STUDIES ON THE PAIN-SENSIBILITY OF ARTERIES

II. PERIPHERAL PATHS OF AFFERENT NEURONES FROM THE ARTERIES OF THE EXTREMITIES AND OF THE ABDOMINAL VISCERA

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In the immediately preceding communication (This Journal, p. 259) evidence is presented which indicates the existence of a numerous group of afferent neurones subserving pain-sensibility which end in close functional relation with the finer arterial branches and which are subject to stimulation by irritants. The course of these fibers has been traced by experiment in an attempt to determine the peripheral paths of conduction of impulses arising in arteries and giving origin to painful sensation.

METHOD. Cats were used in most of the determinations. Sodium-amytal anesthesia was used for the nerve-sections and for the intra-arterial injections. The injections were made immediately following the nerve-sections or after a period of several days. A concentrated solution of sodium iodide was the irritant used in the majority of instances (100 grams of the salt added to 100 cc. of water). The reflex reaction to the irritating injection was graded as ++ + +, ++ +, ++, +, ?, or 0, as defined in the preceding report.

Following complete denervation of an extremity the intra-arterial injection of an irritant still produces a visible local reaction confined to the extremity injected. In the hind limb this local response consists of a slow but sustained extension and stiffening of the extremity, and, in the fore leg, of a gradual flexion of the paw at the wrist joint. This direct stimulation of local structures by the irritant is detected only after all afferent fibers concerned in the reflex response have been divided; otherwise it is obscured by the generalized activity which involves the entire body.

In the experiments to be reported care was exercised to distinguish between local and general responses and in cases in which the reaction was confined to the extremity injected the reflex response was graded as absent.

THE ARTERIES OF THE EXTREMITIES. Femoral artery. As control observations, in 39 animals (34 cats and 5 dogs) an irritant was injected into a normally innervated femoral artery. A pseudoadhesive response occurred in every case and in 36 instances (31 cats and 5 dogs) was of at least three-plus intensity. In 11 cats a similar injection was made after the ipsilateral
lumbar sympathetic chain had been removed in its entirety. Again in every animal a pseudoeffective reaction occurred upon injection of the irritant into the artery, and in 10 of the animals it reached a three- or four-plus intensity. In 3 cats an attempt was made to interrupt all of the peripheral spinal nerves to one posterior extremity by section on one side of all branches of the lumbosacral limb-plexus. In each instance the subsequent injection of the femoral artery on that side gave a slight reflex response. However, autopsy revealed that in each animal the lowermost branch to the extremity—the posterior femoral cutaneous nerve—had escaped section. The experiment was then repeated in 5 cats and 2 dogs, particular care being exercised to include this nerve in the section. In these animals injection of an irritant into the femoral artery of the operated side gave rise in no instance to any visible reflex effect. Evidently resection of the lumbar sympathetic trunk did not interrupt any appreciable number of the afferent fibers concerned whereas section of all of the peripheral spinal nerves to the extremity interrupted all of the fibers in question.

In 3 cats the posterior spinal nerve-roots were sectioned on one side, just central to their ganglia, from the 5th lumbar to the 3rd sacral segments inclusive. In each animal the injection of the irritating solution into the femoral artery on the side on which the posterior roots had been divided resulted in no visible reflex response whatever; subsequent injection into the contralateral artery elicited reflex response of four-plus degree. Obviously the fibers in question enter the cord by way of the posterior roots.

**Brachial artery.** As a control series, in 18 animals (13 cats and 5 dogs) an irritant was injected into a normally innervated brachial artery. In every instance a reflex response occurred and in 16 cases (11 cats and 5 dogs) it was of three- or four-plus intensity. In 2 cats the right cervical sympathetic trunk was removed with its middle and inferior ganglia, following which the right pleural cavity was opened and the stellate and next subjacent thoracic sympathetic ganglia were resected together with the connecting segments of the sympathetic trunk. Injection of the irritating solution into the right brachial artery gave a marked reflex reaction in each animal. Similar injections into the contralateral brachial arteries gave reactions of apparently identical intensity. No appreciable number of the afferent fibers concerned in the reflex from the brachial artery had been interrupted by the operation.

In 3 cats and 1 dog the cords of the right brachial plexus were divided in the axilla, and, as an additional precaution, the lateral divisions of the anterior rami of the 3rd and 4th cervical and of the 2nd and 3rd thoracic nerves were sectioned. In each animal injection of the brachial artery on the side of the operation gave rise to no visible reflex effect whereas injection of the opposite artery gave a four-plus response. The afferent fibers concerned in the reaction had been interrupted in their entirety by division of the appropriate spinal nerves.
In 3 cats the posterior spinal nerve-roots of the right side were sectioned, just central to their ganglia, from the 3rd cervical to the 2nd thoracic segments inclusive, and an injection was then made into the right brachial artery. In none of the 3 animals did any visible reflex effect follow. Subsequent injections into the left brachial arteries gave reactions of four-plus intensity. It was found at postmortem examination that all anterior roots were intact and apparently unharmed. These experiments demonstrate that the afferent fibers concerned in the reflex reaction traverse the posterior roots to reach the cord.

