AN ANALYSIS OF THE NERVOUS CONTROL OF THE CARDIOVASCULAR CHANGES DURING OCCLUSION OF THE HEAD ARTERIES IN CATS

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STATEMENT OF THE PROBLEM.[1] The relations dealt with in this study are the cardio-vascular relations found in the mammalian organism under extreme conditions of stress. The procedure of the experiments, occlusion of the head arteries, gives a complete anemia of the brain, and thus produces a profound change in the internal environment of the animal. To this the mammal tends to respond by a series of vigorous reactions. These reactions, moreover, seem to go in a direction opposite to that of the change in internal conditions of a particular group of cells. Thus, with an asphyxial accumulation of carbon dioxide in the medium surrounding the critical medullary cells, there is released an entire series of reactions which, could they all be carried to completion, would reduce the tension of this gas in the body fluids of the cerebral region. Prominent among these reactions is a great and prolonged rise of blood pressure, involving the extreme resources of the organism, tending to send a greater volume of blood to the anemic regions, and hence to decrease the concentration of the carbon dioxide in the nerve cells of the medulla oblongata. In the cat, this anemic rise of blood pressure can be well controlled anatomically, and is suscep-

[1] A preliminary note has been published in Proc. Soc. Exper. Biol. and Med., 1921, xviii, 155.

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tible of rather exact registration. Moreover, artificial respiration may be maintained throughout the reaction, and thus the activity of the peripheral mechanisms, the heart, blood vessels and internal secretions, be kept free from the central asphyxial changes. Furthermore, under artificial respiration, the reaction may be obtained repeatedly in the same animal. It has therefore offered an opportunity for analyzing the factors involved in such an emergency reaction to inimical conditions in the central mechanism.

Since the work of Ludwig, Cyon and Bezold in the sixties, the importance of the splanchnic vasomotor fibers for the production of extensive changes in blood pressure has been recognized. The related action of the discharge of adrenalin into the blood stream has recently received considerable emphasis. However, the degree to which either the splanchnic constrictor fibers or the secretion of the adrenal glands is involved under such conditions of stress as evoke the anemic rise, has not been evaluated with sufficient accuracy. This study has therefore been concerned particularly with the efferent nervous pathways of the "anemic rise" of pressure: above all, with the degree to which it involves the splanchnic constrictor fibers. The extent to which splanchnic involvement has made for adrenal activity has then been investigated. Finally, the influence of the cardiac innervation, insofar as this may directly effect changes in the level of blood pressure during anemia, has also been examined.

Through the restriction of the effect of the arterial occlusion to the head region alone, the activation of the vascular response by the medulla oblongata is under close experimental control. Accordingly, the central relations of the various nervous levels controlling the efferent channels could also be investigated. Indeed, the analysis of the peripheral factors was in large part undertaken in order to establish more accurately the functional organization of the central nervous mechanism upon which the vascular response depends, that is, the extent to which the peripheral agents executing the vascular responses of the intact animal are activated either by the higher nervous levels, or by the spinal cord alone.

This analysis was undertaken in connection with the studies on the central nervous system carried out under Prof. F. H. Pike, which have dealt particularly with the bearing of its organization on the problem of "spinal shock." In connection with the problems here opened up it was necessary to ascertain the exact nature of the peripheral and central factors controlling the typical vascular response in animals in

which either no lesions within the central system were undertaken, or when these were inflicted, no interval for recovery after the operation was allowed. In comparison with such data, a study of the vascular responses after recovery from transection of the spinal cord could be undertaken more intelligently, and the actual changes wrought by the so-called shock effect evaluated with greater precision.

HISTORY OF THE METHOD. Initiated by the very early work on abdominal ligation of Stenson (1) and Swammerdam (2), Magendie and Poiseuille (3) and Sir Astley Cooper (4) in the early nineteenth century worked out the procedure of cerebral ligation, particularly the isolation of the four chief arterial channels to the head, and noted the circulatory changes which followed. Batelli (5) and Hill (6) have given the earlier history of the procedure in some detail.

The experiments of the eighteen fifties and sixties led to the recognition of the nervous organs as the chief agents in activating the changes following arterial ligation: thus the work of Kussmaul and Tenner (7), Brown Sequard (8), (9) and Vulpian (10) on the head area and of Schiffer (11) on the spinal cord. The emphasis of the importance of the medulla for the maintenance of life as given by the work of Le Gallois and its extension by Flourens (12) was still more increased by the localization in the same region of the vasoconstrictor center as soon accomplished by Ludwig (13), Owsjannikow and Dittmar, and soon led up to the most complete studies on occlusion of the head arteries carried out by Sigmund Mayer (14), (15). Mayer not only described the series of changes following anemia with great detail and accuracy, but also recognized that the elicitation of the anemic rise was dependent on conditions of functional conductivity within the brain stem. He also saw that occlusion of the head arteries was comparable to decapitation with the knife, and that the various functions retained following cerebral ligation were all to be attributed to the activity of the spinal cord, notably the residual spinal level of blood pressure of 50 to 60 mm.

Couty (16) produced circulatory obstruction in the head region by the injection of lycopodium spores. This work, contemporaneous with that of Mayer and equally detailed, but carried out under the influence of the earlier work of Goltz (17), (18) and Vulpian, stressed the residual spinal functions, maintained following isolation of the medulla. Subsequent work on cerebral anemia was almost exclusively done from this point of view. Thus the papers of Schlesinger (20), Kowalewsky and Adamük (21), Bochefontaine and Vulpian (22), Mayer (23), attempted to combat this viewpoint by an analysis of the differential

effect of compression of the abdominal aorta. Konow and Stenbeck (24) and Landergren (25) more recently stressed the functional survival of the cord in the decapitated animal preparation. The residual spinal blood pressure was analyzed by Pike (26) (1912) who showed that afferent impulses, presumably from skeletal muscles, were responsible for it. His observation that a further fall occurs on paralysis of skeletal muscles by curare has recently been confirmed by Langley, 1919 (27).

A revival of interest in the central relations of the asphyxial picture, particularly to the higher nervous levels, was in part achieved through the reëxamination of the problems of resuscitation of the organism by Stewart, (28), (29), (30), (31), (32), (33) Pike and Guthrie. These observations threw sharply into relief the dependence of resuscitation on the medullary respiratory and vasoconstrictor mechanisms rather than on other organs, which, whatever their importance, were found neither as sensitive nor as susceptible as the medullary and higher cells. The functional activity of the medulla was abolished 15 minutes or more, and in its abeyance, no independent existence of the animal could be reëstablished. An analysis of the conditions of so-called spinal shock was undertaken by Pike (34), (35), (26), who employed the procedure of cerebral anemia, and the vascular response obtainable from it, as a means of comparing the various functional levels of the central nervous system. In this way the central relations, particularly to the bulbar levels, of the vascular response in anemia were clearly indicated. A further extension of this problem is found in the study of Yates (36), in which the response to anemia was used as a criterion of the degree of recovery of the vascular system following spinal transection. These studies bring out the importance of the maintenance of medullary activity as the essential factor in the avoidance of a shock effect and the relative incompetence of the spinal cord in the initiation of significant adaptive responses.

Consideration of the excitatory and depressing effects of the blood gases has led toward a recognition of their importance in influencing the behavior of the medullary cells. The literature of the subject is reviewed by Bethe (37), Hill and Flack (38), Hasselbach (39). Pike, Coombs and Hastings (40), (41) have pointed out the adaptive nature of the nervous changes induced by a rapid lowering of CO_2 tension in dyspneic blood, and have suggested that in thus acting in a direction opposite to environmental change, the organism meets the conditions by adjustment of physical equilibrium as prescribed by le Chatelier's

theorem. Mathison (42), (43) has shown the very much greater sensitivity of the medullary over the spinal cells in their response to the asphyxial agents such as increased CO_2 or lactic acid, or decreased oxygen. Pike and Scott (44) have discussed the regulation of H-ion concentration in connection with the regulation of mammalian internal environment.

METHOD. In the present study advantage was taken of the reversibility of the procedure of cerebral anemia. The ability to repeat the initial stimulating effect of the insult on the medullary cells was exploited, rather than its abolition of conductivity within them. The specific problems attacked were dealt with in terms of the intensity and duration of the anemic rise, under given central and peripheral lesions. A seemingly significant series of observations on the changes at the periphery could be obtained by means of the pronounced differences in the character of the curves recorded.

Mayer (14) had called attention to the fact that the magnitude of the vasomotor effect under asphyxia could be approached only by the effect of compression of the thoracic aorta, or injection of strychnine. From Mathison's work (42), (43), especially from his conception that all forms of asphyxia are due to definite increase of the acid content of the blood, cerebral anemia can probably be assumed always to be acting at a maximum. The procedure followed was essentially that indicated by Stewart (28). As here used, the emphasis lay especially on the restriction of the occlusion time to as narrow a limit as possible, in order to insure more rapid recovery. Accordingly, the shortest possible occlusion period was uniformly employed and as a routine procedure the head arteries were released as soon as the spontaneous fall of pressure at the end of the response set in.

The experiments were all carried out on cats. Ether was the anesthetic uniformly employed, and administered by tracheal cannula. The purpose of the study was essentially to determine the degree of involvement of the chief factors concerned, rather than their minute evaluation. This has been left for subsequent study. The extensive series of Stewart served as a basis of comparison and control.

The head arteries were all secured outside the thoracic wall, the branches of the left subclavian, separately secured in the axilla, the right carotid, and right subclavian from within the carotid sheath in the neck; the left carotid held the blood pressure cannula. All the arteries were kept under ligatures ready to be occluded by clamps at the convenience of the experimenter. Since there was no interference

with extra-pulmonic pressure through the operative procedure, artificial respiration could be dispensed with as long as the medullary cells remained functional.

Prior to occlusion, ether was reduced until various obvious tests of the activity of the brain stem could be secured, the return of a vigorous corneal reflex always being awaited before the circulatory arrest was made. With the elicitation of the corneal reflex, artificial respiration was begun, and the clamps on the arteries immediately adjusted. Care is needed to include all the arterial branches isolated in the clamps.

With the adjustment of the clamps, the entire series of peripheral effects follows; the eye reflexes are immediately lost, and within about 20 seconds the more marked peripheral effects are released. Deep and labored breathing sets in, skeletal convulsions appear, and a sharp rise of blood pressure is recorded which often reaches 200 mm. Hg. or more (fig. 5a). This frequently outlasts the other functions; the pressure may not begin to fall until some 10 to 80 seconds after respiratory failure.

The time from the shutting off of the arteries to the circulatory failure is then taken as the complete occlusion time. On the average, this occupied 3 minutes.

Immediately following reëstablishment of the circulation there is a profound depression of all functions. Blood pressure continues falling markedly when the arteries are released, and finally reaches a level of about 50 mm. No other medullary responses are elicitable at this time. Artificial respiration is, of course, maintained throughout the period of depression, and until such time as the bulbar functions again become evident.

If no further lesions are inflicted, occlusions of 3 to 4 minutes are usually followed by a beginning of recovery within 5 to 7 minutes after release of the arteries. Blood pressure usually starts rising first, and after a rise of 10 to 15 mm. spontaneous respiratory gasps reappear. Pressure continues to rise, respiratory movements become more and more frequent; soon normal pressure is regained and the animal breathes quietly and regularly. Ten to 15 minutes after release of the arteries, pressure is usually normal, vibrissae are erect, and the corneal reflex is again elicitable. At this point, a renewed occlusion of the head arteries may be done and the entire cycle repeated.

