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SYMPATHETIC ACTIVITY AND THE SYSTEMIC CIRCULATION IN THE SPINAL CAT

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In the spinal animal, some sympathetic preganglionic neurones show background discharge and some can be reflexly excited or inhibited. Recent work has pointed out that while only a fraction of the total sympathetic outflow is involved, elements responsive to reflexes are present in each of many segments (Beacham & Perl, 1964*a*, *b*). The fact that only a limited number of the cells in each segment participate in a reflex could reflect differences either in the excitability of various preganglionic neurones or some other feature of organization. As a step toward further understanding of the role of the spinal cord in sympathetic mechanisms, the present study aims to establish effector organs controlled by preganglionic neurones active in the spinal preparation.

Our attention was directed to the circulatory system because several investigators have described cardiovascular responses in spinal animals (Sherrington, 1906; Langley, 1924; Brooks, 1933; Alexander, 1945; Mukherjee, 1957). Difficulty in recording from sympathetic preganglionic and post-ganglionic cells simultaneously forced the use of an indirect approach. In most experiments the effects of nerve volleys or adequate stimuli known to initiate spinal preganglionic reflexes were tested on post-ganglionic neuronal activity, arterial pressure, blood flow or heart rate. Alternatively, preganglionic discharge and cardiovascular events were recorded in parallel. The results indicate that not all effector organs are influenced by sympathetic reflexes or autogenous activity in the spinal cat. In addition, cyclic or periodic changes in preganglionic discharge and in the systemic arterial pressure were noted which could be modified so as to suggest some form of sympathetic control of the circulation at the spinal level.

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METHODS

All experiments were done on adult cats made spinal at the C 1 level under ether anaesthesia. The brain rostral to the section was destroyed by permanent bilateral occlusion of the carotid and vertebral arteries. Fixed and maximal pupillary dilatation with absence of corneal and other reflexes and *rigor mortis* of the head muscles was used as evidence of death of the head. Anaesthesia was discontinued, and the animal maintained by artificial respiration with constant monitoring of the end-tidal CO_2 concentration. The results to be described were accumulated from forty-five preparations which survived the initial procedures in good condition (i.e. mean arterial pressure over 50 mm Hg and evidence of somatic spinal reflexes). In two animals, the spinal cord had been transected aseptically at the mid-thoracic level more than one month previously and then prepared for the acute experiment as above. Intravenous injections were made through a cannula in the left radial vein.

Blood pressure was recorded from a cannula inserted into the right carotid artery, using a strain-gauge pressure transducer (Statham P 23 A) excited by a 25 kc voltage; a phase sensitive 'carrier' type amplifier was utilized for demodulation and to indicate the pressure variations. Blood flow was measured in selected arteries by a gated sine-wave electromagnetic system (Kolin, 1959). The probes which were employed for blood flow did not require opening the artery in question and the system could indicate a range of flows from less than 5 ml./sec to 100 ml./min. In placing the flow probes, care was exercised to minimize damage to nearby nerves. Initially, attempts were made to quantitate flow measurements; however, the small size of the arteries and probe made this difficult and unreliable so that only qualitative changes in the mean flow (electrical filtering was used to damp oscillations appearing with each cardiac cycle) were recorded in the majority of the experiments. An approximate indication of the magnitude of illustrated changes is given in the figure legends as a percentage of the control value. The output of the flow-measuring system was linearly related to flow over the range utilized. Zero flow was recorded at the end of the experiment by leaving the probe in place and killing the preparation. The heart rate of the preparation was measured either from the central arterial pressure recording or from an electrocardiogram obtained by needle leads placed in the forepaws.

The preparations were held in a lateral position (left side up) by clamps grasping the dorsal spinal processes and, in experiments with structures of the left hind limb, by a clamp or bone pin securing the foot. All dissections and procedures, except as noted, were performed on the left side. Exposed nerves were protected by liquid paraffin equilibrated with 95 % O_2 and 5 % CO_2 and exposed tissues in the vicinity of the magnetic flow probes were covered by cotton waste soaked with Locke's solution (without glucose). Complete skeletal muscle paralysis was obtained by intravenous administration of gallamine triethiodide (Flaxedil; Amer. Cyanamid).

Electrical signs of neural activity were recorded from the preganglionic neurones by techniques previously described (Beacham & Perl, 1964*a*). Records from post-ganglionic nerve branches or from peripheral nerves were obtained with the same methods. Peripheral nerves were electrically excited by pairs of platinum electrodes, using short pulses (0·1 msec) repeated at rates from 0·5 to 30/sec.

The recorded activity was displayed on a multi-channel oscilloscope. In addition, certain data were stored on magnetic tape using an FM analogue system with a uniform frequency response from 0 to 5000 kc/s. For blood-pressure and blood-flow measurements, a recorder writing directly on paper was used in parallel with the tape recorder and the oscilloscope. Magnetic tape records were replayed on to the oscilloscope and the direct writing recorder. The frequency response of the direct writing recorder was uniform from 0 to 40 c/s. All the illustrations with the exception of nerve action potentials were made from records obtained with this direct writing machine.

Analyses of the frequency of nerve discharge and heat rate were made by two means:

(1) photographic records made from the oscilloscope with moving film were measured by hand and plotted; (2) in most of the later experiments, records stored on magnetic tape were replayed and converted to standard voltage pulses by a pulse generator with adjustable trigger levels. These standardized pulses were then fed into either a frequency meter generating a voltage proportional to the average frequency (with an adjustable time constant) or a device generating an analogue voltage proportional either to instantaneous impulse interval or the $\log_{10}$ of this interval (H. Fein, unpublished).

RESULTS

Evoked responses

Activity in post-ganglionic nerves. A single volley of afferent impulses in a spinal nerve evokes a reflex discharge of preganglionic neurones of the same and nearby segments (Beacham & Perl, 1964*a*). Such preganglionic impulses should, in turn, initiate discharges in neurones of the sympathetic ganglia. To explore the post-ganglionic distribution of the reflex, a series of experiments was performed in which the activity from individual post-ganglionic branches was sampled following the initiation of afferent volleys in spinal nerves of the region. From such experiments on the stellate and upper lumbar ganglia it became evident that the various post-ganglionic nerves were not uniform in their reflex activation. In six of nine successful experiments on the stellate, one or two post-ganglionic branches did not contain a reflex discharge while several others exhibited relatively large evoked responses. A typical example of this separation in post-ganglionic distribution is depicted in Fig. 1: recordings were made from three lateral branches of the stellate ganglia which, upon subsequent dissection, proved to have post-ganglionic distribution. A single afferent volley from T2+T3 nerve evoked a complex response in the two caudally located post-ganglionic nerves (Fig. 1*B* and 1*C*). Figure 1*A* shows that the most rostral of these lateral branches was essentially silent. Even in those animals in which all post-ganglionic nerves contained a reflex response, considerable difference in its size was found in different nerves. In the most rostral post-ganglionic branch leading from the lateral edge of the ganglia either a very small reflex appeared or none at all. With equal consistency, the middle branch exhibited a relatively large reflex. The reflex responses in the more posteriorly located branches were more variable; in some preparations the response was comparable to that of the middle branch (Fig. 1*C*), while in others the response was much smaller or totally absent. In similar experiments, the response to afferent volleys from the L2 or L3 spinal nerves was examined in post-ganglionic branches from ganglia located at the L1 or L2 levels. In two successful experiments, one or more of the post-ganglionic branches from these lumbar ganglia was silent while others showed reflexly initiated discharge.

