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THE PHYSIOLOGY AND RELIEF OF TRAUMATIC ARTERIAL SPASM*

BY

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When these lectures were founded by Edward Arris in 1646 the lecturers were called the "Readers of the Muscular Lecture." Such a title would be appropriate to-day because the studies to be described deal largely with muscle. It is not, however, the striped muscles described in the old "Public Anatomies" but the smooth muscle of blood vessels which will be considered here.

The clinical aspects of traumatic arterial spasm must be briefly discussed before considering the physiology of its production and relief. The larger vessels of the limbs such as the brachial or femoral arteries are those usually affected, and the spasm follows injury near by, often a fracture, dislocation, or gunshot wound. Sometimes the cause may be dissection of an artery during a surgical operation such as arteriography or vein ligation. A length of vessel may remain in spasm for hours or even days, and ischaemic contracture of muscle or gangrene of the limb may result. This contractile power of major arteries has been known for many years. Hunter, who with Pott gave the first Arris and Gale lectures under the Company of Surgeons, was aware of it. He described many instances in man and animals, and knew that it was part of the natural mechanism for suppressing bleeding (Hunter's Works, 1835). When, however, an artery is injured without being opened this protective mechanism is unnecessary because there is no bleeding to stop, and harmful because the circulation to the part is arrested. More recently the clinical side of the problem has been well described by Cohen (1940) and Griffiths (1940) in Hunterian Lectures, but until the work of Barnes and Trueta in 1942 there had been few investigations of the cause or cure of arterial spasm under experimental conditions. This is unfortunate, because the difficulty of obtaining standard conditions has always made it hard to judge the effects of treatment in clinical practice. The artery affected, the type of injury, and the time that has elapsed before the treatment starts may all vary from one patient to another. The present studies were chiefly made in the laboratory. They will be considered in two parts: (1) the causes of arterial spasm or other alterations in the size of large arteries; and (2) the cure of arterial spasm.

Causes of Spasm or Other Alterations in Size of Large Arteries

The concept of a nervous reflex arc has been widely held. Barnes and Trueta (1942) and Trueta and his colleagues (1947) described experiments in rabbits in which a tourniquet applied to the thigh for several hours produced shrinking of the femoral artery on the other side. These findings were taken as the basis for studies made at Harvard in 1948. The details of some of these earlier experiments have already been published (Kinmonth, Simeone, and Perlow, 1949), so that it will now only be necessary to outline them in order to understand what follows. The tourniquet experiments of Trueta and his co-workers were repeated, using a technique which allowed continuous observation and measurement of the arterial diameter. The arterial tree on the side opposite to the tourniquet shrank in the way in which they had described. This shrinking occurred gradually and coincided with a slow fall in blood pressure in a way suggesting a close relation between the two. Tourniquet experiments were then done on rabbits in which bilateral lumbar sympathectomy or denervation of the hind limb had been performed. The same shrinking of the arterial tree on the opposite side took place except in animals in which the blood pressure remained level. This suggested that a gradual fall in blood pressure might cause a parallel shrinking of the femoral artery independently of the presence of intact nerve pathways.

The next step was to see whether alterations in the blood pressure due to other causes might change the arterial diameter. Different methods of altering the blood pressure were used and the effects on the upper third of the femoral artery recorded. The results are shown in Table I. They refer to findings in the rabbit

TABLE I.—*Effect of Blood-pressure Changes on the Femoral Artery*

	Blood Pressure	Arterial Diameter
Open ether	↓	↓
Pentobarbitone sodium (i.v.)	↓	↓
"Shock" due to tourniquets, haemorrhage, etc.	↓	↓
Priscol (i.v.) (cat)	↓	↓
Afferent nerve stimulation	↑	↑
Adrenaline (i.v.)	↑	↑
Tracheal obstruction	↑	↑

except in the case of "priscol," where these experiments were done on the cat. Priscol (tolazoline hydrochloride) is a benzyl-imidazoline compound which dilates the small vessels of the peripheral circulation. It has a depressor effect in the cat, and this makes the femoral artery shrink.

The arterial diameter follows the changes in blood pressure whatever the effect of any particular agent may

*Based upon an Arris and Gale Lecture given at the Royal College of Surgeons on May 29, 1951.

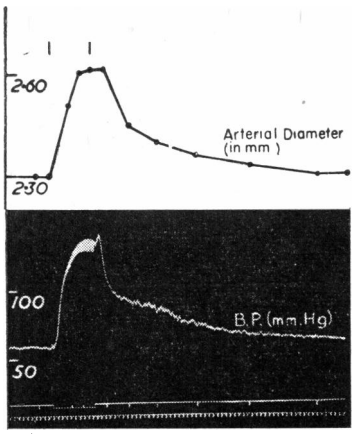

FIG. 1.—Effect of tracheal obstruction on the systemic blood pressure and femoral artery of the rabbit. Anaesthesia with urethane. Arterial diameter measured just below inguinal ligament. Trachea obstructed from second to fifth signals. Time signal (lowest record), 10 seconds.

be upon the peripheral part of the arterial tree. Fig. 1 shows how the femoral arterial diameter changes with the rise in systemic blood pressure when the trachea is temporarily closed.