Discussion. Friedrich (1924), Schilf and Stahl (1925) and Abrashanow (1927) have concluded that many of the sensory fibers which are stimulated by injection of irritants into the femoral artery pass centrally along the artery to traverse the lumbar sympathetic trunk on their way to the spinal cord. Dennig (1924, 1925), Brjussowa and Lebedenko (1929), and Burget and Livingston (1931) have reported experiments in which section of the posterior spinal nerve-roots has proved more effective in abolishing such pain than has resection of the sympathetic trunk or division of the femoral artery.

The experiments reported at this time demonstrate beyond doubt that the pain-fibers which are stimulated by injection of irritants into the brachial or into the femoral artery pass to the spinal cord by way of the peripheral spinal nerves and their posterior roots. It is certain that no appreciable number of the fibers in question traverse either the sympathetic chain or an anterior spinal nerve-root. Their peripheral course is analogous to that of the posterior-root fibers which subserve cutaneous sensations.

The conclusions of Schilf and Stahl and of Abrashanow are, in our opinion, unwarranted. These observers worked with animals in which only the femoral and sciatic spinal nerves had been sectioned. The hind limb of such an animal is in no way deprived of its entire somatic innervation. Experiments which we have reported demonstrate the presence of afferent fibers which subserve the pain-sensibility of the femoral arterial tree in other peripheral branches of the lumbosacral plexus, e.g., in the posterior femoral cutaneous nerve. The observers mentioned performed their experiments upon the dog and used a 50 per cent solution of lactic acid as the irritant. In order to be certain of our conclusions we repeated the experiments upon the femoral artery of the dog and used lactic acid for the injection. Section of all branches of the lumbosacral plexus completely abolished the reflex response to lactic acid in the dog just as it had abolished the response to sodium iodide in the cat.

We have been unable to confirm Abrashanow's report that after section of the femoral and sciatic nerves in the dog a part of the residual reflex reaction to the intra-arterial injection of irritants is abolished if the femoral
artery is divided proximal to the site of injection. In our experiments the injection of 50 per cent lactic acid into the divided artery gave as marked a reflex reaction as did injection of the contralateral vessel. Abrashanow used ether as the anesthetic agent. In our experience anesthesia under light etherization is apt to vary so greatly in depth from moment to moment as to invalidate the comparison of reflex effects which are elicited in temporal series. Under the more constant anesthetic action of sodium amytal we could obtain no evidence that a part of the fibers in question ascend in the coat of the vessel.

The arteries to the abdominal viscera. These experiments were performed upon cats. A midline laparotomy was done under sodium-amytal anesthesia and the artery to be studied was injected from the exposure thus afforded. When a neurectomy preceded injection of the artery an autopsy was performed to determine whether the nerves had been sectioned as intended. As reported in a previous communication, arteries to the abdominal viscera are somewhat less acutely sensitive to irritants than are arteries to somatic tissues.

Hepatic artery. As a control series, of 22 normal cats in which an irritant was injected into the hepatic artery, in 17 a definite pseudoadvective reaction followed and in 8 it was of three-plus or four-plus intensity.

In 8 animals both major splanchnic nerves and both lumbar sympathetic trunks were divided at the level of the diaphragm. Injection of an irritant into the hepatic artery at an interval varying from a few minutes to one week after the nerves had been sectioned gave rise to no sign of reflex reaction in any animal of the 8. Hence all afferent fibers concerned in the response to injection of this artery ascend either the lumbar sympathetic trunk or the major splanchnic nerve to enter the cord in the thoracic region.

In 5 animals in which both major splanchnic nerves were divided at the level of the diaphragm but the lumbar sympathetic chains left untouched so that impulses might still ascend in the chains from lumbar to thoracic levels, subsequent injection of an irritant into the hepatic artery gave rise to no reflex effect. These cases prove that all of the fibers in question ascend to the thorax by way of the major splanchnic nerves and that none of them enter the lumbar sympathetic trunk by way of the more posterior or minor splanchnic branches.