The modification of anatomical conditions was usually carried out in the interval of depression following a control occlusion. In this way further etherization was avoided. Except under certain specified

conditions, the various lesions did not materially change or delay the picture of the recovery outlined.

THE EXPERIMENTAL RESULTS. *1. The rôle of the splanchnic constrictor fibers in the rise of pressure during cerebral anemia:* Following the work of Claude Bernard in 1848 who showed that the section of the cervical cord caused a considerable fall of blood pressure, Bezold, Ludwig and Cyons (46), (47), (48), (49), (50) measured the magnitude of these changes and showed their dependence on the integrity of the splanchnic system. There was thus demonstrated the relation of the blood pressure changes to the level which is maintained after the continuity of the cord with the brain has been interrupted.

Mall (51) showed that frequently 27 per cent of the blood in dogs was transferred by the splanchnic system, thus explaining the great increase of volume in the extremities during rises of systemic pressure (52). Edwards (53) calculated that 85 cc. of blood in dogs were translocated under splanchnic stimulation. In spite of its probable involvement in the powerful vasomotor response of the anemic rise, very little direct evidence for its participation has been obtained. Hill's (46) reference to the splanchnic nerves in cerebral anemia is, so far as can be ascertained, largely by way of implication. For asphyxia itself both V. Anrep (54) and Cathcart and Clark (55) have argued for considerable splanchnic participation from the dependence on the central nervous system of the adrenalin release obtained. Finally, some indirect evidence for splanchnic nerve involvement has been obtained by section of the spinal cord in cerebral occlusion. Nawalichin (56) found that the vasomotor changes following obstruction of the cerebral circulation were practically obliterated when the cord had been sectioned in the cervical region. The same observation was made by Stewart (28).

In order to obtain any exact, or possibly even quantitative, evaluation of the actual involvement of the splanchnic system, other factors concerned in the maintenance and change of blood pressure must be isolated. Three factors in the nervous regulation must above all be properly controlled. These are (*a*), the indirect effect of the activity of the skeletal muscles; (*b*), the influence of the cardiac innervation; and (*c*), the non-splanchnic constrictor (or possibly dilator) fibers in the vasomotor system.

a. The influence of the skeletal muscles in the anemic rise. The older authors, Mayer and Couty, used curarized animals, rabbits and dogs, for their experiments on cerebral occlusions, and reported anemic

rises as great in magnitude and duration as those recorded by Stewart (28) or those herein obtained. The relative volume of blood held in these animals within the splanchnic system, as compared with that controlled by the somatic innervation is, however, somewhat different from that in cats. Little experimental attention was here given to this problem. In one animal, however, curare was injected and a vigorous anemic response was obtained. The occlusion time was normal (3 minutes); the anemic increment, however, was below the average, being only 80 mm. In another cat, both sciatics and the brachial plexuses on both sides were divided. Pressure did not fall after the lesions. Both stellate ganglia were then removed. The animal gave an anemic increment of 100 mm. Hg.

It seems accordingly that the muscular factor is of no primary significance in either the initiation or the maintenance of the anemic rise. The fact that no great depression of the level of blood pressure results in spite of extensive elimination of muscular innervation is interesting in comparison with subsequent results, and effectively contrasts the influence of skeletal innervation and visceral innervation on blood pressure.

b. The influence of the cardiac innervation on the anemic rise. The influence of the cardiac nerves on the anemic rise may be exerted in either of two ways. The change in rate and amplitude of the heart beat may affect the output per minute as emphasized by Tigerstedt, (57) or afferent impulses aroused within the heart may affect reflexly the efferent cardio-vascular innervation as discussed by Hill (59). It is conceivable that in either of these ways, or both, the heart may influence significantly the level of blood pressure.

Frank (57), mathematically, and Erlanger (58) by sphygmomanometric measurements, have attempted to show that the output of the heart remained a constant, or in other words that pulse pressure times pulse rate remains a constant. Wickwire (60) has shown that the usual compensatory changes in heart rate to a change in the systemic blood pressure may be absent in deep anesthesia or in cases of restriction of the volume of blood flow to the brain. Under normal circumstances, Erlanger's statement probably holds true, but may not necessarily apply under critical conditions.

1. Effect of the vagus. Mosso (61), Couty and Stewart found that following the first short rise in blood pressure (which in the intact animal is never very great) there is a considerable slowing of the pulse. As long as this slowing of the pulse persists, pressure ceases to rise, and

is indeed often lowered. After about half a minute of this effect, the heart seems to break away from this retardation, and the beat is, if anything, accelerated and pressure immediately rises to the maximum level which is maintained until its final fall. The slowing of the heart rate and the depression of blood pressure gives the anemic rise its typical double crest. Both Couty (16) and Stewart (26) saw this double crest disappear on section of the vagi, leaving a smooth curve, which attains its maximum height somewhat more rapidly, but is not otherwise greatly altered in time or intensity.

Bilateral vagotomy has been done only incidentally to other lesions. The results confirm the earlier findings.

2. *Excision of the stellate ganglia.* Section of the accelerators as the only lesion was undertaken in five cats, all except one dissection being made in the open thorax under artificial respiration. In all cases the entire stellate ganglion was removed. The mass of nervous tissue was secured by a hemostat and this then cut away from all the connections by which it was held, until the hemostat could be removed without tearing. All the records therefore give a picture of the effects obtained by excision of the entire ganglion including, of course, those additional accelerator fibers recorded by Ranson, Spadolini and Wickwire (60), which reach the stellate ganglion by way of the superior cervical ganglion.

Hunt (62) recorded a loss of pressure on section of the stellate ganglia. Wickwire found a considerable loss (60 mm.) on their section, when this was undertaken without a previous vagotomy. In two cats, 1 and 3, a similar depression was noted. In cat 2, however, the fall was only 20 mm. In cat 7, in which pressure was already very low, no change at all was noted.

Section of the accelerators on both sides seems, like double vagotomy, to have a typical effect on the contour of the curve. It also tends to obliterate the double nature of the curve, which then more closely approaches a single peak. Characteristically, section of the accelerators imparts to the anemic rise a marked plateau effect. After a relatively restricted latent period, pressure rises sharply to its maximum level (fig. 1, occlusion 2), near which it is maintained until just prior to its final fall, when it may again strike the greatest height. The anemic increment of pressure for the five cats examined lay between 120 and 160 mm. Hg. Such a vagus effect as made itself felt, curiously enough, appeared somewhat later than when the accelerators were intact, and the slowing was recorded at the crest of the wave at a very

high level of blood pressure. Occasionally a sharp depressor effect may be recorded, which is rapidly compensated for; this effect gives an M-shaped appearance to the curve. On the whole, with the stellate ganglia excised, pressor responses are more promptly executed and longer maintained. In six additional cats, section of the accelerators was complicated by other lesions. In the two cases in which it was preceded by low section of the sympathetic chain, an anemic increment of 80 mm. was obtained in each.
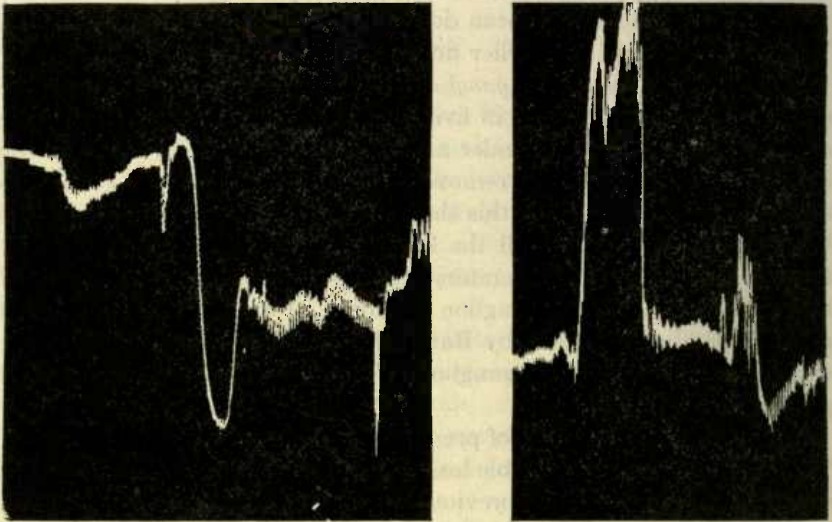

Fig. 1. Cat 4; Occlusion 1. Cerebral anemia, anomalous contour of curve. In this, great fall of pressure replaces the rise ordinarily obtained. The levels of blood pressure before anemia, after anemia and after recovery of bulbar function are shown. Head arteries were released immediately after the rise of pressure, in which the pre-occlusion level was partially recovered. Pressure fell subsequently as low as the lowest point obtained during anemia, but regained 90 mm. above this level with the return of bulbar function.

Occlusion 2: Cerebral anemia; record following excision of both stellate ganglia. When anemia is induced, pressure is 50 mm. lower than after recovery of bulbar function, prior to section of the stellates; M-shaped curve, showing sharp immediate rise of pressure, almost to its maximal height; vagus effect appears at crest of wave. Temporary recovery on release of head arteries, followed by fall to lowest level of pressure (55 mm. Hg. above base line). This low level was three times reached in this animal. Final rise of pressure on renewed return of respiration and other medullary activities.

Each occlusion occupied 3 minutes.

3. Excision of the entire cardiac innervation. In three cats the section of both vagi and accelerators was undertaken without any previous lesion. In two of them, section of the vagi was undertaken first, and in both cases a rise of 20 mm. obtained. Subsequent section of the stellates did not appreciably lower (by more than 5 mm.) the original level. The order in which the section of the cardiac nerves is carried out is, therefore, significant for the general level of pressure, and is again in agreement with Miss Wickwire's findings. Several successive curves were obtained from cat 5. The anemic increment was in these cases somewhat reduced, increments of 80 to 100 mm. being obtained after elimination of all the extrinsic cardiac nerves. When all cardiac nerves were sectioned, the curve tended to be smooth, the initial acute rise not being at all delayed. No change in the occlusion time was noted.

Recovery from occlusion after excision of one or both sets of the extrinsic cardiac nerves was uniformly obtained. The time interval of recovery was in no way different from that in normal animals.

In additional cats to be mentioned later, excision of the extrinsic innervation was preceded by a low section in the sympathetic chain. One animal gave an even higher anemic increment (125 mm. Hg.) than is usually obtained after section of the cardiac nerves alone.

In all the curves of reaction to anemia from animals with denervated hearts, pressure was not uniformly maintained at the maximal level. In two cases the pressure dropped immediately; in the rest (4 cases) a plateau was maintained.

4. Effect of the cardiac innervation on the anemic rise. Neither lesion of the cardiac innervation, as a whole, nor of the vagi, nor of the stellate ganglia separately, greatly affects the blood pressure response. Its duration seems to be fairly constant for the given individual tested. Excision of the entire cardiac innervation may reduce the anemic increment in some cases, but the reduction when it occurs does not seem to be considerable.