It follows that the blood pressure should always be recorded in experiments on arterial spasm, otherwise changes in arterial size due to alterations in blood pressure may be falsely attributed to efforts to produce or to relieve spasm.

The concept of a nervous reflex arc was further examined by tests on its possible efferent components. The femoral artery was chosen for detailed study in the rabbit, and tests were made in three ways. First, the artery was stimulated directly with a faradic current. This had no effect on the upper third near the inguinal ligament, but further down marked contraction resulted. Secondly, the lumbar sympathetic chain was stimulated electrically. This had no effect upon the upper third of the femoral artery although shrinking of the paw recorded by a plethysmograph showed that the stimulus was effective Lumbar sympathetic stimulation provoked a marked contraction of the more distal part of the femoral artery. The third method of testing for the efferent component of a reflex arc was to give an intravenous injection of adrenaline and record the change in the femoral arterial diameter. Fig. 2 shows the effect of an intravenous injection of adrenaline on the blood pressure and the diameters of the upper and lower parts of the femoral artery observed simultaneously with two microscopes. The lower part of the femoral artery was seen to contract, but the upper part actually dilated in phase with the rise in blood pressure. Had there been adrenergic sympathetic motor-nerve endings in the upper one-third of the artery the adrenaline would have been expected to have acted upon them to cause contraction.

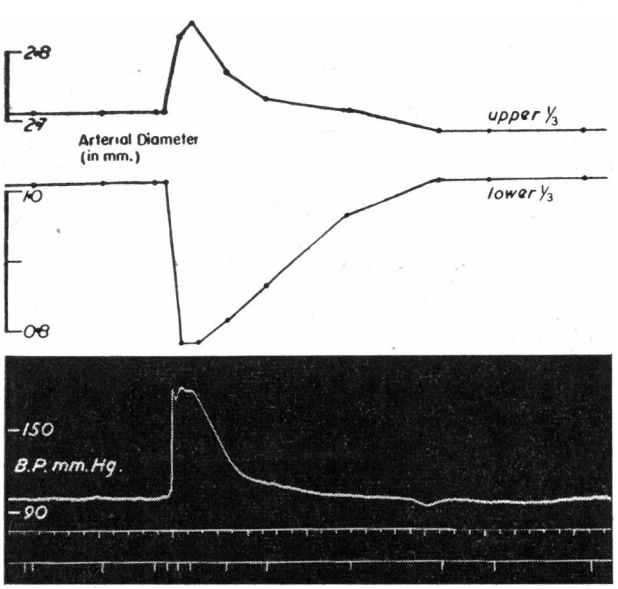

FIG. 2.—Effect of adrenaline on the systemic blood pressure of a rabbit and on its femoral artery measured simultaneously 3 mm. and 80 mm. below the inguinal ligament. Urethane anaesthesia. Injection of 1 ml. of 1 in 50,000 adrenaline intravenously at fifth signal (lowest record). Time signal, 30 seconds.

These observations were repeated many times with consistent results and recorded in detail elsewhere (Kinmonth and Simeone, 1952). They revealed no evidence of vasoconstrictor nerve supply to the upper third of the femoral artery, and yet this part of the vessel may be readily put into spasm by mechanical trauma, and on microscopical examination is found to contain much smooth muscle in its wall.

A similar state exists in man, although it has not yet been possible to determine in detail the level at which the motor-nerve supply becomes evident. Fig. 3 shows how electric stimulation of the dorsalis pedis artery of a patient during the course of a surgical operation produced a definite contraction.

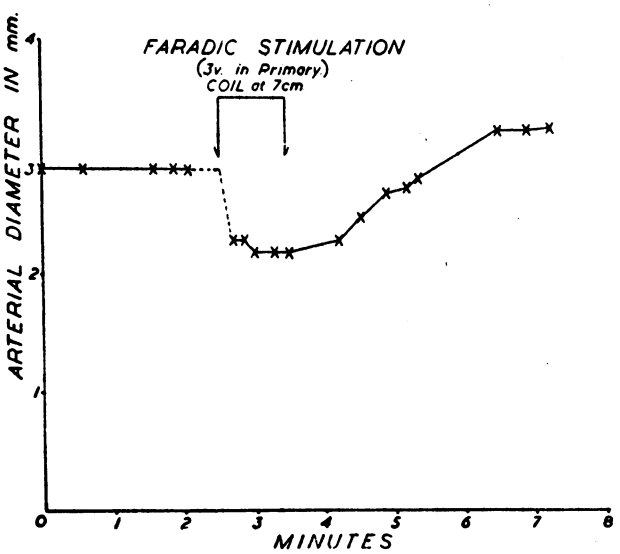

FIG. 3.—Contraction of a healthy small artery (the dorsalis pedis) in response to direct electric stimulation in a woman aged 27.