After testing for reflex activity in several experiments, the active post-

ganglionic branches were traced peripherally by dissection. From the left stellate, the post-ganglionic nerves excited by the spinal reflex usually passed down along the left subclavian artery and seemed to by-pass the heart, joining plexuses around the arteries. Branching of the plexuses followed a variety of blood vessels and some disappeared into the hilum of the lung. In the lumbar region, the peripheral distribution of the reflexly excited post-ganglionic nerves was extensive; branches ran with each major artery emanating from the descending aorta.

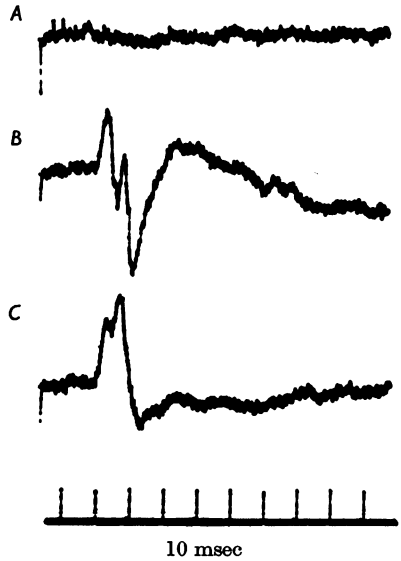

Fig. 1. The response in three post-ganglionic branches (*A*, *B*, *C*, see text) of the left stellate ganglion evoked by single afferent volleys from the combined T2 and T3 spinal nerves, 10 hr after C1 spinal section. Body temperature, 37° C. End-tidal CO_2, 5·8 %.

Blood-flow measurements. These observations on the distribution of post-ganglionic branches containing reflex discharge led to study of the systemic arterial pressure and blood flow in specific arteries after stimuli which had been shown to initiate spinal sympathetic reflexes. In one series of experiments, afferent volleys were initiated by repetitive stimulation of peripheral ends of divided segmental spinal nerves. The afferent volley was often monitored by recording centrally on the nerve. The classical observations that repetitive stimulation of a mixed peripheral nerve evoked changes in the arterial pressure of spinal animals were readily confirmed (Sherrington, 1906; Langley, 1924; Brooks, 1933). In our hands, the blood pressure changes initiated by such stimuli were often considerably greater than those reported by Brooks (1933) and Langley (1924). In two chroni-

cally prepared spinal cats, blood-pressure changes of 75–100 mg Hg followed stimulation of either a segmental spinal nerve or one of the branches of the ipsilateral sciatic nerve (see also, Sherrington, 1906). In one chronic spinal cat, both adrenal glands were removed without significantly altering the responses of the arterial pressure to spinal nerve stimulation.

Although the observed rise in arterial pressure may have resulted from several causes, a probable factor was vasoconstriction and consequent increased resistance to flow. This possibility was evaluated in twenty experiments in which flow through selected peripheral arteries and central arterial pressure were measured simultaneously. Only preparations exhibiting some form of sympathetic reflex excitability were considered. In the majority of these experiments electrical stimulation of a distally sectioned spinal nerve at over five times the threshold for afferent fibres evoked a temporary decrease in flow through certain arteries synchronous with the beginning of the rise in systemic pressure. This effect is illustrated in Fig. 2 by femoral arterial flow and carotid arterial pressure records taken from a preparation in which the spinal cord has been cut at the T 8 level 50 days previously. The effect could be graded by grading the intensity of stimulation of the afferent nerve. The bar *1* in Fig. 2*A* marks the time of L 2 nerve stimulation at 10/sec; this resulted in a small depression in blood flow and a concomitant slight rise in the arterial pressure. At the time of the bar *2* (Fig. 2*A*), a weaker stimulus at the same frequency was delivered and no change in arterial flow occurred. In Fig. 2*B*, the stimulus intensity was roughly double threshold for the blood flow effect and this produced a diphasic depression in flow and a more marked increase in the systemic blood pressure. At the end of the stimulus period in Fig. 2*B*, the flow temporarily rose to a value slightly above that recorded in the control. Increasing the stimulus intensity to five times threshold (Fig. 2*C*) produced still greater reduction in arterial flow with a more rapid onset in parallel with a systemic pressure increase of roughly 75 mm Hg as well as subsequent oscillatory variations in both arterial flow and blood pressure. In the experiment illustrated in Fig. 2 and in a number of others, differences in the effects produced by various stimulating frequencies were evaluated. Changes induced in the systemic arterial pressure or regional arterial flow were usually not seen with volleys repeated at 1/sec or slower. Increasing the stimulus frequency from 2 to 10/sec ordinarily increased the magnitude of the reflex decrease in blood flow, but higher frequencies did not significantly alter the effects observed at 10/sec. While the effects upon arterial flow in the chronic spinal animal illustrated in Fig. 2 were unusually clear and large, similar observations were made in acutely prepared animals 7–8 hr after spinal transection. The importance of time from the

moment of acute spinalization for demonstration of cardiovascular responses has been documented by Mukherjee (1957).

It was clear that excitation of the most rapidly conducting afferent fibres was not related to a change in arterial flow. With graded intensities of electrical stimuli, the flow alterations appeared only after some of the slowly conducting myelinated fibres (under 25 m/sec) were present in the