However, the cardiac nerves seem to have considerable influence on the level of blood pressure in the more detailed relations of the anemic rise, especially in the early part of the reaction. From the results of the section of the accelerators, particularly the abruptness with which an intense rise appears immediately on occlusion of the head arteries, it seems that the conception of the action of the accelerators must be extended. Marey asserted in 1881 that with the vagus intact no very great rise of pressure can be obtained. Indeed, as long as the vagi are

functional the maximal anemic increment is not immediately obtained, and cannot be reached in the early part of the occlusion unless the vagi be sectioned. The same seems to follow also for the accelerators since, when they are removed, the vagus cannot prevent the immediate and considerable augmentation of pressure. In the earlier part of the anemic response, the combined action of the entire cardiac innervation seems to effect a considerable check on the rapid rise of blood pressure. This may be due to afferent or efferent impulses, but the accelerators seem to be involved as well as the vagi.

The relations of the cardiac innervation to the second rise of pressure are not so clear. Stewart (28) attributed this in part to accelerator fibers in the stellate ganglion, and possibly in the vagus, but recently Stewart and Rogoff (63) have demonstrated the possibility of producing
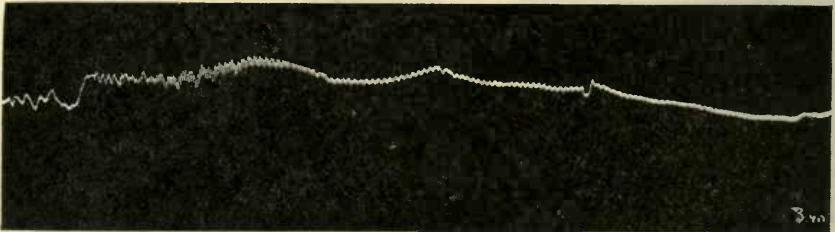
Fig. 2. Cat 23; cerebral anemia. Splanchnic nerves sectioned at their entry to coeliac ganglia. Occlusion time 3 minutes. Skeletal convulsions and respiratory spasms evident. The only factors in the vascular reaction recognizable in the tracing are the changes in heart rate. This is accompanied by a very slight change in level as the heart is breaking away at the usual time from its slow rate. Two respiratory gasps are later imposed on the tracing.

cardiac acceleration by sciatic stimulation even after the heart is completely denervated. In this series of experiments the rise appears very definitely in cats with accelerators removed and vagus intact. It must, therefore, be referable to vasomotor or endocrine effects under these conditions. Ordinarily, there is no break in the curve after double vagotomy, the fall due to vagus slowing being absent. In two cats, however, such a second rise has also been seen when the heart was completely denervated. It seems that the cessation of the vagus effect, while undoubtedly significant, is only one of the factors involved.

In the absence of the influence of the cardiac nerves on the initiation and maintenance of the reaction to cerebral anemia, it seems that we must look to the vasomotor mechanism itself.

It is interesting to note, however, that when the animal is no longer intact, and the peripheral resistance has been markedly lowered by a high transection of the cord, these relations are changed. Yates (36) has observed that cats which showed a considerable anemic rise after recovery from such a section, completely lost their ability to react to cerebral anemia following a subsequent excision of the stellate ganglia. However important for all practical purposes the vasomotor control may be, the considerable involvement of cardiac factors in the integrated response, particularly in the event of injury to the vasomotor nerves, must not be overlooked.

c. Influence of the splanchnic nerves on the anemic rise. The wide distribution of the splanchnics, gives a possibility for various lesions within the system. Section of the splanchnics was therefore undertaken *1*, in the base of the sympathetic chain before leaving the thorax; *2*, in the abdomen, just prior to their entrance into the coeliac ganglion; *3*, in various levels of the spinal cord in the thoracic region.

The anatomical relations of the splanchnic outflow in the cat have been described by Langley (64), who concludes that the fibers destined to enter the splanchnic nerves leave the cord in large part below the level of the sixth thoracic, though occasionally fibers can be traced at the level of the fifth and even fourth thoracic. Langley's statement appears based only in part on his own observations, and is largely founded on the work of other investigators embodied in the papers quoted. Several authors included higher levels for the effects studied based on experimental rather than anatomical evidence though all have stated that the effect elicitable is relatively slight. Bayliss and Starling gave 3rd thoracic as supplying the portal circulation, Bradford, the 3rd thoracic as supplying the kidney; and Schäfer and Moore, 3rd thoracic as supplying the spleen.

In a more recent study on cats Ranson (65) has re-investigated the problem. He confirms Langley's findings and considers the 4th thoracic the highest limit of the splanchnic outflow. Ranson's material, however, was in part restricted to animals in which only the levels below the 6th thoracic were examined. Ranson has investigated further the level at which the splanchnic nerve leaves the sympathetic chain. In far the greater number of cases (13 out of 17) the nerve was given off between the 1st lumbar and 13th thoracic ganglion, in the remaining four cases, the nerve left between the 1st and 2nd lumbar ganglia. The relation of this branching to the diaphragm was not stated.

1. Lesions within the splanchnic outflow: Section of the sympathetic chain; thoracic section of the splanchnics. In 12 animals the splanchnic outflow was interrupted in the lower thorax. Under artificial respiration, a low midventral incision was extended bilaterally on either side of the diaphragm, and the lungs held back while the sympathetic chain was isolated and sectioned.

Section of the sympathetic chain below the level of the 8th or 9th thoracic vertebrae usually gives a very marked fall of pressure. When the splanchnic branch from the sympathetic chain itself is cut, this depression amounts at least to 80 mm. Hg. In spite of this low level of pressure, spontaneous respiration is not usually lost, and when ether is reduced, eye reflexes and other skeletal responses are readily elicitable. The condition of the animal, however, is precarious, and prolonged operative manipulations with too great a depth of anesthesia will readily cause complete loss of the bulbar responses. This precarious condition is in fact met with in all extended lesions within the splanchnic system, and offers some difficulty in the further manipulation of the animals.

Occlusion of the head arteries in this series generally gave a relatively vigorous response. The intensity of the response varied, the degree of variation from the normal being dependent apparently on the nature of the lesion.

Group I. In these animals section of the sympathetic chain was undertaken in its lower levels, post-mortem examination showing no lesion above the level of the 8th thoracic. In two of these animals autopsy showed the lesion incomplete on one side, thus amounting largely to a unilateral injury. The anemic response obtained in four of these animals was very considerable, the values being 100, 120, 140, 150 mm. Hg., respectively. The contour of the curves was typical of the normal anemic responses, and the rise of pressure easily over-reached the original control level of blood pressure. All these cats showed a normal recovery from the occlusion. In nos. 12 and 15, excision of the stellate ganglia was done subsequent to recovery and a third occlusion obtained. Cat 15 that had shown an unusually vigorous response in its first occlusion gave an increment of 125 mm. Hg. after excision of both vagi and both stellates. The thoracic chain was sectioned at the level of the 8th and 9th thoracic on one side, between the 10th and 11th on the other. Cat 11 was slightly different. The original depression of blood pressure after section of the chain was 80 mm. Hg.; the anemic increment was somewhat reduced, amounting only to 70 mm. so that

the anemic rise fell short of reaching the original level. The cat recovered, however, and subsequently made up the 10 mm. difference in an anemic rise obtained after the stellate ganglia had been excised. The greater splanchnics may have been involved in this case.

Group II. This comprised the remaining 7 cats of the series. In all these animals a complete bilateral section of the splanchnic nerves was done in the thorax between their branching from the sympathetic chain and before their entry into the diaphragm. On cutting the splanchnic nerves the initial fall of pressure was great, averaging 80 mm. In four cats the effect of occlusion was well marked, the curves differing from the normal only in a slight reduction of the anemic increment of blood pressure, this being 70 mm. in three cases. In these cases also pressure did not reach the level held prior to section.

In the three remaining cats of the series a still greater depression of the anemic response was obtained. Cat 20 gave a most complete picture. The anemic rise reduplicated all the characteristics of the normal response on a smaller scale. A vagus effect appeared prominently. The maximum anemic increment of pressure in these experiments was 40 mm. When pressure fell spontaneously after occlusion it reached the identical level maintained after section of the splanchnics prior to occlusion. Low section of the spinal cord at this time induced a further fall of only 10 mm. Hg. In cat 22 the acclerators were also removed, and an even greater depression of the anemic response was obtained, the entire change of level on occlusion amounting to only 5 mm.

Cat 21 was slightly anomalous but yet highly instructive. The animal showed a great resistance to anemia, and it took some 15 minutes before the respiratory and vasomotor responses fully faded out. At first the record clearly approximated that of cat 20, an initial rise of 30 mm. being shown. With the persistence of the bulbar functions, however, there was reproduced on a different scale, the wide oscillations procurable in all animals difficult to asphyxiate. At first the vasomotor oscillations were slight and rather irregular, but they gradually developed into large and rapid waves in which the greatest excursion of blood pressure was developed, amounting to a fluctuation of 60 mm. at the height of the response. The level of blood pressure from which these oscillations developed was not raised, the whole response being simply recorded within this maximum variation of 60 mm. This offers a striking contrast to the analogous records of incomplete occlusion periods of similar length obtained in intact ani-

mals. In such animals the level of pressure shows similar oscillations, but these vary within a much greater range, usually approaching 200 mm. difference in level. No recovery of bulbar functions was elicited from any of these animals. That this was not the necessary consequence of a lesion at this level, but merely an indication of the precarious conditions of animals exposed to this double lesion, is shown in the following experiments.

Section of the sympathetic chain; abdominal section of the splanchnics. Although the blood pressure response is seriously reduced by section of the splanchnic nerves above the diaphragm, a slight degree of response still seems elicitable. It seems possible, however, completely to eliminate all rise of blood pressure as the result of bulbar anemia, while maintaining all other evidence of medullary activity, by section of the greater splanchnic nerves in the abdomen.

Dissection for the splanchnics in the abdomen was made by the method indicated in Sherrington's *Mammalian Physiology* (66). The incisions were made from the back, through the latissimus dorsi muscles, and the nerves were cut just before their entry into the coeliac ganglion. The identity of the nerves was first tested by electrical stimulation with shielded electrodes.

A striking example of the result of this section was obtained in cat 23. In this animal (fig. 2) the greatest excursion of blood pressure amounted to 10 mm., yet all other effects of occlusion were noted. An asphyxial effect on the vagi appeared in the pressure curve followed by a very slight improvement in the level. From this point on, however, pressure fell very gradually, until, at the end of 3 minutes, it remained constant. In this very gradual fall, pressure reached a level some 20 mm. below that of the original pressure before occlusion. After digital compression of the abdominal aorta, spontaneous respiration returned in this animal. When respiration had become completely reëstablished and a corneal reflex again obtained, the trachea was clamped. No asphyxial rise of pressure to speak of was obtained, the entire subsequent variation of pressure being well within 20 mm. Hg. Respiratory waves and some vagus effect were recorded; failure of the heart soon followed.

Section of the thoracic spinal cord. Section of the spinal cord was undertaken in 16 cats. The laminectomy was carried out immediately following tracheotomy, the wound temporarily closed by hemostats and the head arteries then prepared for ligation. Finally the cord was sectioned, and blood pressure allowed to reach a constant level

before inflicting any further lesions.   Several successive sections of the cord were frequently carried out in the same animal before occlusion was produced.

