observed as the result of this operation that the vessels of the ear on the same side visibly expanded, small arteries and veins standing out distinctly which before could not be recognized. The temperature of the ear rose, and from a divided vein blood of a bright hue flowed in a rapid stream. The spontaneous changes of calibre had disappeared. On stimulating the head end of the divided nerve, the arteries again contracted, the venous blood streamed out slowly with the usual dark color, and the temperature of the ear once more fell. Nerves which thus bring about contraction of the vessels when stimulated are called vaso-constrictor nerves, and the experiment cited above shows that the vaso-constrictors distributed to the rabbit's ear are in tonic activity so long as their normal connection with the central nervous system is left intact.

Since the time of Bernard's classical experiment the distribution of nerves of similar function to practically every vascular area of the body has been demonstrated and their anatomical course traced out. In general their path is much the same for all the mammalia, and may be briefly described as follows. Leaving the spinal cord in the anterior roots of the nerves belonging to the middle region, say from the second thoracic to the fourth lumbar nerve, they pass by the visceral branches of the mixed trunk to the corresponding thoracic and abdominal sympathetic ganglia. Those destined for the head and neck come out chiefly in the second and third thoracic nerves, then turn upward through the annulus of Vieussens to the lower cervical ganglion, and thence up the cervical sympathetic nerve to their final distribution. Similarly those for the abdominal viscera pass to the splanchnic and to smaller nerves joining the inferior mesenteric ganglion. The fibres which are intended for the extremities and trunk, after a longer or shorter course along the sympathetic chain, return in the gray rami communicantes to the spinal nerves, and so reach the brachial plexus, the sciatic plexus, or other spinal nerve, as the case may be, to pass out to their appropriate area of distribution.

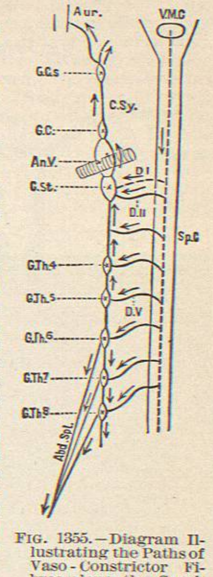

FIG. 1355.—Diagram Illustrating the Paths of Vaso-Constrictor Fibres along the Cervical Sympathetic and (Part of) the Abdominal Splanchnic. Aur., Artery of ear; G.C.s., superior cervical ganglion; Abd.Spl., upper roots of and part of the abdominal splanchnic nerve; V.M.C., vaso-motor centre in spinal bulb; C.Sy., cervical sympathetic; G. C., lower cervical ganglion; An.V., annulus of Vieussens; G.St., stellate ganglion; G.Th.[4], G.Th.[5], G.Th.[6], G.Th.[7], G.-Th.[8], thoracic ganglia; D.I, D.II, D.V, thoracic spinal nerves. The paths of the constrictor fibres are shown by the arrows. The dotted line along the middle of the spinal cord, Sp.C., is to indicate the passage of constrictor impulses down the cord from the vasomotor centre in the spinal bulb.

The vaso-constrictor nerve fibres are of the fine medullated variety when they leave the spinal cord, but it has been shown by the nicotine test of Langley that they early lose their medullary sheaths in some one or other of the sympathetic ganglia through which they pass and are continued as non-medullated fibres. Thus the vaso-constrictor fibres of the cervical sympathetic lose theirs in the superior cervical ganglion. The fibres of the abdominal splanchnics are connected with cells of the solar plexus, while others still undergo this change while yet in the main sympathetic chain. Two apparent exceptions to the above general statement are found in the vaso-constrictor fibres which occur in the n. auricularis cervicalis and in the vagus. The former have been traced through the second and third nerves of the cervical plexus and are distributed to the tip and sides of the ear. The vagi, according to various authors, contain vaso-constrictors going to the heart, stomach, intestines, kidneys, spleen, and lungs. The majority of authors agree that the lungs receive their chief supply in the usual way from fibres coming out in the third to fifth thoracic spinal nerves, and it is possible that the apparent exceptions noted may in reality be derived from the sympathetic system.

Another type of vaso-motor nerve is represented in the fibres supplied by the lingual nerve to the submaxillary gland and adjacent structures.

When these fibres are divided no effect is observed; but on stimulating their peripheral ends the vessels of the gland are seen to dilate and swell, and the blood gushes from the efferent veins with a distinct pulse and a bright arterial color. This class of fibres, designated "vaso-dilator" nerves, is not in tonic activity like the vaso-constrictors and their influence can be exerted in one direction only, viz., to dilate the blood-vessels. They seem to be used on special occasions only, while the vaso-constrictor nerves, which owing to their tonic activity can be worked both in a positive constrictor and in a negative dilator direction, appear to find a more general application in the body. At the same time the vaso-dilators have also been shown to be widely distributed and possibly occur wherever the vaso-constrictors are found. The demonstration of vaso-dilator fibres when they occur alone as in the lingual nerve or in the nervi erigentes is not difficult, but when they are combined in the same nerve trunk with vaso-constrictor fibres, as is usually the case, special devices must be used to show their presence. Simultaneous stimulation of both kinds of fibres generally produces vaso-constriction, although marked dilatation may appear as the after-effect.