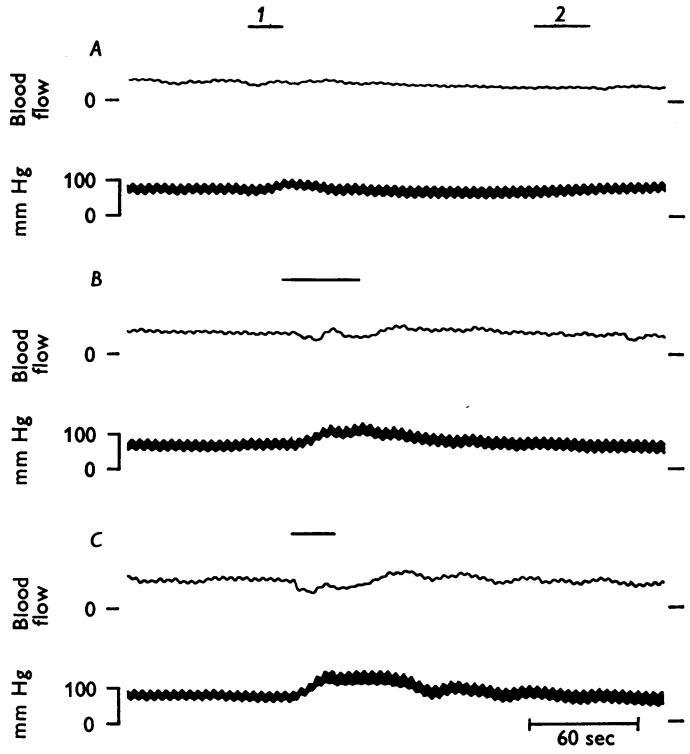

Fig. 2. Parallel records of flow in the left femoral artery and carotid arterial pressure showing response to stimulation of the central stumps of L 2 and L 3 spinal nerves. T 8 spinal section, 50 days previously. 7·5 hr after C 1 spinal section. Stimulation periods indicated by bars over flow records. Zero level for flow and pressure shown both on left and right of each pair of tracings. Electrical stimuli at 10/sec. *A*: *2* stimulation at ½ intensity used for *1*. Flow decreased approximately 20 % at *1*. *B*: stimulus twice *A 1*. Flow decreased approxmately 30 % during initial dip. *C*: stimulation 5 times *A 1*. Flow decreased approximately 50 % during initial dip. Body temperature, 37° C. End-tidal CO_2, 4·9 %.

volley. Observations leading to this conclusion are illustrated by recordings in Fig. 3. In Fig. 3, parallel measurements of blood flow in the femoral artery and systemic arterial pressure are shown for an acutely prepared spinal cat. In Fig. 3*A*, the bar indicates 10/sec stimuli to the L 2 nerve at an intensity giving the compound action potential of the inset *a*

(the arrow indicates the stimulus artifact; *1* marks the deflexion produced by the most rapidly conducting fibres; *3* marks the reflex discharge of skeletal motoneurones in this mixed somatic nerve). In Fig. 3*B*, similar records of blood flow and blood pressure show the effects elicited when the stimulus intensity to the L2 spinal nerve was increased so that the compound action potential appearing in the inset *b* resulted. A transient depression and subsequent increase in arterial flow was evoked, parallelled by a very small change in systemic pressure. In Fig. 3*B* a new component (*2*) in the compound nerve potential appears which represents activity of afferent fibres conducting under 25 m/sec. Thus, the afferent fibres which evoke

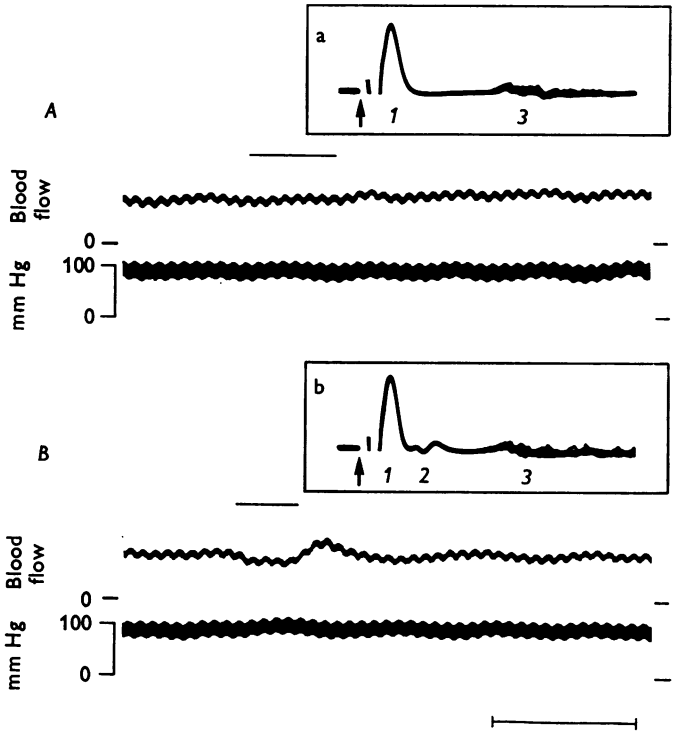

Fig. 3. Response of flow in the left femoral artery and the carotid arterial pressure to stimulation of the left L3 spinal nerve. 5·5 hr after C1 spinal section. Details as in Fig. 2. *A*: 10/sec stimulation at intensity evoking compound action potential shown in inset *a*. *B*: 10/sec stimulation at intensity evoking compound action potential shown in inset *b*. Flow decreased by approximately 15% during initial dip. *Insets*: Compound action potentials in L3 spinal nerve evoked by shocks at 10/sec delivered to same nerve 40 mm distally. Several sweeps allowed to superimpose on one photograph. (Arrow: stimulus artifact. *1*: rapidly conducting component. *2*: component produced by afferent fibres conducting under 25 m/sec. *3*: reflex discharge in somatic motor fibres.) Time bar is equal to 60 sec for *A* and *B* and 5 msec for insets *a* and *b*. Body temperature, 36·5° C. End-tidal CO_2, 3·8%.

changes in blood flow are of the same conduction velocity range as those responsible for the reflex discharge of preganglionic neurones (Beacham & Perl, 1964*b*).

Reflex discharge of preganglionic neurones in the spinal animal can be evoked by pressure against deeply located structures such as muscle (Beacham & Perl, 1964*a*). This form of stimulus also proved effective in altering blood flow and, in certain preparations, deep pressure evoked changes in arterial flow even when nerve volleys produced equivocal results. The greater effectiveness of a pressure stimulus as compared to electrical excitation of a mixed nerve may have resulted from the presence of afferent fibres in segmental spinal nerves which inhibit preganglionic discharge (Beacham & Perl, 1964*b*). In addition, pressure stimuli commonly demonstrated some regional localization in the arterial flow effect. For example, flow in the inferior mesenteric artery and the carotid arterial pressure were measured in one animal whose spinal cord was transected 25 hr earlier. When the left upper forelimb musculature was firmly squeezed, no change occurred in either blood flow or blood pressure. Similar pressure on the hamstring musculature of the left hind limb was followed by a brief and very small decrease in arterial flow in association with a slight increase in systemic arterial pressure. However, when pressure with a blunt probe was directed against the exposed vertebral musculature at the L3 level a moderate (20 %) and reproducible decrease in flow through the inferior mesenteric artery resulted at the time of a small increase (5–10 mm Hg) in systemic blood pressure. The response to deep muscle pressure in some preparations was a simple decrease in flow while at other times the flow recording showed the diphasic form illustrated in Figs. 2 and 3. Some local sign was also evident in the changes of arterial flow evoked by nerve volleys: stimulation of forelimb or upper thoracic nerves or regions did not regularly induce flow changes in the femoral artery. In general afferent fibres entering distant segments were less likely to initiate flow changes than those of nearby levels.