Section of the thoracic cord was carried out at various levels.   The effect of section varied considerably with the level of the lesion, and to some extent also with the individual animal.   Certain results, however, are patent.   Lesion in the lowest levels of the thorax elicited only a slight permanent fall of pressure, and did not seriously affect the anemic response.   Lesions in the midthoracic, at the level of the 8th thoracic and 9th thoracic vertebrae were more apt to elicit a profound fall of pressure, and seriously to reduce the anemic increment.   Lesions in the upper thorax also elicited a great fall on section and often completely
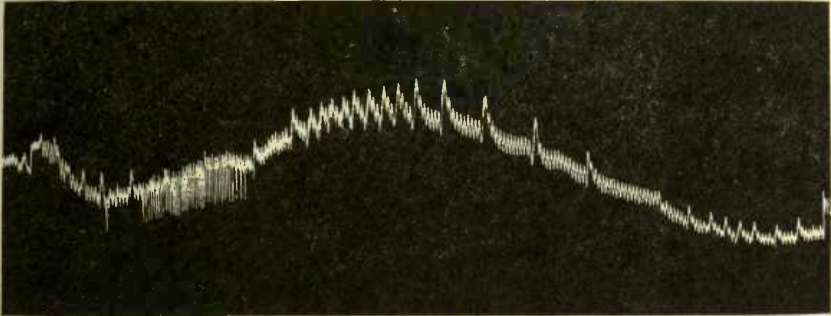

Fig. 3. Cat 30: cerebral anemia.   Spinal cord sectioned at the level of the 5th thoractic verterbra.   This reaction shows the features of the typical blood vascular response to anemia in every respect, but the level to which the maximal rise of pressure (second rise) attains.   The anemic increment here is only 50 mm. Hg.   Cardiac effects of slowing and acceleration recorded as usual.

abolished the rise of pressure.   There were, however, certain individuals in which even a high thoracic lesion did not evoke a maximum fall of pressure, and in which a relatively vigorous response was obtained even after a high dorsal section.   Accordingly the experimental material can be roughly classified into three groups:

Group I.   Lesions in the lower thoracic region.   Very vigorous responses to cerebral anemia can still be obtained from animals with a lesion at the level of the 10th to 12th thoracic vertebrae.   Cat 25 with section at T 10–11 showed an anemic increment of 125 mm. Hg.   In cat 24 an anemic response lasting over 5 minutes was obtained, in which the variation of pressure extended over 75 mm. Hg.   The contour of

TABLE 1

Section of the sympathetic chain and thoracic section of the splanchnic nerves

CAT NUMBER	DATE OF EXPERIMENT	NATURE OF LESION	DECREMENT ON SECTION	ANEMIC INCREMENT	DESCRIPTION OF CURVE
			mm.	*mm.*	
11	Nov. 20, 1918	Chain sectioned left 9-10 T, right 8-9 T	60	70	Smooth curve, gradual ascent and descent
12	Nov. 19, 1918	Chain in lower thorax right lesion incomplete	No record	100	Normal double peaked curve
13	Nov. 29, 1918 Cat I	Chain in lower thorax left lesion incomplete	70	140	Smooth curve, gradual ascent and descent
14	Nov. 26, 1918	Chain cut above diaphragm	No record	60	Smooth curve, gradual ascent and descent
15	Jan. 28, 1919	Chain sectioned right 8-9 T, left 10-11 T	40	150	Typical curve, great rise long maintained, occlusion time—10 minutes
16	Jan. 14, 1919	Low section of chain and splanchnics	60	120	Typical double curve, pronounced vagus effect, rise long maintained, occlusion time—10 minutes
17	Feb. 1, 1919	Section of splanchnic nerves above diaphragm	80	70	Double curve, marked vagus effect, pressure does not quite reach original level

18	Jan. 7, 1919	Section of splanchnic nerves above diaphragm	No record	70	Double curve, marked vagus effect
19	Jan. 16, 1919	Section of splanchnic nerves above diaphragm	80	70	Double curve, marked vagus effect
20	Feb. 8, 1919	Section of chain and splanchnic nerves just above diaphragm	80	40	Marked vagus effect, further section of cord (low) shows loss of only 10 more mm.
21	Jan. 21, 1919	Section of chain and splanchnic nerves just above diaphragm	No record	60	Cat difficult to occlude, respiration fades out after 15 min. Great oscillations of pressure towards end of time
22	Nov. 29, 1919	Section of chain and splanchnics just above diaphragm	80	8	Corneal present just before occlusion, but no appreciable effect of vagus slowing, etc.

TABLE 2

Section of the spinal cord at various levels

CAT NUMBER	DATE OF EXPERIMENT	LEVEL OF SECTION	DECREMENT ON SECTION	TOTAL DECREMENT	ANEMIC INCREMENT	DESCRIPTION OF CURVE
			mm.	mm.	mm.	
34	Apr. 15, 1919	T 10–11	60	30*		No occlusion
		T 8– 9	30	60	60	Sharp ascent and descent, pressure just reaches height prior to last section
		T 10	78	44		No occlusion
38	Mar. 18, 1919	T 9– 7	20	60	50	Sharp rise marked vagus effect, with loss of 10 mm. pressure
		T 6– 2	10	70	5	Some slowing of the heart shown, no increment
31	Apr. 9, 1919	T 2	110	110	40	Double curve, sharp 2nd rise
		T 6	55	55		No occlusion
				40		
35	Apr. 16, 1919 Cat II	T 4	40	95	20	Depression of pressure only during occlusion; very slight effect
	Apr. 16, 1919	T 8	68	68		No occlusion
39	Apr. 16, 1919	T 6	30	98	10	No appreciable effect although slight vagus slowing

* 30 mm. again recovered.

No.	Date					Remarks
42	Oct. 22, 1920	T 8	100	100	20	Rather marked slowing
		Vagotomy	30 rise	70	50	Poor record, difficulties with manometer
44	Nov. 19, 1920	T 6	75	75	20	No marked vagus effect, respiratory oscillations show in curve
33	Apr. 21, 1920	T 8	30†	30	30	Marked double rise pronounced vagus effect
		T 6	20	50	10	Effect extremely reduced
24	Feb. 19, 1919	T 10-11	40	40	80	Great fall instead of rise (Cf. text)
		T 8-9	80	120	30	Marked vagus slowing, curve very flat
		Splanchnic nerves cut	No further fall	120	30	Rise obtained on clamped abdominal aorta
25	Feb. 20, 1919	T 11-12	80	80	150	Absolutely typical curve, very sharp rise
29	Mar. 11, 1919	T 11	50	50	70	Marked vagus effect, pressure drops 40 mm. lower after occlusion
30	Mar. 15, 1919	T 11-10	10	Level completely recovered rise above control level		No occlusion
		T 9-5	60	60	50	Very marked curve obtained, vagus effect, second rise accentuated

† Pressure only 80 mm. Hg. to begin with.

TABLE 2—*Concluded*

CAT NUMBER	DATE OF EXPERIMENT	LEVEL OF SECTION	DECREMENT ON SECTION	TOTAL DECREMENT	ANEMIC INCREMENT	DESCRIPTION OF CURVE
			mm.	*mm.*	*mm.*	
26	Feb. 22, 1919	T 12	No record		40	Vagus effect appears, curve highly reduced
		L 3	40			Marked vagus effect, pressure
28	Mar. 8, 1919	T 10	No further fall	40	30	Rises only 30 mm. but falls 30 more
		T 8	30	70		No asphyxial increment
		T 9– 6	40		40	Very marked vagus effect
		T 6– 5	20	60	50	Sharp ascent and descent, marked vagus effect
40	Apr. 22, 1919	T 4	No further fall		42	Sharp ascent and descent, marked vagus effect, pressure drops 30 mm. lower
		T 2	24	84	28	Clear double curve, vagus depression
		Sympathetic chain cut low in thorax	20	104		No asphyxial increment

this curve will be discussed below in connection with similar anomalous curves obtained from control records in other animals. In these cats a fall of pressure replaces the usual rise; the variation of level being of the same order of magnitude. In cat 24, despite the great drop of pressure, the original level was regained toward the end of the anemic response at the time usually occupied by the second rise of pressure.

Measurements of loss of pressure after section in the lowest levels of the thorax show a maximal total loss of 50 mm. Hg. Frequently only a few millimeters are lost. In cat 30 the 10 mm. lost after section at the 10th thoracic were completely recovered within 10 minutes, pressure rising even above the level recorded prior to transection.

Group II. Abolition of the anemic response. Lesions of the cord in the region of the 8th thoracic usually entail a rather severe effect; the loss of pressure following this section may amount to 80 mm. Hg. If the fall is as great as this, the anemic response is apt to be seriously diminished. Cat 25, which gave a very vigorous response after section at T 10, showed a further loss of 80 mm. when the cord was sectioned at T 8, the level falling 100 mm. below that held when the animal was intact. The anemic increment after section at T.8 was only 30 mm. Hg. The reduction of the anemic increment to a variation of pressure of only 30 to 40 mm. was seen in five other experiments, (cats 24, 30, 38, 40, and 42) in which section in the region of the 8th to 10th thoracic gave a considerable depression of the level of blood pressure and in which anemia of the bulb failed to evoke an increment of pressure greater than 40 mm. That the vagus is partially responsible for this effect is indicated by cat 42, in which an initial response after section in the 8th thoracic gave an increment of only 20 mm. This increment, however, rose slightly above 40 mm. in a subsequent occlusion after the vagi had been sectioned.

Section of the cord above the 8th thoracic in three animals, cats 35, 39 and 44, gave a very marked fall of pressure in all these cases and no anemic response greater than 30 mm. was obtainable in any one of them. In cat 44, only one section was made at T 6, and no anemic increment at all was obtainable after occlusion. In the other two animals several successive sections were undertaken before occlusion was tested. In cat 39, the first section was carried out at T 7; this was followed by a fall of 55 mm.; 40 mm. more were lost in successive sections ascending to the level of T 4. In cat 35, 80 mm. were lost by section at T 8, and only 20 mm. more by successive sections to T 6. The level of pressure above base line from which only a minimal sub-

sequent fall occurs under further manipulations, lies between 35 to 50 mm., the residual pressure maintained by the spinal cord alone.

Group III. Retention of an anemic effect. The midthoracic region is apparently not critical for vasomotor responses in all animals. In cat 34 section at the 8th thoracic gave a loss of only 30 mm. Hg. and an anemic increment of 68 mm. Hg. was obtained. The relatively slight loss of pressure following section at T 7 in cat 39 above mentioned also shows that in some animals the higher levels of the cord are of great importance.

However, the most significant indication of participation of the upper levels of the cord in conveying fibers significant for the vasomotor response was obtained in four additional animals. A strikingly complete anemic rise was obtained from cat 30, in which the cord had been sectioned as high as T 5 (fig. 3). The anemic increment here was 54 mm. In cat 38 a well-maintained response of 44 mm. was obtained on occlusion after section at T 6. In cat 31 a rise of the same magnitude (40 mm.) was obtained after section at T 2. The level maintained after section at T 2 prior to occlusion was 65 mm. Hg. above base line and did not reach the level of 50 mm. until after occlusion. An interesting record of the potency of the higher levels in certain individuals for both the maintenance of blood pressure and its variation is best given in the following protocol—cat 40.

Condensed protocol, cat 40 (pressure here given in level above base line) April 22, 1918

Tracheotomy, blood pressure, cannula, laminectomy, head arteries prepared for ligation.