Stimulation of larger vessels such as the common femoral artery (Fig. 4) produced no contraction. This particular common femoral exhibited partial traumatic spasm when a needle was introduced later for arteriography.

Dr. F. A. Simeone has tried the effect of a variety of direct electric stimuli on large arteries during the course of surgical operations, but always without causing contraction. I have found the same, and yet these arteries will go into spasm if subjected to mechanical trauma.

Arterial spasm may be produced in the experimental animal by applying mechanical trauma to the artery in different ways. Pinching, longitudinal traction, handling with forceps, or rubbing with gauze may cause it. Sometimes additional trauma may produce a localized fusiform dilatation with spasm at each end similar to that described by Grant (1930) in the main artery of the rabbit's ear. The actual irritability of the vessels and their response to trauma vary. It is difficult to produce spasm a second time after relaxation has occurred, and sometimes an animal is found in which it cannot be produced at all. The causes of these variations in irritability are not clear, and are being studied further.

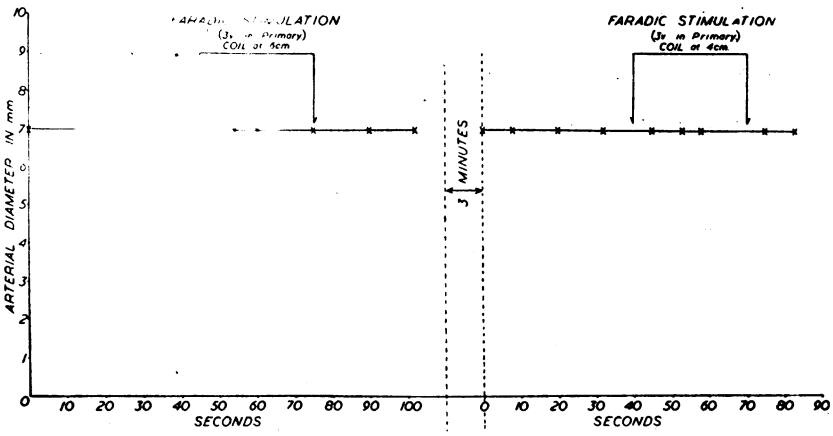

FIG. 4.—Direct electric stimulation of large arteries, in this case the common femoral of a woman aged 42, causes no contraction, although mechanical stimuli may do so.

That an intact sympathetic nerve supply was unnecessary for the maintenance of arterial spasm was shown by experiments in rabbits in which spasm was produced by deliberate periarterial stripping of the vessel. The arterial wall was cleanly stripped of its adventitia and possible nerve supply, and yet the spasm lasted for one to two hours. In man, also, local arterial spasm can persist for long periods after the sympathetic nerve supply has been removed from vessels by the operation of periarterial stripping.

It was accepted as a working hypothesis that traumatic spasm is due to mechanical stimulation of the vessel wall resulting in a sustained contraction of smooth muscle in the maintenance of which nervous factors do not play a demonstrable part. With this conclusion in mind, methods of relieving traumatic spasm were considered.

Methods of Relieving Arterial Spasm

At least a dozen different methods of relieving arterial spasm have been tried in clinical practice. They have included the intravenous injection of drugs and simple exploration as well as more drastic procedures like periarterial stripping or arteriectomy, and success has been claimed at times for almost all of them, even the most unlikely. The probable reason is that arterial spasm lasts for a variable time after the injury, and spontaneous relaxation may coincide with treatment.

In the laboratory, controlled experiments under standard conditions are possible and provide a more reliable test of the success or failure of therapeutic measures. Most of our experiments on the relief of traumatic spasm have been done on rabbits anaesthetized with urethane or "dial." A continuous record of the systemic blood pressure has been kept throughout with a carotid cannula and mercury manometer to prevent confusion due to possible changes in arterial diameter caused by alterations in blood pressure. The arterial diameter was measured by direct observation with dissecting microscopes fitted with micrometers. The upper third of the femoral artery just below the inguinal ligament was chosen for particular study, and this was put in spasm by deliberately rough dissection and then covered by normal saline solution to prevent drying. The vessel on the opposite limb was dealt with in the same way, and so far as possible at the same time, to provide a control. A series of animals were observed in this way to see how long the untreated spastic arteries took to relax. Fig. 5 is a typical example of the slow and gradual natural relaxation of the vessels, which was similar on the two sides. The rate of relaxation slowed down after two hours as the animal's condition deteriorated and the blood pressure fell.

