STUDIES ON THE PAIN-SENSIBILITY OF ARTERIES

I. SOME OBSERVATIONS ON THE PAIN-SENSIBILITY OF ARTERIES

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Various observers, including Odermatt (1922), Friedrich (1924), Schilf and Stahl (1925), Dennig (1924, 1925), Abrashanow (1927), and Burget and Livingston (1931), have described the painful effect of the injection of irritants into arteries. No very determined attempt seems to have been made to ascertain the mechanism whereby such pain is produced. In view of the meager knowledge of the sensibility of arteries it seems desirable to report the results of a series of experiments upon intravascular injection of irritants and to attempt to correlate this evidence with observations on other conceivable types of arterial pain-sensibility.

In this laboratory, during the course of experiments in radiographic visualization of arteries, it was noted that in animals anesthetized with sodium amytal to a sufficient degree to permit the performance of laparotomy without notable reflex response, the injection into the femoral artery of a small quantity of a concentrated solution of sodium iodide invariably provoked a marked reflex response. The entire body stiffened and the extremities strained at the leashes; a hyperpnea developed and the pupils became widely dilated; the head was tossed from side to side and there was an accompanying vocalization.

Such activity is an integral part of the external manifestation of the perception of acute pain during conscious states. Woodworth and Sherrington (1904) called attention to its occurrence in response to afferent stimulation after section of the brain-stem below the diencephalon. When appearing in the absence of consciousness it has been termed pseudoadaptive or quasi-emotional behavior. In the experiments described it was not accompanied by subjective perception of pain since the higher centers had been rendered inactive by the general anesthetic agent. However, it was initi-
ated, we may presume, by afferent impulses which would have evoked pain had the functions of the brain been intact.

This pseudoadfective reaction of the amytalized cat has been used in studies to determine the sensibility of arteries to various types of stimulation. Since the reaction does not lend itself readily to mechanical recording methods the results to be reported are based upon simultaneous judgments of two observers as to the absence, presence and intensity of reflex motor response. In each case the response, if present, has been graded according to the following plan: ++++—marked struggling and hyperpnea with vocalization, +++—marked struggling and hyperpnea without vocalization, ++—moderate struggling and hyperpnea, +—definite but slight muscular response and change in respiration, ?—questionable response, and 0—no response.

The majority of the experiments were performed in the cat with occasional observations on the dog. An aqueous solution of sodium amytal was administered by intraperitoneal injection in doses of 50 to 70 mgm. per kgm. for the cat and of 45 to 60 mgm. per kgm. for the dog. A period of 20 to 40 minutes was necessary for induction of anesthesia of moderate depth, providing indifference to ordinary surgical procedure combined with an active corneal reflex. Occasionally a greater amount of the drug was required.

In the majority of experiments the irritant consisted of a concentrated solution of sodium iodide (100 grams of the salt added to 100 cc. of water). Occasionally other irritants were used, including less concentrated solutions of sodium iodide or of potassium iodide, 10 to 30 per cent sodium chloride, 5 to 50 per cent lactic acid, and 10 per cent barium chloride; 0.25 to 0.5 cc. of the irritant was injected. To prevent excessive dilution the artery was occluded temporarily just above the site of injection by tension on an encircling silk thread.

In all over 200 intra-arterial injections of an irritant were made in approximately 100 animals. As a usual result there was a surprisingly strong reflex motor reaction following injection of any of the irritants used into any artery. The sensibility in question is therefore widespread. It is more acute in the arteries to the extremities than in those to visceral organs. Including injections into the abdominal aorta, which were made immediately above its bifurcation, in 93 instances an irritant was injected into an artery supplying the tissues of an extremity. In no case did a pseudoadfective reaction fail to appear, whereas in only 16 instances was it of less than three-plus or four-plus intensity. In contrast, in 68 cases an irritant was injected into an abdominal artery of visceral distribution (hepatic, splenic, superior mesenteric, renal); in 20 instances a pseudoadfective reaction was absent or but questionably present whereas in only 13 or the remaining 48 cases did it warrant a three-plus or four-plus designation. This greater
sensitiveness of the arteries of the extremities may be due to a more liberal distribution of the afferent nerve-endings concerned.