2:30   Control blood pressure—130 mm. Hg.
2:35   Section of cord at T 8
2:40   Level of blood pressure—118 mm. Hg.
2:45   Section of cord at T 6
2:47   Level of blood pressure—90 mm. Hg., total depression of pressure—40 mm.
2:48   Corneal reflex
        Occlusion. Sharp rise of pressure to 114 mm. drop to 90 mm. Hg., great vagus effect, rise again to 130 mm.: *anemic increment—40 mm.*
2:51   Pressure released before spontaneous fall began, gasps immediately return, fall to 80 mm.
2:57   Respiration reëstablished, section of cord at T 5
2:58   Level of blood pressure—70 mm. Hg., total depression of pressure—60 mm.
2:59   Corneal reflex, *occlusion:*—incomplete
3:01   Further manipulation of clamps, immediate rise of pressure to 114 mm., *anemic increment—44 mm.*
3:04   Released before spontaneous fall, pressure drops to 50 mm. Hg., but immediately begins again to recover

3:05   Gasps return, pressure continues rising
3:10   Pressure reaches 90 mm. Hg. again, regular waves in blood pressure curve, respiration reëstablished
3:17   Section of cord at T 4, pressure drops to 70 mm.
       Corneal reflex, *Occlusion:* sharp rise of pressure to 100 mm. fall to 60 mm. during vagus slowing, subsequent rise to 112 mm.; *anemic increment*—42 mm.
3:23   Pressure released before spontaneous fall, drops sharply to 44 mm. but immediately begins to rise again
3:25   Gasps return
3:33   Pressure at 84 mm. again, respiration reëstablished
3:39   Section of cord at T 2, pressure falls to 46 mm. Hg. total depression of pressure, 84 mm.
3:40   Corneal reflex, *Occlusion:* initial rise to 64 mm. Hg. fall to 30 mm. during vagus slowing, second rise to 74 mm. Hg. *anemic increment*—28 mm.
3:42   30 Head arteries released before spontaneous fall, pressure immediately falls to 20 mm. but again regains level
3:45   Pressure has reached 54 mm., gasps return, further rise to 60 mm. respiration reëstablished
       Thorax opened, artificial respiration administered
4:05   Sympathetic chain cut in midthoracic, pressure fall to 40 mm. total depression of pressure—90 mm.
4:07   Corneal reflex: occlusion, rise to 52 mm. slight fall, rise to 48 mm. *anemic increment*—12 mm.
4:11   Release of head arteries, pressure drops to 30 mm.
4:14   Gasps return, pressure rises to 40 mm. respiration reëstablished
4:55   Splanchnics cut in psoas muscles, no effect on blood pressure, no recovery of level or return of respiration
5:10   Artificial respiration intermitted, pressure drops to base line.

Effect of the splanchnic constrictor fibers on the anemic rise.   The burden of the anemic response seems to lie in the vasomotor apparatus, and, if the evidence of these experiments is adequate, almost exclusively on the splanchnic constrictor fibers.   Peripheral section of the splanchnic nerves, with its great depression of blood pressure, and the subsequent inability to obtain any anemic increment whatever, speaks strongly, almost unequivocally, for such an interpretation.   Additional evidence for the importance of the splanchnic pathway for the vasomotor changes during anemia is the relation of the level of blood pressure after section within the splanchnic outflow to the anemic increment elicitable on occlusion.   The data show quite clearly that *the greater the initial depression, the less powerful the response.*

This very definite grading of the blood pressure level to the magnitude of the anemic rise gives a further insight into the anatomical relations of the splanchnic outflow.   In the cats examined the greatest
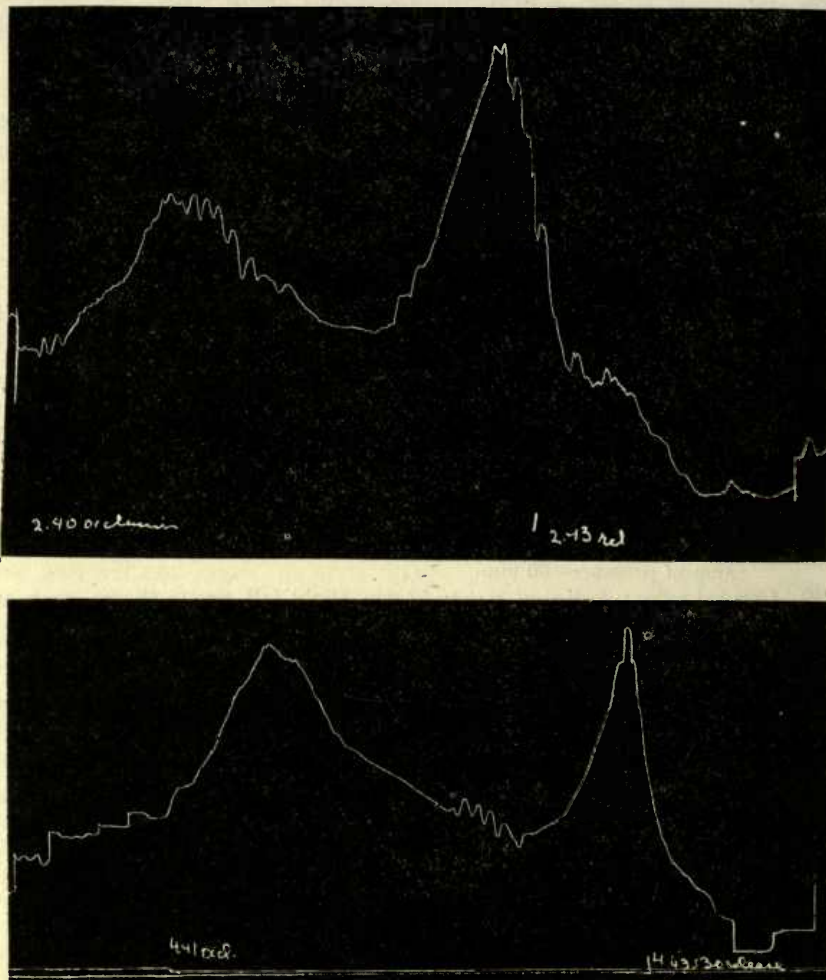
Fig. 4. Cat. 45. Repeated cerebral anemia; double vagotomy; 10th successive occlusion; dissociation of reaction curve into two distinctly separated peaks is shown fully established. Second peak in this occlusion is still considerably greater than the first. Pressure falls very low at the end of the response (30 mm. Hg. above base line). Each curve occupies approximately half the period of the reaction.

Seventeenth successive occlusion: Dissociated curves show little difference in time relations compared with those obtained 2 hours earlier. Difference in contour found in the greater emphasis of the first as compared with the second peak of pressure. The rise in level prior to occlusion represents the recovery of blood pressure after the preceding occlusion following the return of respiratory gasps.

average ouflow from the cord to the sympathetic chain is apparently in the region of the 6th to 8th thoracic.   Yet the outflow is not restricted to the lower thoracic region, for fibers in the higher thoracic region even as high as the 1st or 2nd, have in these experiments been found of some importance both for the maintenance of the level and the changes of blood pressure.   Such a curve as that obtained from cat 30 (fig. 3) shows convincingly that in some animals a good proportion of fibers leave the spinal cord to enter the sympathetic chain above the level of the 5th thoracic vertebra.

While therefore the anatomical findings of Langley and Ranson for the average level of outflow have in the main been verified, the involvement of higher levels already indicated by the various physiological researches quoted by Langley has received a rather striking confirmation.

In such an instance, the physiological evidence may well have precedence over the anatomical, for whereas a small bundle of fibers is most difficult to stain and trace microscopically, a weak physiological effect, when definitely isolated, is quite unmistakable.   The involvement of these fibers from the higher levels within the splanchnic system, becomes of particular importance when the entire burden of the splanchnic function is restricted to these levels.   Since the very high outflow presumably goes by way of the stellate ganglion, it is necessary to differentiate between the effect of the splanchnic fibers proper and the accelerators.   However, in these cats in which an abdominal or high spinal section completely abolished the rise, the cardiac nerves seemed completely impotent against the lowered peripheral resistance.

Accordingly, the vasomotor impulses that travel through the splanchnic nerves to the coeliac ganglion may leave the cord as high as the first or second thoracic.   They may, however, stay in the cord throughout the thoracic region and leave it even below the diaphragm.   Ranson's results on the very low level at which the splanchnic nerve leaves the chain in cats, is in close agreement with these findings.

There thus appears to be a double pathway for the splanchnic outflow in the thorax, one within the cord, the other outside of it.   The outflow of the splanchnic fibers from the cord to the sympathetic chain seems distributed over the entire thoracic region, the relative distribution varying from one individual to another.

In this light the impossibility of abolishing the anemic rise by a section which implicates only part of the splanchnic system is explicable. The wide distribution of the splanchnic fibers would make it difficult

to compromise the response by a definitive lesion. Such a lesion could, it seems, be secured only when the section falls sufficiently far out in the periphery or sufficiently high up in the cord, *definitely to interrupt the conduction pathways from medulla to coeliac ganglion*. Unless this interruption is accomplished, the fibers that are left in continuity with the medulla and the periphery are able to initiate an anemic rise which, even if considerably diminished in intensity, repeats all other characteristics of the usual vasomotor response.

To the splanchnic innervation, therefore, the most significant factors in the blood vascular reaction to cerebral anemia can be attributed: the initiation of the rise and the level which this reaches. Since these factors can be controlled by differential lesions within the splanchnic system, the influence of the non-splanchnic vasomotors may be neglected for the purposes of the present survey.

On the influence of the splanchnic system on the maintenance of the normal level of blood pressure: The splanchnic fibers seem involved when the level of pressure is above 50 to 60 mm. for unless a complete interruption of the conduction path from medulla to coeliac ganglion has been demonstrated, pressure returns to a higher level the height depending apparently on the number of fibers in the splanchnic system remaining functional. The level of 50 to 60 mm. is that shown by Mayer, Couty and later workers to be that maintained by the spinal cord alone. Yates also finds this level to be approximately that reached by blood pressure after recovery (2 to 32 days) from high transection of the spinal cord at 8th cervical to 5th thoracic. Her average level of pressure lay somewhat lower than this, between 40 to 50 mm. From Pike's and Langley's studies this residual spinal level appears rather as a skeletal or somatic, than as a vascular or sympathetic phenomenon.

The difference between the residual spinal level and the normal one— a difference of 80 to 100 mm.—would therefore appear as accounted for largely by the action of the sympathetic neurones within the splanchnic system. When the range of variation during anemia is examined, this is seen to be three to four times as great in the animal with splanchnics intact as in the animal which is largely dependent on its skeletal musculature. The variation of pressure in cats with low thoracic section of the sympathetic chain is greatly restricted where the animal was highly resistant to anemia and a period as long as 15 minutes elapsed before the processes activated by the higher levels ceased. Furthermore, as long as the splanchnic system is functional, pressure does not drop below the level of 50 to 60 mm. Hg., however great the variation

of pressure and no matter how exigent the inimical conditions. This is well illustrated by the variation of pressure noted in figure 3. The protocol of cat 40 where pressure in maintained in excess of 60 mm. until after a section of the spinal cord at the level of the 4th thoracic, also emphasizes the relation of this level to splanchnic activity.