A number of drugs were applied to arteries which had been put into spasm in the way described to see if they would relax them. The chief drugs chosen were known to have a direct action on smooth muscles, because the preliminary work had suggested that smooth-muscle contraction was the important factor in the spasm rather than nervous activity. Direct application was chosen because it was considered that substances circulating in the blood would have little chance of reaching the muscle in the arterial wall. Under clinical and experimental conditions the lumen of the spastic vessel is often totally closed and the vasa vasorum damaged by the injury which caused the spasm. Each drug was tested several times in different animals, and the results shown in the figures are typical examples.

The first substance to be used was papaverine, and Fig. 6 shows the result of applying a 2.5% solution of the sulphate to vessels which had been put in spasm in the usual way. Intravenous injection of papaverine was without effect on the spastic vessels, nor did it have effect on any of the numerous occasions on which it was tried in other animals—a finding in agreement with results in man (Learmonth, 1950, personal communication). The drug relaxed the vessels rapidly when applied direct to them, and they remained relaxed after it was replaced by saline. There was no rise in blood

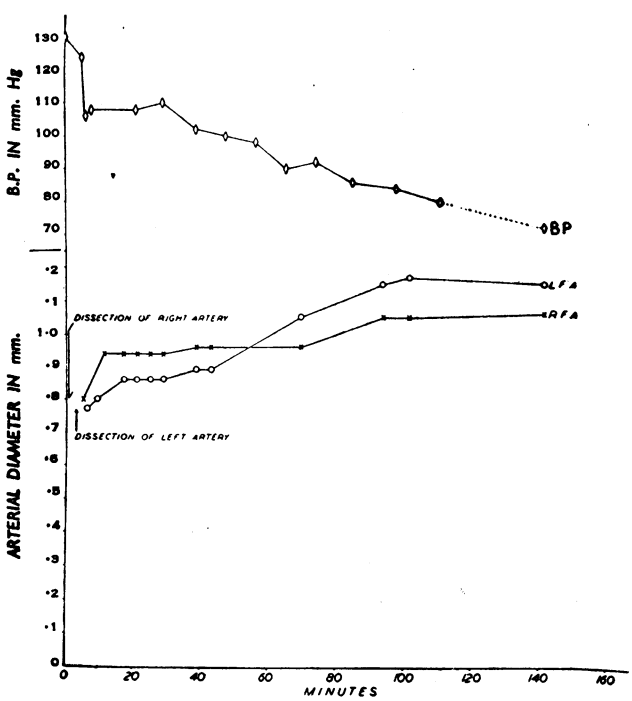

FIG. 5.—Example of the gradual and symmetrical way in which natural relaxation of traumatic spasm occurs in the femoral artery of a rabbit over a period of about two hours. Urethane anaesthesia.

pressure which could have accounted for the changes. In other animals more dilute solutions, 1% or 1.25%, were also effective when applied direct to spastic arteries.

The effect of caffeine, which is another smooth-muscle-relaxing agent, is shown in Fig. 7. Intravenous injections were without effect. Local application dilated the spastic vessels, but they contracted again after the caffeine solution was removed. The blood pressure showed some abrupt falls, perhaps due to the irritant effect of the caffeine citrate solution, but there were no peaks which could have caused the swelling of the vessels.