In four successful experiments in which renal arterial flow was measured, decreases in flow (as described for the femoral, mesenteric and brachial) were not seen during reflex rise in arterial pressure. Some flow increase always accompanied systemic pressure rise and renal artery flow decrease in the absence of arterial pressure change was never seen. In one animal, after section of the renal nerves, the renal artery flow increase associated with the rise in systemic pressure seemed to be larger. In the absence of quantitative pressure–flow curves it was impossible to evaluate these patterns, since flow increased with rises in systemic pressure. Small increases in resistance in the renal vasculature synchronous with increases in systemic blood pressure could have been masked. On the other hand,

there may have been no change in renal vascular resistance and the observed increases in flow may have been simply a direct consequence of increased systemic blood pressure. The possible relevance of 'autogenetic' regulation of renal blood flow (Winton, 1956) is beyond the scope of the present work.

It was often found, as in Fig. 2*C*, that following an evoked change in arterial flow, instabilities in flow and (usually) systemic pressure existed for some minutes. Such post-stimulus periodicities or instability in blood flow or blood pressure were common and seemed to be more prominent in preparations with mean arterial pressures over 70 mm Hg.

Heart rate. The observations on the anatomical course of post-ganglionic stellate branches which were reflexly excited suggested that the heart was not innervated by these nerves. However, the eventual termination of fibres from the sympathetic plexuses could not be established by dissection alone. Various post-ganglionic stellate branches were directly stimulated in some preparations to test more definitely for the presence of cardioaccelerator fibres. Because of the movement of the thoracic viscera, stimulation in isolation of the various post-ganglionic divisions was difficult, but in certain cases post-ganglionic branches were sufficiently long to permit division and recording from the proximal end with later stimulation of the distal end. Results from an experiment of this type are shown in Fig. 4. The upper three plots in Fig. 4 indicate the heart rate as measured from photographic records of the blood pressure before and after a period of stimulation of the distal portion of three post-ganglionic nerve branches. These were the same three nerves whose reflex responses to spinal nerve stimulation are illustrated in Fig. 1. For the uppermost graph of Fig. 4, the stimulus intensity to the nerve of Fig. 1*A* was adjusted to above threshold for the indicated effect. The second and third plots in Fig. 4 illustrate the absence of an effect on heart rate by stronger (2×) stimulation of other post-ganglionic nerve branches, those reflexly excited by afferent volleys (Fig. 1*B* and *C*, respectively). The lowest graph of Fig. 4 shows the heart rate for tetanic stimulation of the T2 and T3 spinal nerves before division of the stellate branches. This latter result is typical; stimulation of mixed spinal nerves which evoked reflex response in post-ganglionic nerve branches never initiated a reflex change in heart rate. A clear separation in the post-ganglionic appearance of reflex response existed similarly in four other experiments which were physically suitable for direct stimulation, and in these also, the active branches did not initiate an increase in heart rate. Such results are impressive because the sympathetic connexions to the cardiac pace-maker were clearly intact: stimulation of a branch which was silent during reflex excitation could induce a marked increase in heart rate (Fig. 1*A*). From such observations

it appears that an anatomical separation in the outflow from the stellate ganglia exists in some cats and that those fibres which have significant numbers of endings upon the cardiac pace-maker are usually not excited by the spinal reflex.

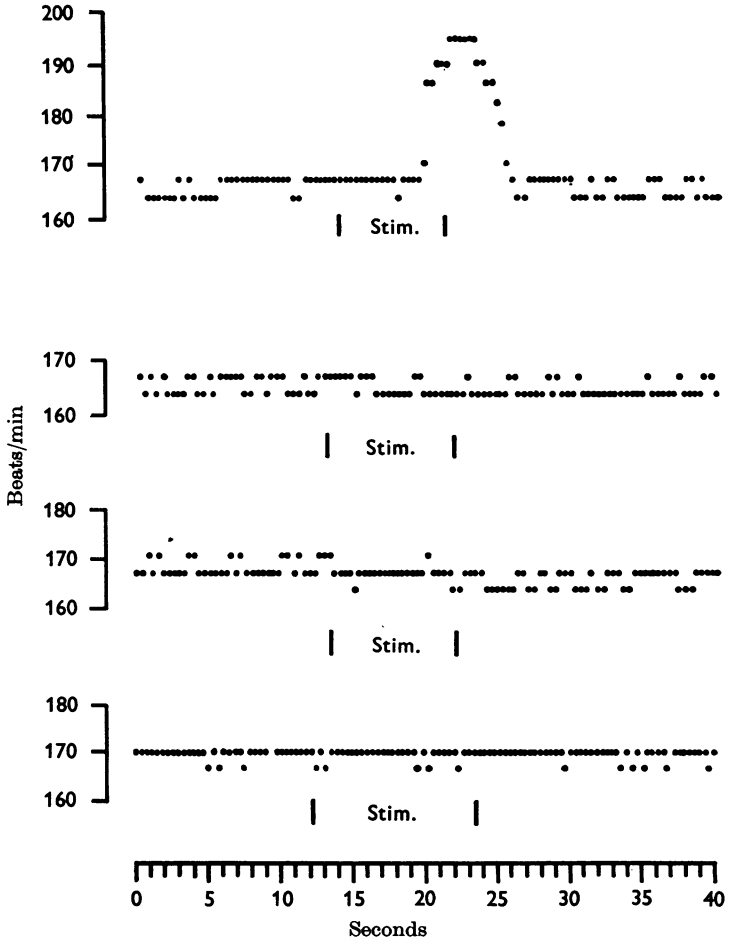

Fig. 4. Response of heart rate to stimulation of several nerves. Same experiment as Fig. 1. Heart rate indicated as instantaneous frequency (1/interval) measured from photographic records of blood pressure. All stimuli at 10/sec. *Upper*: stimulation of the distal end of the stellate post-ganglionic branch whose response is shown in Fig. 1*A*. *Second*: stimulation of the distal end of the stellate post-ganglionic branch whose response is shown in Fig. 1*B*. *Third*: stimulation of the distal end of the stellate post-ganglionic branch whose response is shown in Fig. 1*C*. Stimulus intensities for *B* and *C* approximately twice that for *A*. *Bottom*: stimulation of combined T2 and T3 spinal nerves at same intensity used to obtain Fig. 1 before cutting post-ganglionic nerves. 10 hr after C1 spinal section. Body temperature, 37° C. End-tidal CO_2, 5·8 %.