On some anomalous curves. In a relatively large number of cats (8 in 60) a depression of blood pressure was obtained on occlusion instead of the usual anemic increment. This depression of the level of blood pressure was great, approaching the order of magnitude of the usual positive effect. In six of these cats, pressure fell 100 mm. and more below the original level of blood pressure. Most of these curves represented control occlusions, one example of which has been figured (fig. 1, occlusion 1) in which no previous lesion had been inflicted the vagi being intact in all cases. In one case, cat 24, also mentioned, this depression appeared after low section of the spinal cord. In these cats on occlusion there followed no initial increment, or only a very slight increase in the level (5 mm.). Pressure then continued constant for some 20 seconds. Following this a great and very rapid fall of blood pressure set in from which recovery occurred at about the time ordinarily occupied by the second rise of blood pressure. In this recovery from the low level of blood pressure, however, pressure approached but never completely attained the original level observed before occlusion.

The magnitude of the effect might argue for the involvement of the splanchnic system. As such, it might be aroused by an afferent excitation of the depressor fibers in the vagus. The relation of the depressor to the splanchnic system and also to the discharge of adrenalin (which would of course be involved in all splanchnic excitation) has been discussed by Ludwig and Cyon (48) and Oliver and Schäfer. Bayliss (67) has dealt with the antagonism of asphyxia and depressor stimulation.

On the other hand, the depression of blood pressure, instead of being due to the cardiac innervation set into action through an afferent channel, might be affected directly through a change in the minute volume of the heart, especially under changed conditions within the vagus system. Wickwire (60) has particularly noticed that different degrees of the depth of anesthesia gravely influence the changes in the level of blood pressure due to the vagus system.

II. RELATION OF THE ADRENAL GLANDS TO THE RISE OF PRESSURE DURING CEREBRAL ANEMIA. The extensive involvement of the splanch-

nic system in the anemic response makes the activity, or some product of the activity, of the adrenal glands of considerable significance for the problem of its control. Following the discovery by Oliver and Schäfer (68) of the pressor action of injected extract of adrenal tissue, workers have tended to emphasize the close physiological relation of the glands and their pressor activity to the splanchnic system. The literature is extensive (69), (70), (71), (72), (73), (74), (75), but it will not be reviewed at this time. Nor will the literature on the liberation of adrenalin (75 to 90) be considered here. The evidence for the participation of adrenalin in the response to asphyxia and other conditions of stress is also extensive (91 to 98), but its consideration will be left for a later paper. The relation of the contour of the typical curve obtained on electrical stimulation of the splanchnic nerves to the adrenals, and also to the cardiac mechanism, has been dealt with by several authors (104), (105), (106), (107). A further analysis of this contour is also postponed.

Effect of repeated occlusion on intact cats. Elliott's assumption (75) that adrenalin is consumed under conditions of stress makes it conceivable that the rapid repetition of so radical a procedure as arterial occlusion could influence the amount of circulating adrenalin. Since the relation of adrenalin to the myo-neural junction has been experimentally demonstrated, Professor Pike has suggested that, physiologically, it may be associated with the process of conduction from sympathetic nerve fiber to smooth muscle, and directly or indirectly with the processes of excitation in smooth muscle. The work of Keith Lucas would suggest such a possibility (108). Accordingly, such an increase of activity of sympathetic nerve and smooth muscle as accompanies cerebral anemia should lead to a more rapid consumption of adrenalin. This conclusion follows from Elliott's hypothesis of the consumption of adrenalin. The procedure of repeated occlusion has accordingly been attempted first in intact animals in order to reach a control condition of maximal exhaustion of circulating adrenalin, and then in animals in which the adrenal glands had been permanently ligated.

The great resistance of the animals to repeated occlusion has been frequently demonstrated in the experimental material already given. Numerous other evidences of the relative indefatigability of vasomotor responses are found in the literature. Notable here are the analogous experimental conditions in the work of Cushing (99), who found that the process of raising the blood pressure by increasing the intracranial tension, and thus also inducing a partial anemia, could be repeated

indefinitely. The difficulty of inducing fatigue of the central vasomotor cells under normal conditions has been discussed in various connections by W. T. Porter (100), (101).

The experiments already described in this series on repetition of occlusion have been complicated by the infliction of lesions in the splanchnic system so that the actual ability of the animals to withstand repeated occlusions, and the effect of this procedure on the anemic response, was not clear. Furthermore, not more than six or eight successive occlusions at most were obtained. Accordingly, in five cats the effects of repeated occlusion were tested. Occlusion was done and when the final spontaneous fall of pressure occurred, the clamps were promptly released and recovery awaited. The corneal reflex was used as before as an index of returned bulbar activity. With its elicitation clamps were again adjusted on the head arteries, and this process repeated several times.

If the occlusion period was not too long maintained in any one closure, it was possible to repeat the procedure practically indefinitely. In the three most striking experiments, cats 45, 46 and 48, the experiments had to be halted arbitrarily because of extraneous reasons, the time consumed being too long. Cat 45 yielded 18 successive occlusions (fig. 4); cat 46, 13 successive occlusions; cat 49, 11 successive occlusions. These experiments lasted over 3 hours in addition to the time necessary for the preliminary operative manipulations which always consumed over half an hour. Cat 46 was intact, cat 45 had suffered double vagotomy, and in cat 48, (fig. 5A) both stellate ganglia had been removed. No marked difference in the behavior of these cats under the test could be noted. In fact, the cats showed a remarkable constancy in behavior. The characteristic occlusion time—2 to 4 minutes—in each individual was retained with considerable uniformity throughout each series. Furthermore, the time needed for recovery of the bulbar functions after release of the arteries was almost uniform for each cat examined. The recovery time which, on the whole, may be said to vary directly with the occlusion time, did not in all cases follow this relation. Cat 46, which gave a constant occlusion time of 2 minutes usually showed a recovery of a corneal reflex within 7 minutes subsequently. Cat 45, however, (vagotomized) invariably showed a 20-minute interval between occlusions. In this interval a well-marked recovery of blood pressure was noticeable and, with the return of respiration, blood pressure rose at least from 60 to 80 mm. above the level after occlusion, before a corneal reflex was

obtained. The average level between occlusions was relatively high, pressure seldom falling below 60 mm. Hg.

The first four or five occlusions obtained differed in no very striking detail from control occlusions. The main change from the type of these earlier occlusions appeared gradually. This was a slight delay in the appearance of the first rise in pressure and a gradual increase in the magnitude of this first effect. The fall of pressure from this first level also became more pronounced; pressure dropped to increasingly lower levels at this time on successive occlusions. By the time of the seventh or ninth occlusion the emphasis on this first part of the curve became so well marked that the entire response appeared more as two separate curves rather than one, the two summits in the tracing being very symmetrically distributed both in time and space. The fall of pressure following the initial rise was so great in some of the animals as to approach the base line very closely, dropping to a level of only 10 to 20 mm. Hg.

The characteristic new contour of the rise, once established, is retained in all subsequent tracings in the same animal with great uniformity (fig. 5B). The latter part of the series of occlusion records accordingly shows this new type of anemic rise. The marked drop in the double curve is quite different from the dip due to vagus action seen in the ordinary control pressure curve of anemia. It comes much later (fig. 4); it is also decidedly more abrupt and greater. In fact, it seems much more like an actual collapse of blood pressure. It appears uncomplicated by slowing of the heart. The very definite time relations established in these dissociated curves are striking. Indeed, the supplementary rise, once it has become separated from the initial rise by the marked temporary collapse of blood pressure, is recorded at exactly the same point in all later occlusions obtained in a given animal. This time closely approximates half of the occlusion time of the animal in which it appears, namely, at 1 minute in cats of 2-minute occlusions, and so forth. A decrease of the anemic increment was obtained in the course of the repetitions. Rises of 80 to 100 mm. gradually replaced the original increment of 120 to 140 mm.

One further observation on these cats is worth noting. Post-mortem examination showed that the blood of these animals failed to clot readily. It frequently flowed freely from the carotid artery when the cannula was removed. In a prolonged dissection in one animal, the blood flowed freely from every rupture of a large vessel, even as late as one hour after death.

Effect of repeated occlusions in cats deprived of adrenal glands. The procedure of repeated occlusion in the same animal was undertaken in a final series (six cats) in which both adrenal glands were ligated. In each of these animals one control occlusion was made, then by means of dissection through the latissimus dorsi (double incision from the back) the adrenals were isolated and secured by ligatures. No significant fall of pressure was obtained immediately on ligation of the adrenals, thus confirming the observation of Hoskins and McClure (102) and Young and Lehman (103). Following this, the procedure was
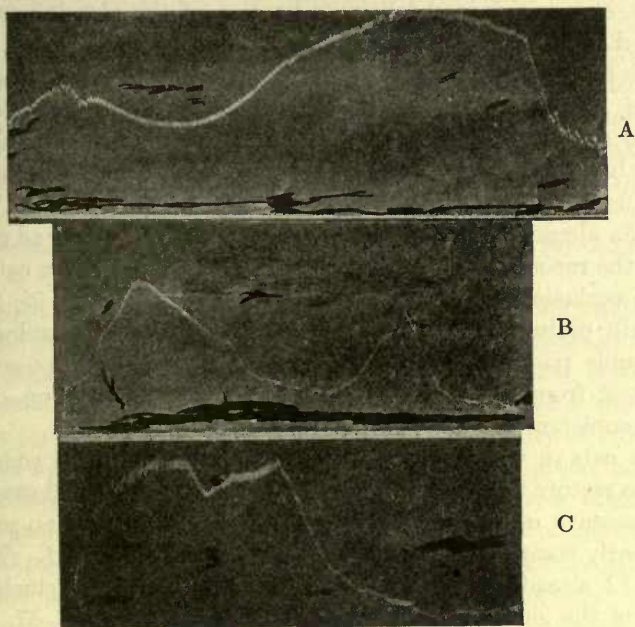
Fig. 5 A: Control curve of 3 minute occlusion. Ligation of the head arteries in the intact and fresh animal. Initial rise is followed by a depression level coming together with a slowing of the heart. High level of pressure maintained throughout the response. ·

B. Cat 48: Repeated cerebral anemia; stellate ganglia excised; 14th successive occlusion. Dissociation of two peaks very well marked. Level of pressure between occlusions extremely low (20 mm. Hg. above base line).

C. Cat 53: Repeated cerebral anemia; adrenal glands ligated; 7th successive occlusion, obtained just before collapse. Drum revolving at same rate as above. Time of this reaction, 2 minutes. Control reaction in this animal, when fresh and intact had occupied 3½ minutes. Abruptness of initial rise and final fall characteristic of records after ligation of the adrenals.

identical to that in intact animals: ether was reduced, a corneal reflex elicited, and successive occlusion of the arteries done as soon as recovery from the last preceding occlusion had occurred. The cats differed somewhat in the rapidity with which the effect of the ligation of the adrenals appeared in the anemic blood pressure curve. In two cats, 52 and 56, the first occlusion following ligation showed little difference, and certainly no curtailment when compared with the control curve. In cat 52 the level of maximal pressure was maintained 2 full minutes longer than in the control. However, in the other four cats, the curves obtained following ligation of the glands immediately presented a marked contrast as compared with the normal occlusion and with the records obtained under repeated occlusion in the control series of intact animals. The characteristic feature of this change appeared at once and was retained until failure of the animal. This was an absolute halving of the occlusion time, and the retention, either of a reduced double curve, or of a single vigorous rise. In the two cats, 52 and 56 already referred to, this same reduction appeared somewhat later in the record. The occlusion time was not halved in cat 52 until the fifth occlusion following ligation of the glands; in cat 56, not until the fourth occlusion. In both these cats there also remained a distinct double rise in the pressure curve, which was not observable in the curves from the other animals. Autopsy showed no difference in the completeness of the ligation in these two animals.