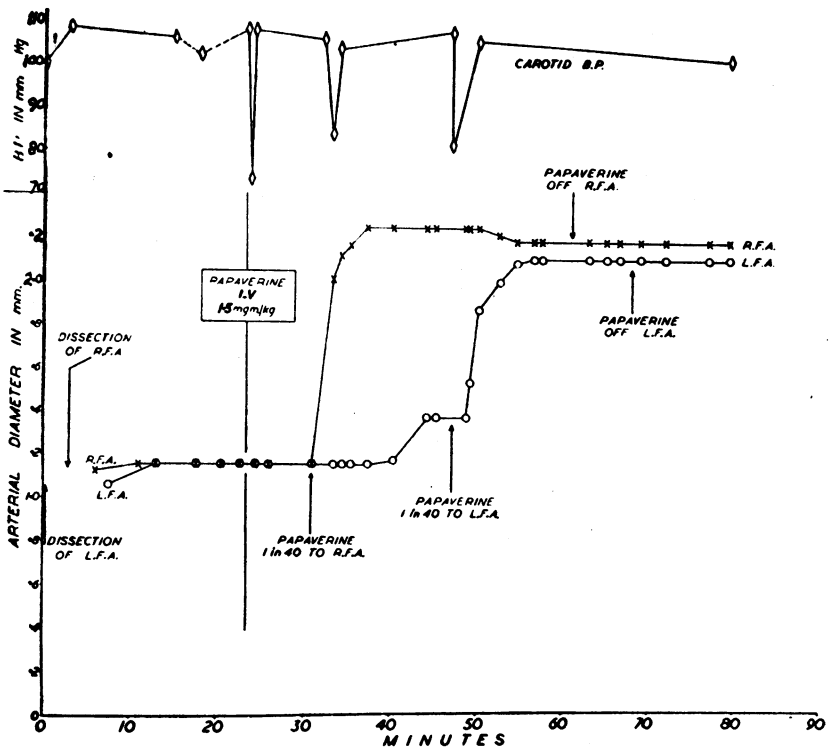

FIG. 6.—Intravenous papaverine, 1.5 mg. per kg., fails to relieve spasm which is subsequently relaxed by direct application of a 2.5% solution of the drug. The vessels remain dilated when the drug is removed. Arteries measured 11 mm. below inguinal ligaments. Rabbits anaesthetized with urethane

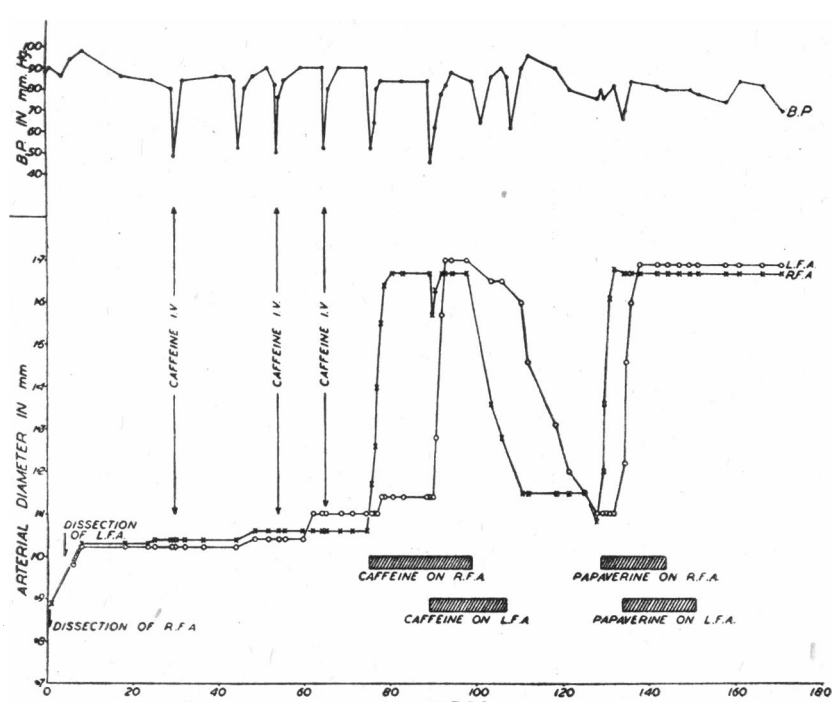

FIG. 7.—Rabbit anaesthetized with urethane. Spastic vessels unaffected by intravenous injections of caffeine citrate, 1.5 mg. per kg. Relaxation produced by direct application of 1% caffeine citrate retrogresses wnen this is replaced by saline. Permanent relaxation by 1% papaverine sulphate Arteries measured 6 mm. below inguinal ligaments.

There have been some clinical reports of relief of spasm by irrigation with warm saline. Fig. 8 shows how repeated irrigation of the wound and spastic artery with saline at 50° C. at intervals produced gradual relaxation over a period of an hour. At the end of this time application of papaverine solution to the control artery on the other side caused a greater relaxation in a few minutes.

The relaxing effect of procaine on arterial spasm is shown in Fig. 9. In this animal there was no contraction of the vessels after the procaine was removed, but in others shrinking was observed. The permanence of the effect of procaine varies.

It was suggested to me by Dr. N. E. Freeman (1949, personal communication) that local application of heparin might be of value in relaxing spasm, as it is considered to have some dilating effects on small vessels as well as its effect on blood coagulation. That this might be so was also suggested by the fact that protamine sulphate, an antagonist of heparin, is known to contract arterioles and had been found in some of our experiments to produce a partial contraction of large arteries. A solution of heparin containing 1,000 units per ml. was therefore applied to the spastic femoral artery of a rabbit, but was found to have no effect upon the diameter. Subsequent application of papaverine produced prompt relaxation. In other animals, when its haemorrhagic effect did not obscure vision, heparin also failed to relieve arterial spasm.