Among visceral arteries those supplying upper abdominal organs (hepatic, splenic) show, in turn, a more acute sensibility than do the superior mesenteric and renal arteries which supply lower abdominal structures. On the other hand the inferior mesenteric artery provides more intense reactions than do the renal and superior mesenteric vessels. The difference, in this instance, probably results from the liberal anatomoses with the vessels of the lower extremity, by way of which an irritant injected into the inferior mesenteric artery rapidly finds its way into the vascular system of the thigh.

The reaction to the intra-arterial injection of the irritant appeared promptly. Usually muscular movements were becoming evident within 1 to 1.5 second after the beginning of the injection and had become well developed at the end of a two-second period. In the cat vocalization did not begin until the reflex muscular effects were under way, the duration of the entire response varying from 5 seconds in some animals to 30 seconds in others. In dogs the muscular response was slight and the vocalization more prominent.

Throughout the entire study there was evidence of strong stimulation of sensory endings. Even when the reaction was slight the stimulation was of necessity considerable since the animals were anesthetized to a degree which permitted ordinary surgical procedures without notable reflex disturbance. Similarly, in man such strong stimulation results from the injection of sodium iodide into the femoral artery as to necessitate the use of general anesthesia (Brooks, 1924; Singleton, 1928). Such evidence clearly indicates the existence of numerous afferent fibers which subservce pain-sensation, the endings of which are in some manner stimulated when an irritant is injected into an artery.

Whether the irritant acts directly upon sensory nerve-endings is a question which arises. Stretching of smooth muscle and spastic contraction of smooth muscle have been considered important mechanisms in determining visceral pain. It can be said definitely that the stimulation of sensory fibers in the experiments reported was not due to stretching of muscle through forced dilatation of the artery. In repeated trials some non-irritating solution such as normal salt-solution was injected so rapidly as to distend the artery visibly without eliciting any sign of painful stimulation. On the other hand the irritating solutions produced marked reflex reactions when injected drop by drop.

Likewise evidence has been obtained which shows that the afferent stimulation did not take origin from a spasm of the arterial muscle. In animals in which one lower extremity had been sympathectomized by lumbar ganglionectomy the injection of the sodium-iodide solution into the para-
lyzed femoral artery caused, without exception, as immediate and as pronounced a reaction as a similar injection into the artery having normal innervation. In other unilaterally sympathectomized animals the arteries of the lower extremities were visualized by roentgenograms taken immediately after injection of sodium iodide into the abdominal aorta. The paralyzed arteries of the sympathectomized limb were seen to be dilated relative to those of the normal limb at a moment when painful stimulation was in progress (Moore, Williams and Singleton, 1933). Therefore, since neither spasm of smooth muscle nor stretching of smooth muscle is present at the time of sensory stimulation, one is led to conclude that the irritating solution must act directly upon nerve-endings.

A number of experiments have been performed to determine the location of the endings which are affected by such injections. That the receptor endings of cutaneous sensibility are not those affected is shown by the occurrence of quite intense reactions upon injection of arteries of purely visceral distribution such as the hepatic. Moreover, the absence of a comparable reaction when the irritant is injected into a vein excludes the possibility that the irritant acts upon some distant structure after it has returned to the general circulation. Then the nerve-endings in question must be situated in the artery, in the capillary, or in the perivascular tissues.

Burget and Livingston (1931) noted that a 5 per cent solution of lactic acid did not give origin to pain when injected into the tissues of the thigh of the dog whereas evidences of pain occurred when it was injected into the brachial artery. Similarly, of 8 animals in which we have injected a concentrated sodium-iodide solution directly into the substance of one or another abdominal organ, in only 2 did any reflex effect occur and in these it was delayed and of slight degree. In the same animals subsequent injection of the same irritant into the artery supplying the organ in question resulted in a more immediate and much more marked response. The only tissue in which we have observed regularly occurring reactions to this form of stimulation has been the subcutaneous fatty tissue and in its case the reactions have been of but one-plus intensity whereas injections into the arteries supplying the same area have given four-plus responses. This has led to the conclusion that irritants act upon receptor endings located somewhere in or about the vascular tree.