In one animal the left major splanchnic nerve was sectioned at the diaphragm. In this animal the injection of the hepatic artery gave a reflex response of four-plus intensity, demonstrating that many of the fibers in question are contained in the right major splanchnic. In 5 animals the right major splanchnic nerve was sectioned. Subsequent injection of the hepatic artery gave no reaction in one instance, a one-plus reaction in 3 instances, and a three-plus response in the remaining case. These experiments indicate that a certain number of the fibers from the hepatic artery ascend in the left major splanchnic.
In summary, all afferent fibers subserving pain-sensation and stimulated by the injection of an irritant into the hepatic artery ascend in one or other of the two major splanchnic nerves to enter the spinal cord at some dorsal segment. Judged by the response, most of the fibers in question seem to ascend the right major splanchnic nerve, but a definite number are contained in the left major splanchnic (see fig. 1).

**Splenic artery.** Injection of an irritant into the splenic artery gave an unmistakable pseudffective reaction in 10 of 12 normal cats. The reac-
tion was quite marked in 4 animals and of but moderate or slight intensity in the remaining 6.

Injection failed to give any reaction whatever in 11 animals in which both major splanchnic nerves and both lumbar sympathetic chains had been sectioned at the diaphragm. Hence all of the fibers which supply the splenic artery enter the cord in the thoracic region.

In 1 animal both major splanchnics were cut but the lumbar sympathetic chains were left unharmed. In this animal injection of the splenic artery gave a two-plus response. In 2 other instances the major splanchnics were left intact but both lumbar sympathetic chains were resected. In each of these animals injection of the splenic artery resulted in a one-plus reaction. Therefore, some of the fibers from the splenic artery ascend in the sympathetic trunks after entering them below the level of the major splanchnics, while others of them ascend in the major splanchnic trunks.

In 2 animals the right major splanchnic and the right lumbar sympathetic trunk were divided at the diaphragm whereas the nerves of the left side were left intact. In 1 of these animals the injection resulted in a response of one-plus intensity and in the other animal a reflex effect was questionable. In 1 animal the left major splanchnic and left lumbar sympathetic trunk were resected and in it the injection of an irritant into the splenic artery was followed by a three-plus response. These cases indicate that the fibers from the splenic artery ascend on both right and left sides although probably a majority of them ascend on the right.

In summary, the afferent fibers subserving the pain arising from irritating injections into the splenic artery enter the spinal cord in the thoracic region. They ascend from the abdomen both in the sympathetic trunks and in their major splanchnic branches, and probably more of them ascend on the right than on the left (see fig. 1).

Superior mesenteric artery. This artery was injected with an irritant in 12 normal animals. In 9 of them a reflex response occurred but in only 1 did it exceed two-plus in intensity. The superior mesenteric artery is less sensitive to irritants than are the hepatic and splenic arteries.

In 10 animals in which both major splanchnics and both sympathetic trunks were interrupted at the diaphragm the injection of an irritant into this artery gave rise to no visible response. A similar absence of reaction occurred in 2 animals in which both lumbar chains had been resected without section of the major splanchnics. In 4 animals in which the lumbar chains were intact but the major splanchnics interrupted the irritant gave rise to a reaction in 2 cases. In 3 animals there was no response after the right chain had been resected and right major splanchnic divided. On the other hand in 1 animal in which a corresponding operation had been performed on the left side only, the injection gave rise to a four-plus response.
It is concluded that the majority of the afferent fibers supplying the superior mesenteric artery enter the right lumbar sympathetic chain posterior to the major splanchnic nerve and ascend the sympathetic trunk to enter the cord in its dorsal segments (see fig. 1).

Renal arteries. One or other of the renal arteries was injected in each of 20 controls but in only 12 instances did a pseudoadfective reaction result and in no instance did it exceed a two-plus intensity. The renal artery is less constantly sensitive to irritants than is any other abdominal artery we have tested.

The renal artery was injected in each of 7 cases in which both major splanchnics and both lumbar chains had been divided at the diaphragm. In 4 of these cases a reaction occurred and in 3 it reached a two-plus intensity. In another animal in which both major splanchnics had been sectioned but the sympathetic chains left intact the renal artery gave a two-plus reaction. These results serve to show that the fibers supplying each renal artery enter the lumbar sympathetic chain of that side and from it pass into a lumbar segment of the spinal cord (see fig. 1). This finding is surprising in view of the frequency with which renal disease causes referred pain which is localized in thoracic segmental areas (Head, 1893).

In 20 other instances a renal artery was injected following one or another combination of neurectomies but in none of these cases did a reflex effect occur. The sensitivity to irritants is evidently very slight in the renal arteries of many animals. In no animal, however, have we seen it in evidence after resection of the lumbar sympathetic trunks.