Priscol, which relaxes small vessels, was also found to relax large arteries, as Fig. 10 shows, but the artery contracted again after the drug was removed. Similar results were obtained in other animals. Intravenous injections were without effect.

Another drug which was tried was benzodioxane. This is known for its so-called sympatholytic effects and its use in the diagnosis of phaeochromocytoma. It produced only partial relaxation, which could be completed by replacing the benzodioxane with papaverine. Inhalations of amyl nitrite were also tried. They produced falls in systemic blood pressure, but did not affect the spastic arteries.

Papaverine was the only drug of all those tried which consistently produced relaxation which did not retrogress if the drug was removed. It was used altogether on 31 spastic arteries, all of which it effectively dilated. Procaine and caffeine were the next most successful drugs.

Effect of Papaverine on Wound-healing

The effects of papaverine on living tissues were studied in rabbits before using it in human wounds. The femoral vessels and nerve were exposed, the artery was put in spasm by rough dissection, and the wound was filled with 2.5% papaverine solution. After fifteen minutes the wound was closed, leaving some of the solution inside. A similar operation was done on the opposite side, using saline. The two wounds healed equally, and histological examination, when the animals were killed at intervals of one to eight weeks, showed no difference between the tissues on the two sides. The papaverine solution sometimes turned blood clot in the wound to a brown colour, but this does not appear to have been harmful.

Clinical Application

The results of the many different forms of treatment which have been tried for arterial spasm are reviewed in Table II. The results of conservative operations, such as simple exploration and perhaps bathing the vessel with warm saline or serum, are compared with those of operations in which periarterial stripping or arteriectomy was performed. The cases in which gangrene or muscle contracture followed are classed as failures. These are the results of 59 cases published by various authors in which the diagnosis of traumatic arterial spasm was definite, and in which full details of the end-results were given.

The brachial and femoral were the arteries most often affected. There were most failures in the group in which stripping or arterial excision was done. This difference was particularly marked in the case of the brachial artery. The popliteal artery maintained its sinister reputation, with gangrene in three cases out of seven, even though treated by conservative operation.

Clinical and laboratory experience suggests the following scheme of management:

1. Early exploration of the injured vessel must be performed. It will then

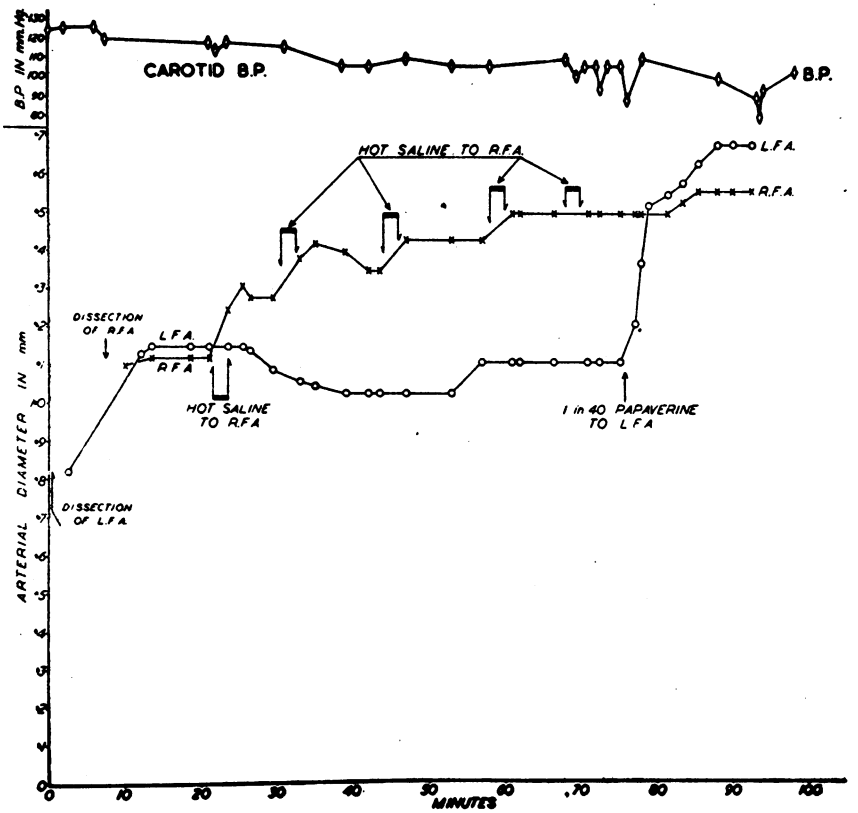

FIG. 8.—Rabbit anaesthetized with urethane. Gradual relaxation of spastic artery by repeated irrigation with hot saline (50° C.), compared with rapid and greater relaxation produced by 1 in 40 papaverine solution. Diameters measured in proximal third of femoral arteries.