Odermatt (1922) concluded that the sensitivity concerned is a function of the capillaries, for he found that when all branches of a stem-artery were ligated so as to prevent access from it to arterioles and capillaries the injection of an irritant into the artery did not cause pain. We have repeated this type of experiment. Such evidence lacks conviction when obtained upon the femoral artery where ligation of the numerous branches requires such isolation of the vessel in its bed as to interrupt conceivably its nerve
The left subclavian artery of the cat, however, courses nearly two inches before branching. When ligated proximal to this branching an injection of sodium iodide evoked no response. Preliminary blocking of the femoral arterioles with lycopodium spores, moreover, definitely delayed the occurrence of the reaction. These results indicate that the sensory fibers in question terminate in close functional association with the finer arterial branchings.

There has been no generally accepted histological demonstration of afferent fibers which penetrate to the intima of arteries (Wollard, 1926; Kuntz, 1929). Our own microscopic studies of the arterial wall following injection of irritants have shown that the endothelium remained intact and apparently uninjured and the deeper layers of the vessel-wall had not become exposed. These facts may be interpreted as an additional indication that the nerve-endings in question are associated with the finer, thin-coated branches where the irritating solution can rapidly penetrate the vessel-wall.

These afferent nerve-endings associated with the smaller blood-vessels are evidently particularly sensitive to some stimulus of a chemical nature. The irritants used caused no comparably intense stimulation when applied to human skin or when applied to the peritoneum or injected into the tissues of anesthetized animals.

Some veins partake to a minor degree of this same sensibility. The portal vein gave slight reactions in 4 of 9 injections, whereas the inferior cava failed to give a response on repeated trials. The diluting properties of the venous blood-volume may be a factor in this finding, although injection directly into the heart-cavity in one instance gave a four-plus response. Various observers have reported that the injection of irritants into the veins of man is followed by pain (Livingston, 1930).

It is possible that means for other forms of pain-sensibility are present in blood-vessels. Surgeons frequently note pain incidental to mechanical manipulation of arteries. It has been suggested that this sensitivity to trauma is a function of the periarterial plexus (Odermatt, 1922). In our own experience manipulation of arteries has occasionally given rise to reflex activity. But in the cases in which this occurred examination revealed the presence of a visible nerve which had been traumatized along with the artery. In cases in which the blood-vessel had been carefully isolated from all of its accompanying nerve-trunks it was found that neither ligation nor clamping nor stretching nor puncture nor any other form of mechanical manipulation gave signs of reflex disturbance. Many of the peripheral nerve-branches course close to the peripheral arteries. The pain which arises from mechanical trauma to arteries is, in our opinion, properly explained on this basis. Such pain results neither from stimulation of nerve-endings nor from a stimulation in the artery proper, but
arises from physical injury to nerve-fibers which are accidentally included in the manipulation. This interpretation might be extended to explain pain incidental to traction on the mesentery, where, of all tissues affected, the nerve-trunks are most sensitive to tension (Forbes, 1928). Thus we believe that much of the pain caused by many surgical procedures results from trauma to sensory fibers rather than from stimulation to terminal receptors.

We are inclined to minimize the importance of distention of arteries as a mechanism determining the occurrence of painful sensation. We have produced visible distention of the femoral artery in amytalized animals by rapid injection of normal saline without eliciting any appreciable pseudo-affective response to indicate that pain-fibers had been stimulated. Knapp (1929) arrived at a similar conclusion. It has been suggested that vascular distention is an important source of pain in inflammations since the pain often follows the rhythm of the pulse and subsides when incision relieves the local swelling and tension (Kuntz, 1929). In this respect it may be pointed out that the increased pressure in inflammatory lesions is obviously both extravascular and intravascular. Incision serves primarily to reduce extravascular pressure, and, were the pain a function of the vascular distention, incision would operate to increase the pain unless there were a secondary adjustment in intravascular tension. It seems more probable that the pain of inflammation arises through some other mechanism, e.g., the mechanical compression of nerve-structures by the increased interstitial pressure.