The absence of alterations in heart rate after various stimuli evoking changes in the systemic blood pressure and in arterial blood flow was the usual finding. An example of this is illustrated in Fig. 5 where heart rate and systemic arterial pressure are compared and then flow in the left brachial artery is shown in parallel with systemic arterial pressure. Localized pressure against the lumbar musculature with a small blunt probe in Fig. 5*A* evoked a relatively large (30 mm diastolic), diphasic increase in systemic arterial pressure. The heart rate did not change during this substantial increase in arterial pressure. In contrast, in Fig. 5*B*,

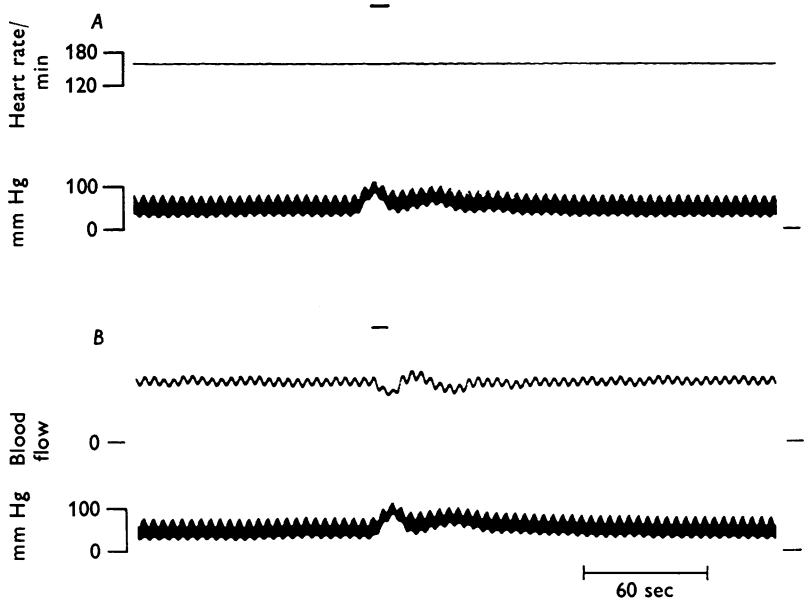

Fig. 5. Response of heart rate, left brachial artery flow and left carotid arterial pressure to pressure on the vertebral musculature of the upper lumbar level by a blunt object. Stimulus of probable noxious intensity. Heart rate in *A* using a device instantaneously generating a voltage proportional to previous interval. Other details as in Fig. 2. *A*: 10 hr after C1 spinal section. *B*: 9·75 hr after C1 spinal section; flow decreased approximately 15% during initial dip. Body temperature, 37·2° C. End-tidal CO_2, 4%.

similar stimulation produced a nearly identical change in systemic blood pressure and the flow in the brachial artery underwent a diphasic change with a decrease in flow appearing at the time of an increase in arterial pressure. The lack of heart-rate response was seen in all but the one experiment from which the examples illustrated in Fig. 6 were obtained. The preparation was a chronic spinal animal (the same as in Fig. 2) which gave large responses in systemic pressure to afferent volleys. The bars above each pair of records in Fig. 6 indicate the approximate period of

stimulation of the hamstring (*A*) and L2 (*B*) spinal nerve at 10/sec. Careful examination of the records in Figs. 6*A* and *B* shows a rise in arterial pressure shortly after the beginning of stimulation, with the heart-rate change taking place some seconds later. During the heart-rate increase in Fig. 6*A*, a notable increase in pulse pressure was also apparent. In this experiment some lag in the process leading to reflex change in heart rate existed in comparison to mechanisms increasing carotid pressure. The primary cause of change in blood pressure obviously could not have been an effect upon the heart, because neither the rate nor the pulse

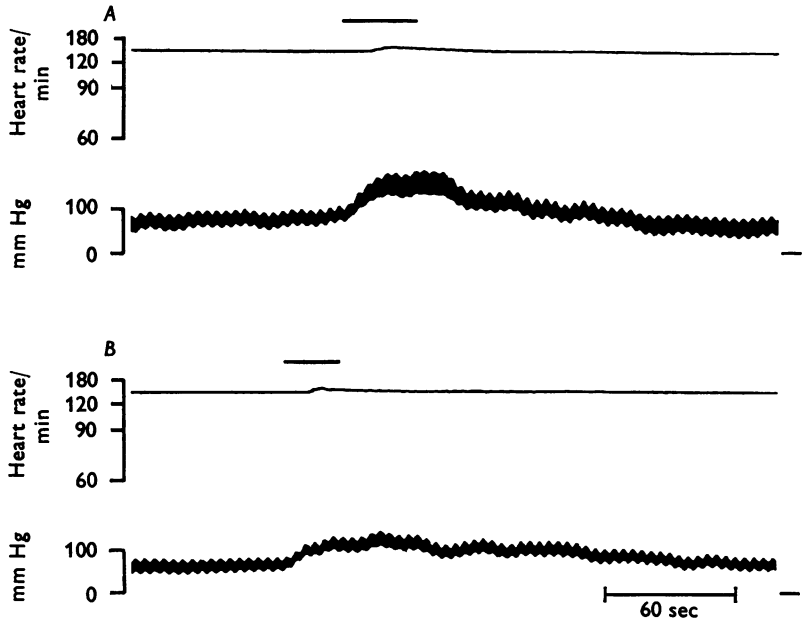

Fig. 6. Response of heart rate and left carotid arterial pressure to tetanic nerve stimulation. Same experiment as Fig. 2. 50 days after T8 spinal section. 8·5 hr after C1 spinal section. Heart rate indicated as in Fig. 5*A*; other details as in Fig. 2. *A*: stimulation of central stump of left hamstring nerve at 10/sec. *B*: stimulation of central stumps of L2 and L3 spinal nerves. Body temperature 37·2° C. End-tidal CO_2, 4·7 %.

pressure changed during the initial rise in blood pressure. Our interpretation of this unique experiment is that an unusually large and relatively generalized sympathetic discharge in post-ganglionic nerves took place as a result of the afferent stimulation. The sympathetic discharge was distributed to the smooth muscles of blood vessels but the massive effect led to the release and persistence in the circulating blood of small quantities of adrenergic material. The dalay between the beginning of the change in blood pressure and the first evidence of change in heart rate can be

accounted for by the circulation time from the peripheral vessels, presumably on the arterial side of the circulation. This interpretation is supported by the small change in heart rate as compared with the large change in systemic blood pressure. The experiment of Fig. 6 also serves as a confirmation of conclusions drawn from observations in another preparation in which large arterial pressure rises were reflexly produced even after bilateral adrenalectomy. It appears that the adrenal glands, like the heart, are not activated in the course of sympathetic reflexes in the spinal animal. If the adrenal release of sympathetic hormone were an important factor, one would expect a heart-rate change to be a regular part of the observed circulatory responses. If adrenal hormone had been released in this particular experiment (Fig. 6), then the heart rate should have shown an increase before or simultaneously with the increase in systemic blood pressure or a secondary rise should have appeared in systemic blood pressure shortly after the increase of heart rate. There is no reason to believe that adrenaline-like compounds have a much longer latency in producing effects upon the cardiac pace-maker than in initiating contraction of the vascular smooth muscle.