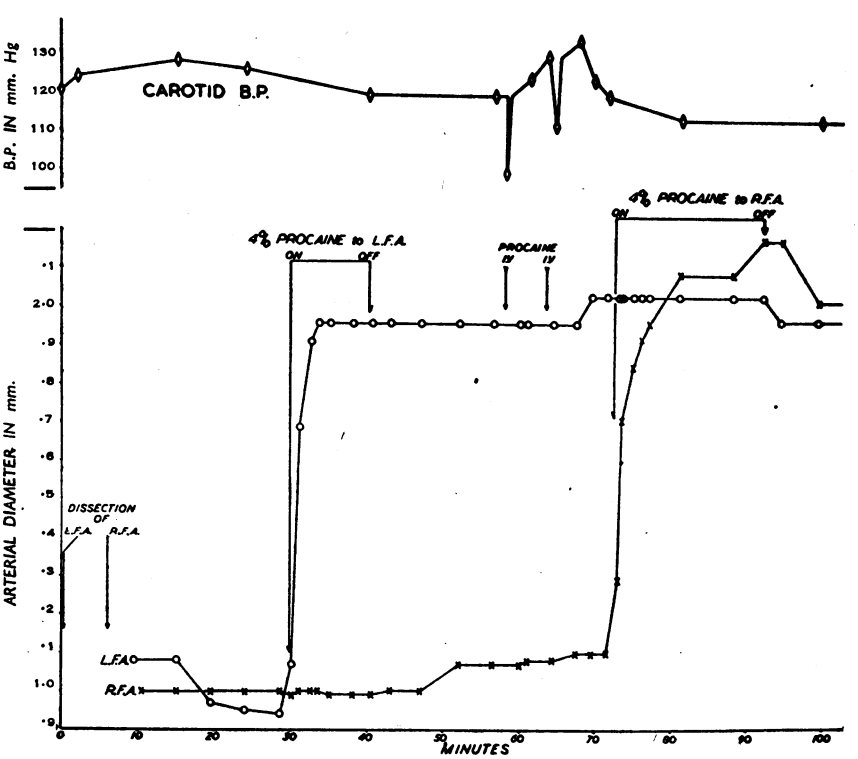

FIG. 9.—Rabbit anaesthetized with urethane. Direct application of 4% procaine solution dilates the left femoral artery, which does not constrict when the drug is washed off with saline. Intravenous procaine, 3 mg. per kg. and 6 mg. per kg., does not affect the right femoral artery, which is subsequently dilated by direct application of the drug. Diameters measured 1 mm. below inguinal ligaments.

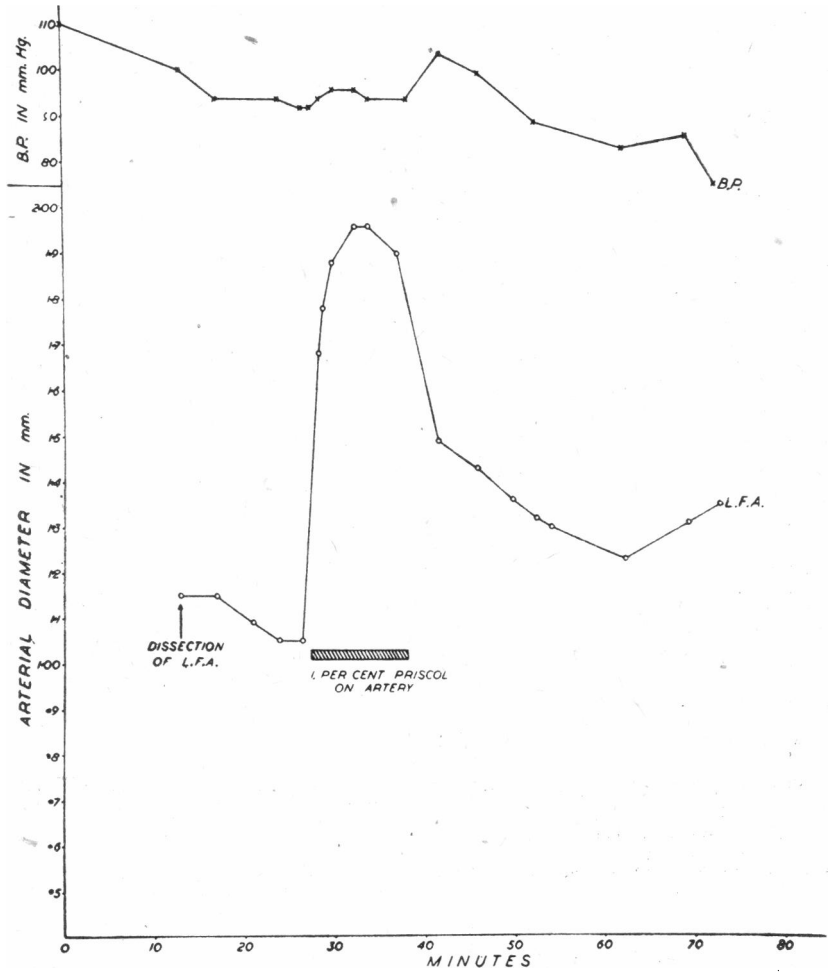

FIG. 10.—Rabbit anaesthetized with urethane. Spasm in left femoral artery is relieved by direct application of priscol, but recurs after the drug is removed. Point of measurement 7 mm. below inguinal ligament.