The inferior mesenteric artery gave a greater percentage of strong reactions than did any other lower abdominal artery. In each of 20 animals a definite pseudoadfective response resulted, and in 5 of these cases was of three-plus degree. No combination of abdominal neurectomies was found that would abolish this reaction in the case of the inferior mesenteric artery. Both lumbar sympathetic chains may be resected and both major splanchnic nerves sectioned without diminution of the intensity of the response, although the latent period may be prolonged. Probably this peculiarity of the artery is a result of its anastomotic connections by way of which the irritant passes to arterial channels in the regions of the hip and thigh. These regions are supplied, as shown in a previous section, by fibers which ascend the peripheral spinal nerve-trunks without traversing the sympathetic chain.

Discussion. It is interesting to note the importance of the sympathetic trunks and their splanchnic branches in relation to the pain-sensibility of the abdominal organs. In four animals in which both vagal cords had been severed at the cardia the injection of irritants into the arteries to the abdominal viscera gave rise to just as strong reflex reactions as were caused by similar injections in normal animals. When the sympathetic
and splanchnic elements were interrupted, however, the arteries became anesthetic although the vagi and the phrenic nerves had not been disturbed. In several animals in which all sympathetic and splanchnic paths from the abdomen had been previously interrupted a laparotomy was done under quite light sodium-amytal anesthesia. There was constant reflex activity during the incision of the skin and again during the cutting of the submucosal layer (the posterior sheath of the rectus fused with the parietal peritoneum). But when this work was completed in the domain of the intercostal nerves and the abdomen opened it was found that the abdominal contents could be traumatized freely without causing the slightest reflex effect.

Bradford Cannon (1932) obtained interesting results in experiments in which a stimulus was applied to one or another visceral nerve in the unanesthetized cat by means of electrodes buried in contact with the nerve during a preparatory operation. Stimulation of the vagus trunk seemed to be disturbing only because it resulted in difficulties in respiration. But as soon as the slightest stimulus was applied to electrodes set on a splanchnic nerve the animal was at once restless.

The afferent neurones which are contained in the vagus and phrenic nerves and which are concerned with referred pain can hardly, in the light of recent interpretations of the mechanism of referred pain (Weiss and Davis, 1928), be classed as true pain-fibers. Moreover, the majority of the afferent fibers contained in these nerves carry impulses which do not, even indirectly, give rise to pain. It is the sympathetic trunks and their splanchnic branches which contain the true pain-neurones supplying the abdominal organs.

It is evident that an abnormal process in a visceral area may result in stimulation of afferent fibers of several orders and of varied peripheral paths. Walton, Moore and Graham (1931) demonstrated that the afferent fibers which operate to produce the vomiting of peritonitis pass centrally both in the sympathetic trunks and in the vagal cords. The results given above, on the other hand, indicate that the pain of peritonitis is a function of sensory fibers which follow, without exception, a sympathetic (or splanchnic) path. Weiss and Davis (1928) found that, although anesthetization of the area of skin to which the pain of biliary colic is referred is effective in abolishing the pain, it is not effective in relieving the vomiting, and, similarly, Schrager and Ivy (1928) have reported that the vomiting which accompanies distention of the biliary ducts in the dog may be relieved by vagotomy but distress persists until the right splanchnic nerves are cut.

**SUMMARY**

The injection of an irritating solution into an artery results in stimulation of afferent fibers which subserve arterial pain-sensibility. In amytal-
ized animals this results in characteristic reflex motor activities of a quasi-emotional nature. The peripheral anatomical paths which these fibers follow have been traced in experiments determining the presence or absence of this reflex reaction after section of one or another peripheral nerve. The fibers of this type which supply the femoral and brachial arteries have a peripheral course identical to that of the posterior-root fibers which subserve cutaneous sensibility. They pass centrally in the peripheral branches of the spinal nerves and enter the spinal cord by way of the posterior roots (see p. 267). No significant number of them course long distances along the arteries, or traverse the sympathetic chain, or enter the cord by an anterior root.

In contrast with these fibers to the extremities, the fibers which are stimulated by injection of irritants into the hepatic, the splenic, and the superior mesenteric arteries are shown by experiment to ascend either the major splanchnic nerves or the sympathetic chains and to enter the spinal cord in the thoracic region (see p. 271, fig. 1). On the other hand, the fibers of similar function which supply the renal arteries enter the spinal cord in the lumbar region after having traversed a minor splanchnic nerve and one of the lumbar sympathetic chains (p. 273).

Experiments are reported (p. 273) which illustrate the importance of the sensory fibers contained in the sympathetic and splanchnic trunks as regards the pain-sensibility of the abdominal organs. Afferent fibers contained in the vagal cords and in the phrenic nerves subserves varied and important functions, but seldom conduct impulses which give rise to painful sensation. In respect to their afferent components, the sympathetic trunks and their splanchnic branches are the true pain nerves of the abdomen.

BIBLIOGRAPHY

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