'Spontaneous' or autogenous changes

Instability in the blood pressure or blood flow after evoked changes has already been mentioned. In addition to such evoked periods of instability, in a number of preparations, 'spontaneous' periodic changes in the blood pressure were observed. It seemed probable that these 'spontaneous' variations were dependent upon central neural activity because afferent volleys usually altered the instability in one fashion or another. In certain instances, such instability was shown to be dependent upon the sympathetic nervous system by the effects of intravenous injection of tetraethyl ammonium chloride (TEA) in preparations during cyclic or periodic variations of blood pressure or blood flow. Two examples from these results appear in Fig. 7. In Fig. 7*A*, taken from an acutely prepared spinal animal, cyclic changes in the systemic arterial pressure are parallelled by cyclic changes in renal arterial flow (flow increasing with increasing systemic pressure). At the time of the arrow, TEA (30 mg) was intravenously injected. Within 30 sec, the cyclic variations in blood pressure and blood flow had largely disappeared. Figure 7*B* illustrates the results obtained in another preparation in which renal arterial flow changed very little during the relatively large periodic change in systemic pressure. At the arrow, TEA (30 mg) was intravenously injected: the systemic pressure and renal arterial flow fell and the cyclic changes in blood pressure disappeared. Results of this type were interpreted as demonstrating that transmission of impulses across the sympathetic ganglia were important for the

'spontaneous' variations in blood flow and systemic pressure, since the doses of TEA used would be expected to block sympathetic ganglionic transmission (Moe & Freyberger, 1950). In some deteriorating preparations exhibiting very low diastolic pressure and lack of reflex excitability, cyclic variations in systemic arterial pressure were not blocked by intravenous injections of TEA. Presumably in these latter cases, the cyclic changes were not of sympathetic nervous system origin, and may have reflected variations in the state of the effector organ due to local hypoxia.

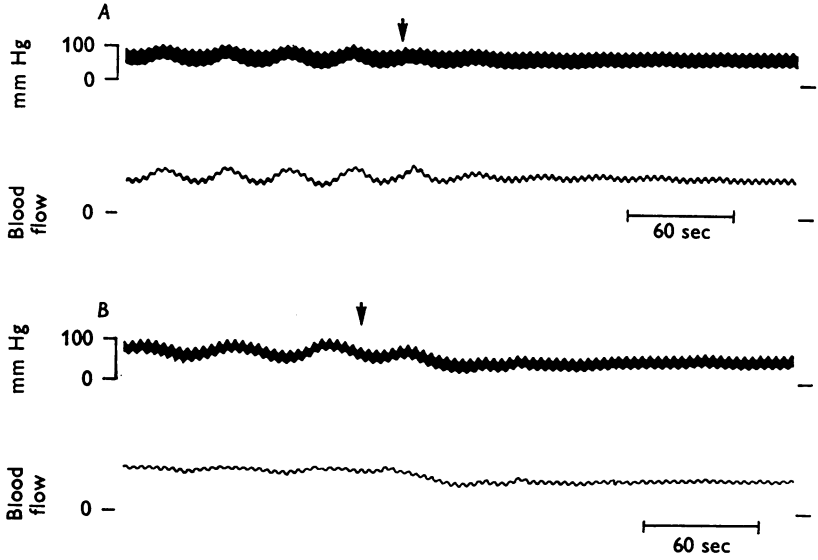

Fig. 7. Effects of tetraethylammonium chloride (TEA) on cyclic variations on carotid arterial pressure and left renal arterial flow. At the arrows, 30 mg TEA administered intravenously in 1–½ ml. of isosmotic solution. *A*: 8·5 hr after C1 spinal section. The cyclic changes in flow represented increases and decreases of approximately 20% of the mean. Body temperature, 37·2° C. End-tidal CO_2, 4·2%. *B*: another preparation, 7·5 hr after C1 spinal section. The drop in flow after TEA was approximately 30%. Body temperature, 36·5° C. End-tidal CO_2, 5·6%.

The two examples of renal artery flow in Fig. 7 further illustrate the point mentioned during discussion of evoked effects, that in this artery flow altered in the direction expected for the variation in systemic pressure, although sometimes (Fig. 10*B*) the alteration of flow during a large swing in pressure was small enough to admit the speculation that a change in renal arterial resistance had contributed to the change of pressure.

In some preparations, large 'spontaneous' changes in flow were observed in a particular artery. Figure 8*A* illustrates changes in flow occurring in the absence of specific stimulation, alterations which consisted of rela-

tively sharp decreases followed by a somewhat smaller increase. This represents essentially the same pattern that was observed in the usual reflexly evoked response. The systemic arterial pressure, while exhibiting small changes at approximately the times of the change in flow in the femoral artery, did not have the obvious cyclic features of the records in Fig. 7. Some time later, in the same preparation, records were obtained of the heart rate in parallel with the systemic arterial pressure. At the particular time of the records in Fig. 8*B*, the arterial pressure was showing relatively large fluctuations over a long time course with smaller cyclic

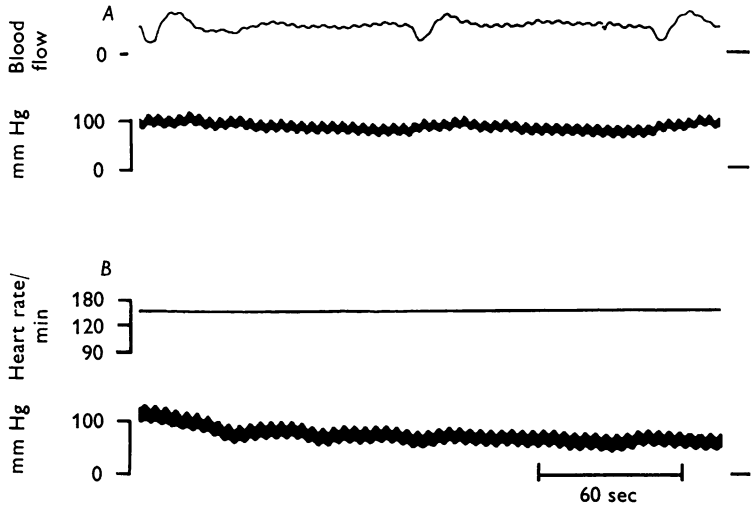

Fig. 8. 'Spontaneous' variations in femoral arterial flow, heart rate and left carotid artery pressure. Same chronic spinal animal as in Fig. 2. *A*: Flow changes illustrated represent approximately a 50% decrease followed by a 40% increase. 6 hr after C1 spinal section. Body temperature, 36·2° C. End-tidal CO_2, 4·2%. *B*: 8 hr after C1 spinal section. Body temperature, 37·3° C. End-tidal CO_2, 4·8%.

changes superimposed. In the sample illustrated by Fig. 8*B*, the heart rate did not alter during changes in mean arterial pressure in excess of 40 mg. The results shown in Fig. 8 are typical of those obtained in over thirty preparations. Heart rate remained very steady despite large 'spontaneous' fluctuations in the systemic arterial pressure. One acutely prepared spinal animal proved an exception in that very small changes in heart rate were observed roughly parallel to relatively large changes in the systemic pressure (heart rate increasing during periods of increasing systemic pressure).