In the cats in which the adrenals had been ligated the complete inability to restore the bulbar functions had to be faced in all cases before nine successive occlusions had been made. There were no exceptions to this early complete collapse in any of the cats observed. Two cats, 54 and 52 already mentioned, gave eight successive occlusions after ligation of the glands. Cat 53 gave seven; (fig. 5 C) cat 57, five; cat 56, otherwise so resistant to a change in its long occlusion periods and retention of normal contour, succumbed after only four occlusions. Only one occlusion was obtained from cat 55. Figured in hours of survival under this procedure, this meant a maximal survival of $2\frac{1}{2}$ hours, a minimal survival of 15 minutes. However, only two cats of the series failed within an hour of the ligation of the glands under successive occlusions. The average survival time was $1\frac{1}{2}$ hours.

Very few indications of the approaching collapse appeared in the record, the only index being perhaps the very low level of blood pressure between any two successive occlusions. This low level was established in all cases immediately after the spontaneous fall of pressure

closing the first occlusion that followed ligation of the adrenals. At this time pressure fell to 30 or 40 mm. Hg.—a level 20 to 30 mm. lower than in the intact animals at a corresponding time. In spite of the subsequent return of respiration and other bulbar activities, the pressure remained uniformly low. A return of the corneal reflex was obtained even at this reduced level. The level of blood pressure maintained between successive occlusions varied somewhat. On comparing the amount of recovery of blood pressure in a given animal after occlusion, and the number of occlusions obtainable, it was found that, at least in the extreme cases, a direct variation could be noted. The two very vigorous animals which gave eight reactions after ligation of the glands, cats 52 and 54, showed a recovery of pressure of 40 to 50 mm. during the period following release of the head arteries; whereas cats 55 (one occlusion) and 57 (five occlusions) never regained more than 10 mm. at the time of the return of respiration. Cats 53 (seven occlusions) and 56 (four occlusions) occupied a rather intermediate position, never showing an increase of more than 20 mm. pressure during recovery of bulbar function.

No change in the time needed for the return of medullary activity, as determined by the return of respiration and ocular reflexes, was noted in these animals. As in the control series of repeated occlusion in intact animals, this was not different after ligation of the adrenals from that obtained in the fresh animal. Periods of recovery of from 10 to 20 minutes were recorded, being fairly constant for the given individual.

No significant decrease in the anemic increment was observed, in cats 53 (seven occlusions) and 57 (five occlusions) where increments of 120 to 140 mm. were obtained just prior to failure. These were oddly enough the smooth curves recorded under early collapse. A much more pronounced decrease in the anemic increment was shown in the other animals in which more occlusions were obtained; in cat 52, (eight occlusions) the last occlusion recorded showed an increment of only 65 mm.

The contour of the curves obtained is of considerable interest. Cats 53 and 56 immediately showed a single rise occupying about half the original occlusion time (fig. 6), and this was a smooth unbroken curve. Though the reduction in time was just as manifest in all the other cats, the obliteration of the double nature of the curve was not so clearly marked. In these cats the characteristic contour of the anemic rise as seen in the fresh animal, merged gradually into the smooth curtailed curve following adrenal ligation. The changes most evident were the

greater abruptness of the initial rise while the depression of level due
to vagus activity was apt to be increasingly delayed and tended to
appear on the crest of the wave, somewhat similar to the effect described
after section of the accelerators. The precipitous fall which occurs in
these animals with ligated adrenals just about half as late as in intact
cats then appears as soon as the point of maximal pressure is gained,
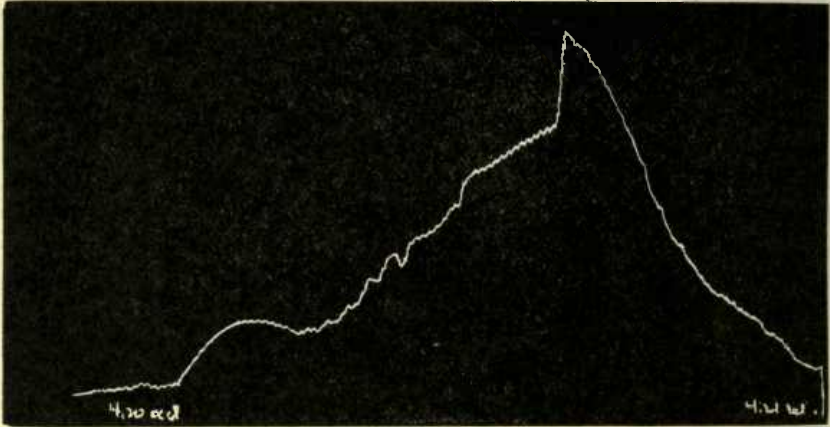namely, immediately after cessation of the vagus depression.

Fig. 6. Cerebral anemia following ligation of the adrenals. Cat. 53. Arterial
occlusion immediately following tying off of the glands. Occlusion time, $1\frac{1}{2}$
minutes. Time of control occlusion obtained from this animal, 3 minutes.

Effect of the adrenal glands on the anemic rise. The marked shorten-
ing of the anemic response eventually obtained in all the animals in
which the adrenal glands had been ligated seems to isolate a further
factor concerned in the production of the anemic rise. Apparently the
great influence which the splanchnic system is able to exert on the level
of blood pressure under the critical conditions of anemia, is due in part
to the adjuvant activity of the adrenal glands. These experiments,
therefore, bear on the discussion of the emergency relation of the glands,
since apparently some involvement of the glands or some product of
their activity must be conceded under the extreme condition of cere-
bral anemia. Furthermore, some clue as to the nature of the activity
of the adrenals is given by inspection of the curves obtained.

Loss of pressure. There has been noted a close parallelism between
the later curves obtained from all animals suffering repeated occlusion,
whether intact or deprived of adrenals. A failure of blood pressure

(temporary or permanent) is recorded under both conditions within half the time normally occupied by the blood vascular response. When the animal is intact, this drop of pressure occurs in the seventh or eighth occlusion and in all subsequent curves of a given series. When the adrenals are ligated, it may be established immediately, although this is not necessarily the case. Under these conditions the halving of the response is recorded before four successive occlusions have been inflicted and is found in all occlusions which follow in these animals. This precocious loss of level in blood pressure can therefore be obtained either when the animal has been exposed to rapidly repeated cerebral anemia, or when the activity of the adrenal glands is completely abolished. Accordingly, the main factor in the production of this early failure of pressure seems concerned in all cases with the availability in the blood stream of some product of adrenal activity.

Restoration of level of blood pressure. An examination of the supplementary rise of blood pressure in the repeatedly occluded but intact cats in comparison with the permanent failure of pressure at half the normal occlusion time when the adrenals are ligated, leads to a consideration of the theories of emergency function of the adrenals. This secondary rise is most probably related to the presence of functional adrenals.

The secondary rise was interpreted in a preliminary report of these experiments as an indication of an increased liberation of adrenalin from the glands, and the constant interval prior to its appearance, as a latent period, relatively long, of adrenal secretion. The argument was advanced that these experiments offered evidence confirming Cannon's position on the increased secretion of adrenalin under emergency conditions. However, in view of the presumable consumption of the products of adrenal activity during cerebral anemia already discussed, the conception of the emergency liberation of adrenalin must be somewhat modified. The further discussion of any of the current hypotheses of the liberation of adrenalin must be deferred until further experimental evidence has been accumulated. Two definite statements, however, appear justified by the facts. In the first place, since curves of perfectly normal contour were obtainable in two animals after ligation of the adrenals, an increased liberation or secretion of adrenalin, one or both, is not necessary for the carrying out of the typical blood vascular response to anemia in the fresh animal.

That these results were due to experimental error can hardly be possible since there was seen in these animals a gradual and relatively slow

transition of the normal curve into the abbreviated response typical
for animals with ligated adrenals. Such a gradual transition is also
found in the intact repeatedly occluded animals. In the second place,
from the premature failure of the vascular response, after the ligation
of the adrenals, particularly in contrast to the secondary rise that is
seen in the intact repeatedly occluded animals, the conclusion may be
drawn that some product of adrenal activity must be available to make
possible the continued action of sympathetic nerve on smooth muscle
for any length of time.

Survival after adrenal ligation. In all the work reported on excision
of the adrenal glands, sudden death has never been noted. However,
when all adrenal tissue is excised, collapse and death follow, the inter-
val of life varying in different animals. The earlier work on cats has
been reviewed by Hultgren and Anderson (109), who particularly
described the prelethal stage. Elliott (73) recorded the failure of blood
pressure in addition to the loss of the pressor reaction in the moribund
cat, and in a later paper he has summarized a series of tests given in
these conditions, demonstrating a complete collapse of vascular tone.
Gautrelet and Thomas, (110) later Hoskins, (111) have confirmed the
depression of the sympathetic system on final collapse. Elliott records
death with simultaneous extirpation under ether after 14 to 18 hours.
Bazett (112) has recently succeeded in shortening this time consider-
ably by decerebration, urethane anesthesia and sensory stimulation.
In these animals the fall of blood pressure occurred within a few hours
after the operation. Elliott (98), moreover, finds that the animal sur-
vives even if the adrenal tissue is separated from the splanchnics. He
concludes therefore that, whereas the increase of adrenalin in the blood
stream under splanchnic stimulation is not necessary to life, the animal
depends for its existence on the continual slow secretion of adrenalin
from the medullary cells. Elliott argues that this continual slow
secretion is independent of nervous impulses. Stewart and Rogoff
(113), (114), however, are unable to demonstrate any appreciable
adrenalin output under these conditions.

It seems that the repetition of the extreme procedure of occlusion is
able to hasten the onset of complete failure most surprisingly. In the
extreme conditions of these experiments Bazett's (97) already curtailed
time of survival after ligation of the adrenals is thus further shortened
by 6 or 8 hours. The only demonstrable factor in the failure under
these conditions is the inability of the sympathetic nervous mechanism
to maintain the normal state of the musculature of the blood vessels

after complete exhaustion of the reserve of adrenalin in the blood. The necessity for the presence of adrenalin or of some other product of adrenal activity in the blood for the maintenance of vasomotor tone, as asserted by Elliott, seems again confirmed. The failure of blood pressure alone seems able to carry with it the failure of all the other functions.

From the evidence, the relative degree of constriction of the vessel walls seems, to a considerable extent, a function of the amount of some adrenal product in the circulation. The loss of this product seems to mean complete failure; blood pressure stays only a few millimeters above base line when the available supply is low, but an increased liberation, or possibly even a redistribution, may give any degree of tonic contraction of the vascular muscles, reaching to maximum constriction, the entire reaction perhaps depending on conditions at the myo-neural junction.