Spastic contraction of arteries has been generally conceded to be painful. The injection of solutions of barium salts into peripheral arteries gives rise to spasm and to pain. The attacks of vasospasm in Raynaud's disease are accompanied by pain. The pain of angina pectoris is thought to be caused by arterial spasm. Such observations, although convincing to many, are not conclusive proof that the spasm itself is painful. In our experiments the pain arising from injections of barium salts was neither abolished nor appreciably diminished by previous or simultaneous injections of vasodilator substances such as nitroglycerine or acetylcholine. The spasm of Raynaud's disease is a result of exaggerated sympathetic vasoconstrictor activity and an identical form of spasm can be produced by administering adrenalin which stimulates the vasoconstrictor endings. But adrenalin does not cause pain when given by intra-arterial injection or by any other mode of administration. All forms of arterial spasm cause a proportionate ischemia. The spasm produced by adrenalin causes only momentary ischemia whereas that of Raynaud's disease may be maintained for hours until such profound chemical changes occur in peripheral tissues that gangrene results. These chemical changes might plausibly affect nerve-endings. We are not in a position to deny that arterial spasm
is ever of itself painful, but we are inclined to discount its importance in
the production of pain relative to that of the chemical changes which take
origin from it.

In regard to the pain of ischemia, Lewis, Pickering and Rothschild (1932)
have demonstrated that in ischemic contraction of skeletal muscle the pain
results from a stimulus which is derived from the accumulation of some
factor as a result of physiological processes. We have reported evidence
of the existence of afferent fibers subserving pain-sensation that end about
the smaller arterial branchings and are particularly sensitive to irritants.
It is interesting to note that a 0.1 percent solution of lactic acid injected into
the stem-artery provides strong stimulation of these neurones in anesthe-
tized animals. During conscious states it is possible that more dilute solu-
tions are effective. Lactic acid is known to accumulate in ischemic tissues
as a result of anoxidative metabolism. These observations provide an
attractive basis for conjecture as to the cause of pain in ischemia. They
suggest a simple explanation which is deserving of critical test.

SUMMARY

In animals under sodium-amytal anesthesia the stimulation of afferent
neurones subserving pain-sensitivity results in reflex motor activity of a
pseudosensitive nature. When an irritant is injected into an artery there
results a strong reflex response which is characterized by movements of the
extremities, dilatation of the pupils, changes in the pulse and respira-
tion, and accompanying vocalization.

This form of pain-sensibility is more acute in arteries of the extremities,
but is present to a comparable degree in arteries to visceral organs (see p.
260). The pain occurs independent of stretching and of spasm of arterial
muscle (see p. 261). It is shown by experiment to result from chemical
stimulation of afferent nerve-endings which are located in close relation to
the finer arterial branches (p. 262). The chemical properties which serve
under natural conditions as an adequate stimulus to these receptors are not
discussed at this time.

A study with reference to other possible types of arterial pain-sensibility
is reported. It is believed that manipulation of arteries gives rise to pain
only as a result of trauma to the accompanying gross nerve-trunks (p. 263).
It is suggested that much of the pain which attends many surgical proce-
dures is caused by trauma to nerve-fibers rather than by stimulation of
terminal receptors.

Observations are noted which indicate that arterial distention and art(e-
rial spasm are of secondary importance in the production of painful sen-
sation (p. 264). In cases in which spastic contraction is accompanied by
pain there is present a secondary factor which is a more probable source of
the pain. In this connection the irritant property of barium salts may be
mentioned and the ischemia which accompanies clinical forms of vasospasm.
The pain which accompanies ischemia is discussed and the efficacy of lactic acid as an irritant stimulus to pain-fibers is noted (p. 265).

It is concluded that there is a numerous group of afferent neurones subserving painful sensation which end in close association with the smaller arterial branchings. These can be stimulated under experimental conditions by the intra-arterial injection of irritants. Under natural conditions it is probable that they function by virtue of a sensitiveness to some chemical stimulus.

BIBLIOGRAPHY