Preganglionic discharge and systemic arterial pressure. Parallel recordings of the discharge of small groups of preganglionic elements and systemic blood pressure were made in a number of preparations. Cyclic changes in

discharge frequency of preganglionic elements have been previously described (Beacham & Perl, 1964*a*). Of particular interest in the present context is that on some occasions cyclic changes in the blood pressure were found to occur with the same periodicity as cyclic changes in the discharge frequency of preganglionic elements. An unusually striking example is illustrated in Fig. 9. The upper tracing of the pair represents the systemic arterial pressure, while the lower record represents the discharge of four preganglionic elements recorded from the same L2 preganglionic filament. The discharges of these four elements were converted into pulses of uniform amplitude and duration and fed to an averaging frequency meter. The output of the frequency meter was displayed as an analogue voltage below the blood-pressure record. The left-hand half of this record shows that during a series of 'spontaneous' cycles, an increased average discharge frequency for these four elements took place before the rise in systemic

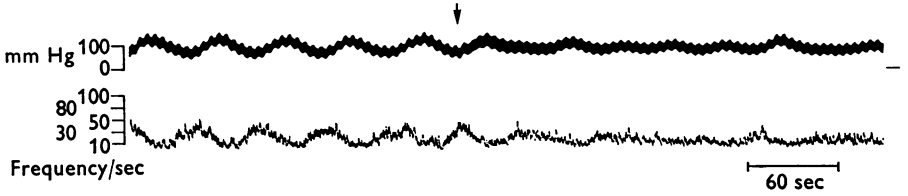

Fig. 9. Carotid arterial pressure (upper) and discharge frequency of L2 preganglionic fibres (lower). Discharges from four different preganglionic 'units' converted to standard amplitude pulses and fed to an averaging frequency meter with time constant of 57 msec. At arrow, 20 ml. of isosmotic salt solution injected intravenously. 9 hr after C1 spinal section. Body temperature, 37·5° C. End-tidal CO_2, 4·6 %.

blood pressure. This relation existed throughout the entire 10 min control period. At the time indicated by the arrow in Fig. 9, 20 ml. of isosmotic solution was injected intravenously. This resulted in an increased pulse pressure and a subsequent disturbance of the magnitude of cyclic changes in systemic arterial pressure. After completion of the cycle during which the fluid injection had begun, the variations in discharge frequency of the preganglionic elements became less obviously cyclic. Toward the end of the record a phasic increase in impulse frequency of these four elements preceded a phasic increase in systemic pressure. In this same experiment, the discharge of one preganglionic unit from the L2 preganglionic ramus was fed to a device providing an instantaneous voltage proportional to the $\log_{10}$ of the previous interval between impulses. The output of this device is illustrated in Fig. 10*A* below a record of the arterial pressure. Note the very large swings in blood pressure. Similarly to Fig. 9, Fig. 10*A* shows that the discharge of this particular preganglionic unit increased irregularly, reaching a peak during the rising phase of the cyclic variation in

pressure, and then decreased to a minimum at or just after maximum arterial pressure.

In some experiments, periodic changes in discharge frequency of a preganglionic unit were noted in preparations in which the systemic arterial pressure did not undergo large phasic changes. In the example in Fig. 10*B* the discharge pattern of an L3 preganglionic element is illustrated with a simultaneous record of the arterial pressure, the latter varying slightly in an irregular manner. Periods of relatively low-frequency discharge of this neurone alternated with silent periods of several seconds duration. The changes in discharge frequency were not regular in timing as in Fig. 10*A*;

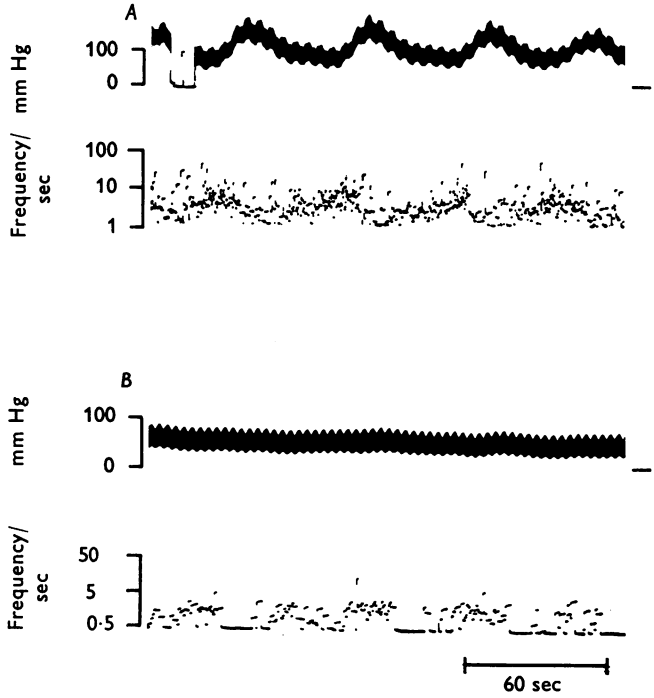

Fig. 10. Carotid arterial pressure (upper) and discharge frequency of single L2 preganglionic fibres. *A*: instantaneous discharge frequency of one unit of the four shown in Fig. 9 8 hr after C1 spinal section. Body temperature, 37° C. End-tidal CO_2, 5·6 %. *B*: another experiment 11 hr after C1 spinal section. Body temperature, 37·5° C. End-tidal CO_2, 5·6 %.

however, increased discharge of the preganglionic neurone did seem to bear a temporal relation to the relatively minor increases in systemic blood pressure.

Other preparations as well as that of Fig. 2 produced examples of a change in a cyclic pattern of preganglionic discharge as a consequence of altering circulatory conditions by the intravenous injection of fluid or temporary withdrawal of blood. It was also noted that procedures tending to increase the

systemic arterial pressure (circulatory volume expansion, adrenaline) reduced the discharge of certain preganglionic neurones, while a fall in pressure was followed by increased numbers of impulses. For some preganglionic neurones the opposite effects were seen; increases in arterial pressure by fluid or adrenaline increased the background discharge. From these preliminary observations, it is apparent that in the spinal animal part of the sympathetic preganglionic output is sensitive to cardiovascular conditions.