TABLE II.—*Results in Published Cases of Traumatic Spasm*

	Conservative Operation		Active Intervention (Stripping or Resection)	
	Success	Failure	Success	Failure
Carotid	1	—	—	—
Axillary	2	—	2	—
Brachial	12	—	6	8
Radial	4	—	1	—
Ext. iliac	2	—	—	—
Femoral	7	1	2	1
Popliteal	4	3	—	1
Post. tibial	—	—	2	—
	32	4	13	10

be possible to distinguish between true spasm and compression of the artery by bleeding and swelling under skin and fascia. They require different treatment. Neither will respond to systemic injections of drugs which will never reach the vessel wall.

2. If arterial compression is found it is dealt with in the usual way; blood clot is removed and skin and fascia are incised longitudinally until all constriction is removed and the artery is seen to expand and pulsate satisfactorily.

3. If the artery is in spasm it must be exposed in the same way. It is important to see a normal pulsating length of vessel above the spastic segment. If this is not done quite a short length of spasm remaining at the proximal end may prevent relaxed vessel below from filling with blood or dilating.

4. The artery is covered by a warm 2.5% solution of papaverine sulphate and left for a few minutes.

5. Should relaxation not occur within 10 to 15 minutes the wound is loosely closed, leaving a fine polythene tube down to the vessel for instillation of 1% papaverine at intervals until the circulation is restored.

6. It is important to treat shock and to restore a normal blood pressure on general grounds, and because spastic vessels will not dilate if the blood pressure is low.

This regime has been tried in two patients with arterial spasm occurring during operation. In both cases papaverine caused prompt relaxation.

Summary

Arterial contraction due to a supposed nervous reflex arc was explained by shrinkage due to falling systemic blood pressure. The diameter of large arteries changed with alterations in blood pressure produced by different means. Attempts to produce contraction of large arteries by electric stimulation of the efferent components of possible reflex arcs were unsuccessful.

Direct mechanical trauma applied to the vessel wall in various ways produced lasting spasm which could not be relieved by sympathectomy.

Attempts to relieve established traumatic spasm were therefore directed at paralysing smooth muscle itself rather than sympathetic nerves.

Smooth-muscle-relaxing drugs were successful in relaxing spasm when applied direct to the vessel. Intravenous injections were ineffective.

Papaverine was the most consistently successful in producing permanent relaxation. It was not injurious to living tissues.

I gladly acknowledge my debt to many people who have helped with this work: Dr. F. A. Simeone, with whom much of the fundamental part of the work was done at Harvard; Professor G. Perkins, at St. Thomas's, and Professor Sir James Paterson Ross, at St. Bartholomew's, in whose departments it was continued; Dr. G. Cunningham for his help with the microscopical histology; Mr. G. J. Hadfield, who helped with many of the operations; and Mr. F. Scholefield and Miss D. Gay for technical assistance.

REFERENCES

Barnes, J. M., and Trueta, J. (1942). *Brit. J. Surg.*, **30**, 74.
Cohen, S. M. (1940). *Guy's Hosp. Rep.*, **90**, 201.
Grant, R. T. (1930). *Heart*, **15**, 257.
Griffiths, D. Ll. (1940). *Brit. J. Surg.*, **28**, 239.
Hunter, J. (1835). *Works of John Hunter*, edited by J. F. Palmer, **1**, 538; **3**, 157, 158. London.
Kinmonth, J. B., and Simeone, F. A. (1952). *Brit. J. Surg.* In press.
—— —— and Perlow, V. (1949). *Surgery*, **26**, 452.
Trueta, J., Barclay, A. E., Daniel, P. M., Franklin, K. J., and Prichard, M. M. L. (1947). *Studies of the Renal Circulation*. Blackwell Scientific Publications, Oxford.

The Society for the Study of Fertility was founded three years ago with the intention of having a yearly congress for the reading of papers and free discussion of problems of fertility and infertility, not only in the human subject but in livestock and laboratory animals. The secretary is Dr. G. I. M. Swyer, University College Hospital, W.C.1.