III. RELATION OF THE SPLANCHNIC SYMPATHETIC SYSTEM TO THE CENTRAL NERVOUS SYSTEM. The central relations of the sympathetic system have been tenaciously disputed, and cannot be entered into at length. On the one hand, there has been the view defending its relative independence from the cerebro-spinal axis, originally advanced by Bichat (115), and supported extensively by Volkmann (116). Goltz in his latest work with Ewald (117) subscribed to this view, in his assertion that the sympathetic peripheral ganglia could maintain normal vascular tone, and mediate reflexes quite independently of the central nervous system.

However, the theory that the nervous outflow is essentially dependent for its activity on cells of central, and particularly bulbar origin, has always enrolled some powerful supporters. Two of Goltz's contemporaries, Eckhard (118) and Mayer (119) have defended this conception. Recently Gaskell (120) and Sherrington (121) and still later Ranson, (122), also endorsed it.

Two points in the evidence on cerebral anemia will briefly cover the relation of the medullary cells to the peripheral response. First, the comparison of the splanchnic response with the other peripheral responses, and particularly the skeletal responses as controlled by the medullary or higher cells, under the different functional conditions of the nervous levels in these experiments; second, the behavior of the blood pressure responses under recovery from various spinal lesions.

Comparison of splanchnic response with other peripheral responses. The following table gives the various stages which can be distinctly separated when different functional levels control the animal's reac-

tion. The rough average of the level of blood pressure maintained is given for each period. The exact correspondence of the involvement of the splanchnic system and the degree of functional activity within the medullary centers is indeed striking, especially in view of the potency of the splanchnic system in maintaining blood pressure. It appears from this tabulation that the splanchnic system behaves exactly as do the respiratory, skeletal and ocular responses. When the skeletal responses dependent on the higher levels are in abeyance, the vasomotor responses of the splanchnic system are also absent. At this time, moreover, that is, during the depression between occlusions, the heart rate shows no appreciable change. The level of blood pressure maintained is that shown by Couty (16), Mayer (14), Pike (26) and Langley (27) to be that held as long as the spinal cord itself remains intact. Additional evidence that the depression of functional activity is due to a complete interruption of conduction in the spinal cord, and not to so-called spinal shock, is brought out by the behavior of the animal in passing through these various stages. The bearing of the validity of the shock hypothesis for any conception of the functional organization of the nervous system has been discussed by Pike (123). A shorter statement of this relation is found in Yates's paper (36).

Comparison of somatic and ocular responses with vascular responses

Control of the animal's responses by various nervous levels	*Average level of blood pressure*
1. Normal intact animal: responds as a whole, pupils narrow, corneal reflex, respiration normal..........	120 mm.
2. Head subjected to anemia: struggles—responses under control of stimulated area (head) skeletal convulsions, respiratory spasms, corneal reflex lost.	180–200 mm.
3. Head functionally dead,—animal spinal:—responses under control of spinal cord only no corneal reflex, pupils widely dilated. No spontaneous respiration. No skeletal reflexes elicitable.............	50–70 mm.
4. Recovery of head centers: gradual return of responses controlled by head area, pupils narrowing—no corneal reflex—spontaneous respiration returns after pressure has risen somewhat, but still sporadic. Skeletal reflexes elicitable in part................	70–90 mm.
5. Recovery completed; animal responds as a whole. Pupils narrow, corneal reflex, respiration reëstablished; functions coördinately, skeletal reflexes present..	120 mm.

When a significant lesion in the splanchnic system has been inflicted by the section of these nerves just before entrance into the coeliac

ganglion and the cerebral circulation shut off, no anemic increment is obtainable. However, all other evidences of bulbar activity are present. A vigorous corneal reflex is obtained prior to occlusion, and when the clamps are adjusted, even though the level of pressure may remain more undisturbed than that obtained under many minor manipulations, the other symptoms of the asphyxial response are shown in full vigor. There are marked respiratory spasms, skeletal convulsions, changes in the pupils, etc.

In marked contrast to such a picture are the effects when, from some physiological disturbance, the medulla itself is thrown out of activity. Here the effects of the interruption of functional continuity are opposed to the effect of anatomical separation. Such a condition is present while the animal is still profoundly under the effect of an occlusion that has just been done, or even during recovery from occlusion, when the functions of the brain stem are not yet fully established. If, under such conditions, the animal is subjected to a renewed occlusion, no response at all can be aroused. Generalized asphyxia, inflicted by clamping the trachea and thus acting directly at the periphery is, in this condition, also impotent to produce any effect. Under this general depression there are no skeletal convulsions, no respiratory gasps, and pressure changes are extremely slight, 5 or 10 mm. The heart just quietly runs down. The condition of the eyes remains unchanged throughout.

All the evidence of these experiments therefore would argue not only for a normal release of the rise of blood pressure through the sympathetic outflow, but also for a complete dependence of the activation of the response on the integrity of the brain stem, and the maintenance of the conditions of conductivity within it. The response transmitted by the sympathetic system is functionally exactly on a par with all the other physiological responses. When respiratory movements, eye movements and skeletal reflexes are obtainable, the changes of blood pressure can also be elicited.

The anatomical relations of the splanchnic outflow in its bearing on recovery after section of the spinal cord. The complete dependence on the brain rather than on the spinal cord is well illustrated by experiments on recovery of blood pressure from high section of the spinal cord. Goltz, (17), (18) and later Goltz and Ewald (117) sectioned the cord of dogs in the midthoracic region and found normal blood pressure responses to subsist. These were attributed entirely to the controlling influence of the cord over the sympathetic system. These experiments have been repeated by later investigators, notably Sher-

rington (121), (124). In view of the very high level of the cord in which a lesion must fall before it can definitely intercept the connections between the medulla and the splanchnic effectors, there is a possibility that the agency concerned in this recovery is none other than the splanchnic constrictors still in functional continuity with the brain stem.

Four early experiments were carried out with Doctor Pike's coöperation in which a transection in the upper levels of the spinal cord was done aseptically, the animal allowed to recover and then the anemic response tested. In two cats the transection was done at the level of the 2nd thoracic. One animal died within 24 hours before the blood pressure could be tested; the other lived 5 days and was then subjected to the test of occlusion. Blood pressure, however, was very low, the bulbar responses failed immediately and no rise was elicitable. Cat 63, however, in which section at the 3rd thoracic was made, recovered fully and when tested a week later showed a level of blood pressure of 120 mm. and an anemic increment of 50 mm. in the first occlusion. Cat 64 with a section at the 6th thoracic was tested 2 days later. Control level of blood pressure was 80 mm. The anemic increment of the first occlusion was 45 mm.

This problem was subsequently taken up by Miss Yates under Doctor Pike's direction, and has been reported on in detail in an earlier issue of this Journal. Miss Yates (36) found that when one or two segments of the thoracic region only are left intact there is a recovery of blood pressure to an adequate level, and vigorous anemic or asphyxial response is readily elicitable. This recovery is attributable to those medullary cells still in connection with the peripheral splanchnic neurones.

It was on the evidence of Goltz's experiments that Langley applied the name "autonomic" to those peripheral mechanisms supplied by ganglionic connection outside the nervous system which he thought could function independently of the brain. The physiological evidence that is now accumulating would gravely discredit this autonomy, and would tend to place the sympathetic responses in the same category as all others. This is of particular importance in connection with the late appearance of the adrenal effect in cerebral occlusion, even after the reflexes are no longer elicitable. However late its appearance, and however independent of any parallel nervous activity, this effect certainly cannot be aroused unless the splanchnic fibers themselves have been previously stimulated. When the splanchnic fibers are no longer excitable because of an anatomical lesion the adrenal effect never appears.

This relationship is of particular interest with respect to the appearance of Traube-Hering waves. These have been noticed by all observers in the downward course of the final fall of blood pressure in the anemic response. Whether nervous centers are no longer excitable to sensory stimulation and whether or not the output of adrenalin is a factor concerned, remains to be tested. It must, however, be borne in mind that such a condition as this where Traube-Hering waves have been elicited, is preceded by an intense activity of the splanchnic outflow as stimulated by the medullary cells.

In the disturbance of the internal medium which the excessive concentration of carbon dioxide in the occluded cerebral vessels brings with it, the increased rate of flow is carried out and maintained by the vascular musculature, and some product of adrenal activity probably makes possible the maintenance of the increased impetus given the blood flow through such a prolonged period of time. However, it is only by virtue of the neurones within the central nervous system that the response is initiated, that it is regulated by changes in the cardiac musculature, and finally that the response is carried out as an integrated whole. The retention of a constant tension of carbon dioxide in the blood by means of an adaptive blood vascular reaction, is therefore mediated in the mammal through its higher central nervous organization, particularly the cells within the medulla oblongata.

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CONCLUSIONS

1. The nerves of the heart are not essential either for the activation or for the persistence of the characteristic pressor phenomena of the anemic rise.

2. In the early stages of cerebral occlusion the cardiac innervation functions as a check on the rapid rise of blood pressure. In this moderating action, accelerators as well as vagi are involved, since on excision of the stellate ganglia, the vagi alone are unable to prevent an abrupt and steep rise of pressure.

3. The activation and maintenance of the vascular response under cerebral occlusion is controlled essentially by the splanchnic nerves.

4. Differential section in various regions of the splanchnic outflow influences the level of the arterial blood pressure. The extent to which the pressure falls on section is an approximate index of the degree to which the anemic rise will be compromised by the lesion.

5. It is impossible to influence the vascular response to anemia by indiscriminate sections within the splanchnic outflow. In order definitely to abolish the response, it is necessary to section either sufficiently far out in the periphery, or sufficiently high up in the spinal cord to interrupt completely the continuity between the medulla and the coeliac ganglion.

6. The level at which the fibers of the splanchnic system leave the spinal cord varies in different individuals. The greatest number of fibers leave the cord in the lower thoracic, especially in the region of the 6th to 8th thoracic. However, constrictor fibers to the splanchnic nerves leave the cord throughout the higher levels of the thoracic cord. In certain individuals, fibers leaving as high as the 2nd and 3rd thoracic will maintain an appreciable level of blood pressure and activate a significant anemic response.

7. Cerebral occlusion, carried out in repeated succession, is borne indefinitely (as many as 18 times) in intact animals. The occlusion time is in no way curtailed and the anemic increment of blood pressure only slightly diminished.

8. The curve of the anemic rise under repeated cerebral occlusion becomes dissociated into two distinct parts after eight or ten successive occlusions have been inflicted.

9. The long-continued maintenance of blood pressure at an extremely high level, characteristic of the anemic rise, is no longer possible after any gross interference with the supply of some product of adrenal activity.

10. An increased liberation of adrenalin under extreme splanchnic stimulation cannot be demonstrated as necessary for the characteristic contour of the anemic rise. This appears dependent on the amount of circulating adrenalin.

11. An increased availability of some product of adrenal activity appears demonstrable in intact animals under extreme splanchnic stimulation, after eight or ten successive occlusions have been inflicted.

12. Survival after ligation of the adrenal glands may be reduced to 1 or 2 hours, when the animal is subjected to successive repeated cerebral occlusions. A complete failure of vasomotor tone seems demonstrable in these animals.

13. The response of the splanchnic nerves is dependent for its release on conditions of functional activity within the brain stem.

14. The vasomotor responses initiated by the splanchnic nerves of the sympathetic nervous system are comparable with skeletal responses

dependent on the higher nervous levels, in respect to their complete dependence on these levels of the central nervous axis.

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