DISCUSSION

The present experiments demonstrate the presence of reflex vasomotor changes in the spinal animal. This concept is not new, since both Kuntz (1945) and Richins & Brizzee (1949) deduced that changes in the diameter of small vessels of the gut were initiated by afferent stimulation in the spinal rat. It appears that part (or all) of the reflex preganglionic discharge described by Beacham & Perl (1964*a*, *b*) has a vasomotor projection. The types of stimuli effective in evoking preganglionic discharge and alterations in arterial flow are the same. Furthermore, when the afferent input consisted of electrically initiated impulses in segmental nerves, the same group of afferent fibres (myelinated and slowly conducting) which evoke preganglionic discharge cause decreases in blood flow. Ordinarily the changes in initial flow were reciprocally related to the arterial pressure; that is, flow decreased in a variety of arteries at the time of reflex increases in systemic arterial pressure. The lack of increase in pulse pressure in most reflexly produced rises in systemic pressure in the face of a constant heart rate argues that little change took place in the venous capacity. Therefore, the changes in flow and systemic pressure resulted from increases in the peripheral (arteriolar) resistance. We recognize that the evidence does not permit exclusion of all other effector organs. The usual absence of reflexly produced changes in heart rate does show that little, if any, of such preganglionic discharge is destined for the cardiac pace-maker or the adrenal medulla. A reflex response limited to neurones controlling one or a few types of effector organs would explain the observation that only part of the preganglionic outflow of a given segment participates in the reflex (Beacham & Perl, 1964*a*, *b*).

Some idea as to a possible effector organ distribution of the background or tonic discharge of preganglionic neurones in the spinal preparation can also be gained from the present results. In the first place, it was shown that the systemic arterial pressure and flow through selected arteries has 'spontaneous' changes. The 'spontaneous' changes were sometimes dependent upon sympathetic discharge because they could be blocked by a ganglionic blocking agent (tetraethylammonium). At the same time, the

stable heart rate during 'spontaneous' fluctuations in arterial pressure again suggests that the sympathetic outflow to the cardiac pace-maker and adrenal medulla usually was not involved. Thus, sympathetic background or tonic activity is also specifically distributed. Finally, in certain instances, there was a clear temporal relation between preganglionic discharge and autogenous variations in arterial pressure, e.g. Figs. 9 and 10*A*. We believe it reasonable to deduce from such evidence that at least some of the tonic discharge in preganglionic neurones in the spinal animal project through specific post-ganglionic cells to the smooth muscle of blood vessels. Thus, in both reflexly evoked changes and tonic or background changes, preganglionic discharges in the spinal animal seem to reflect, in part, a vasomotor control mechanism. On the other hand, one cannot conclude that all the preganglionic neurones 'spontaneously' active in the spinal animal have vasomotor function. A number of 'spontaneously' discharging preganglionic neurones could not be made to alter their pattern of discharge by afferent stimulation (Beacham & Perl, 1964*a*). Therefore, unless there are vasomotor preganglionic fibres which are not affected by reflex discharge, some of the tonic discharge must project to other effector organs.

The selective distribution of the reflexly evoked changes in preganglionic discharge is a strong point in favour of the concept that different portions of the spinal sympathetic outflow can be excited (or inhibited) independently of one another. The graded excitation of the vasomotor, but not cardioaccelerator, neurones during spinal circulatory responses also intimates that controlled activation of sympathetic outflow for the cardiovascular system can take place in the intact animal, as suggested by other investigations (Rushmer, Smith & Lasher, 1960). However, this does not imply that some mechanism for exciting a massive or generalized sympathetic discharge does not exist at the spinal level. Neither the present study nor previously reported experiments (Beacham & Perl, 1964*a*, *b*) have exhausted the stimuli which might induce reflex responses.

The cyclic instability of the systemic arterial pressure and arterial blood flow in the spinal cat is evidence for spinal mechanisms controlling arterial pressure. As shown in Figs. 7, 9 and 10*A*, the cyclic changes may take place about a mean level which may be within the 'normal' range. On purely theoretical grounds, for such instability to be present, some feedback indicating the level of arterial pressure or some phenomenon dependent upon it (e.g. blood flow or vessel diameter) must exist. The influence of circulatory conditions on the cyclic behaviour (Fig. 9) also suggests that a method for monitoring blood pressure or one of its dependent variables is present in the spinal animal. Whether this monitor is a receptor sensitive

to blood pressure or whether it is an effect of blood flow on spinal mechanisms cannot be decided on the basis of the present data, particularly since the only spinal afferent fibres described as responding to cardiovascular events are not capable of sensing slow changes (Leitner & Perl, 1964). These inferences on regulatory mechanisms for the circulation in the spinal animal are in keeping with previous work on the spinal cat which has shown that tonic discharge of sympathetic neurones contributes to the maintenance of its circulatory status and that its vasomotor activity can show appropriate adjustments in response to physiological stress (Brooks, 1935; Alexander, 1945).

SUMMARY

1. These experiments in the spinal cat were aimed at determining the relation of reflex and background discharge of sympathetic preganglionic neurones to the systemic circulation.

2. Reflex discharges evoked by single afferent volleys in spinal nerves usually appeared in only certain post-ganglionic branches of the stellate and upper lumbar ganglia. When branches of the stellate outflow differed in their reflex response, direct stimulation of a silent post-ganglionic branch increased the heart rate while similar stimulation of activated post-ganglionic nerves was without effect on the heart.

3. A number of types of stimuli which reflexly excite preganglionic neurones evoked transient increases in the systemic arterial pressure, and/or altered flow in the femoral, inferior mesenteric and brachial arteries. The magnitude of the change in arterial flow could be graded by grading the afferent stimuli. Afferent fibres associated with reflex variations in arterial flow conducted between 10 and 25 m/sec, the same range of velocities as those evoking preganglionic reflexes. With one exception, the heart rate was not observed to vary during reflex increases in systemic pressure. In the exception, the heart rate began to increase several seconds after an unusually large rise in the central arterial pressure, probably owing to circulating adrenergic material from effector sites in the vascular tree.

4. In many records, the arterial flow or the systemic arterial pressure fluctuated or cycled after a reflex effect. Variations in systemic arterial pressure or arterial flow were sometimes autogenous with long-term and regular cycles (25–60 sec) which often could be blocked by tetraethyl ammonium. The heart rate was noted to vary during autogenous swings of the systemic blood pressure in only one of 30 preparations.

5. In several preparations, periodic fluctuations in preganglionic discharge were temporally related to periodic fluctuations in the systemic arterial pressure. In these preparations, changes in haemodynamics pro-

duced by fluid injection or haemorrhage resulted in alteration of both the neural discharge pattern and the periodic fluctuation of systemic arterial pressure.

6. It was concluded from the present study of the spinal cat that: (*a*) some of the reflexly produced and background discharge of sympathetic preganglionic neurones represent part of a vasomotor mechanism; (*b*) the distribution of preganglionic impulses is specific in terms of effector organs, demonstrating independent control of some portions of the sympathetic outflow; (*c*) the cycling of the systemic arterial pressure with its relation to sympathetic activity indicates some form of vasomotor control at the spinal level.

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