Experimental and Clinical Study of the Development of Spasm of the Cerebral Arteries Related to Subarachnoid Hemorrhage

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One of the most severe complications of the rupture of aneurysms is the resultant spasm of cerebral arteries leading to ischemia, edema, and infarction of large areas of the brain, including some remote from the rupture. It may be postulated that the leading role in the development of the arterial spasm is played by the subarachnoid hemorrhage inevitably accompanying the rupture of an aneurysm. That is why the problem of arterial spasm is so important in surgery of arterial aneurysms of the brain. Nevertheless, our knowledge of the origin and control of arterial spasm is amazingly limited.

The complexity of the problem is aggravated by the fact that its manifestations in individual patients against the uniform background of a subarachnoid hemorrhage vary greatly. Angiographic examinations prove that the arterial spasm may develop immediately after rupture of an aneurysm, as well as several days later. The spasm is usually limited to the main artery on which the aneurysm developed, but it may also spread over the arterial tree, and even to other arteries of the circle of Willis or the contralateral hemisphere. Moreover, after a hemorrhage the arteries surrounded by blood are not always spastic, while spasm may be noted in arteries not surrounded by blood. Finally, the spread and severity of arterial spasm are also not directly dependent on the extent of the hemorrhage or the size, shape, or site of the arterial aneurysm.

The spasm may last several hours or disappear several minutes after intra-arterial injection of various antispasmodic drugs; it may also persist for many days or even weeks. A sequence of factors often underlies the variations in development, intensity, extent, and duration of the arterial spasm both after surgery and after angiography. These factors include reactions peculiar to the individual such as those of the vascular system, and the patient's age and general state of health.

The following three cases were followed both in the acute and late periods (after surgery and after angiography without operation); they illustrate several of these factors rather convincingly.

Case Reports
Case 1. This 30-year-old woman complained of reduction of vision, especially in the left eye, of 2 years' duration. The patient showed a chiasmal syndrome with predominant damage to the left optic nerve plus hyperactive tendon reflexes in the right arm. Pneumocisternography showed caudal displacement of the chiasmal cistern. Carotid angiography showed leftward displacement of the supraclinoid section of the left internal carotid artery, and sharp narrowing of the lumen of the A-1 section of the left anterior cerebral artery (Fig. 1 left). The diagnosis of a tumor of the tuberculum sellae with direct pressure on the left optic nerve and left internal carotid was verified at operation and total extirpation was accomplished.

Angiography performed 6 days postoperatively revealed a considerable narrowing of the supraclinoid part of the left internal carotid artery (Fig. 1 center). The neurological status, however, showed only a slight increase in the severity of the general cerebral symptoms. Angiography repeated 2 months postoperatively demonstrated almost complete disappearance of the spasm of the internal carotid artery (Fig. 1 right).

Case 2. This 36-year-old man with recognized primary hypertension suffered a sub-
arachnoid hemorrhage without loss of consciousness 3 months prior to admission to the Institute; a paralysis of the third left nerve developed soon after the hemorrhage. There was paralysis of the third left nerve, reduction of the left corneal reflex, weakness of the seventh nerve, and slight predominance of the right tendon reflexes. Carotid angiography demonstrated an aneurysm of the supraclinoid part of the left internal carotid artery with good collateral flow via the anterior communicating artery. The aneurysm was isolated by clipping its neck. Bleeding from the temporopolaris vein was controlled by clipping the venous ostium and applying a piece of muscle.

Mild speech disturbances developed after the operation, and right pyramidal signs increased. By the 7th postoperative day the state of the patient had become still worse, with general cerebral symptoms and increasing pyramidal signs and aphasia. Angiog-
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Fig. 3. Case 3. Carotid angiography. Anteroposterior (left) and lateral (right) views show no contrast medium in supraclinoidal part of the internal carotid artery.

angiography performed immediately after the operation had not revealed any vascular alterations (Fig. 2 left) but 7 days later showed a sharp narrowing of the lumen of the supraclinoid part of the left internal carotid artery and slowing of the blood flow in the distribution of this artery (Fig. 2 center). Angiography 16 days postoperatively showed that the spasm had disappeared and the flow had improved (Fig. 2 right). Speech disturbances and pyramidal symptoms had also improved considerably by this time, and had completely disappeared by the time of discharge on the 23rd postoperative day.

Case 3. This patient had a suspected tumor of the right parieto-temporal region. Right carotid angiography was performed, and in the initial series of angiograms, both the anteroposterior and lateral projections showed that the contrast medium had failed to opacify the supraclinoid part of the internal carotid artery (Fig. 3). Repeated angiography undertaken because of a suspected stop-phenomenon produced the same pattern.

Intra-arterial administration of Nospan immediately released the spasm as demonstrated angiographically (Fig. 4).

Fig. 4. Case 3. Later carotid angiography after intra-arterial administration of Nospan. Anteroposterior (left) and lateral (right) views show the spasm has disappeared and the contrast medium has opacified the whole carotid artery tree.
Experimental Study in the Dog

These seemingly contradictory observations are well known to neurosurgeons both from operative and angiographic experiences with cerebral arterial spasm.\(^1\)\(^2\)\(^3\)\(^4\)\(^5\)\(^6\)\(^7\)\(^8\)\(^9\)\(^10\)\(^11\)\(^12\)\(^13\)\(^14\)\(^15\)\(^16\) In an attempt to study experimentally some aspects of the pathogenesis of spasm of the cerebral arteries, we undertook an investigation in the dog based on new concepts of the structure of the leptomeninges and the interrelations of this structure with the vascular and CSF systems of the brain.

Mechanism for Spread of Blood from a Ruptured Aneurysm. It is well known that the circle of Willis and the proximal parts of the arteries arising from it, where aneurysms develop most frequently, are located in the basal cisterns of the brain. As the anterior, middle, and posterior cerebral arteries leave the cisterns, they do not penetrate the cistern wall as is usually supposed. Instead they are surrounded by cisternal extensions having the shape of thick tubes. These tubes prolong the cisterns by becoming the roots of a system of channels. The largest channels surround the main arteries and lie in the depth of the fissures. Branching tubes of various calibers rise onto the gyri with the arterial branches.\(^4\)\(^6\) In other words, the arteries arising from the circle of Willis, their branches, and what is most important, the anastomoses between the anterior, middle, and posterior cerebral arteries found in the nearby circulation,\(^14\) are located in the lumen of these channel extrusions of the subarachnoid space. Beyond the limits of the channels there are only comparatively small branches, and these are invaginated into the pia mater and brain substance. The position of the arteries within the channel lumen is stabilized by special chordae, one end of which is fixed to the channel wall, and the other penetrates the arterial adventitia. The fluid washing the arterial adventitia flows along these channels. In this movement of the fluid along the channels, two components can be distinguished: first, a very slow “circulation” of the fluid in one direction along the channels from the basal cisterns to the arachnoidea, where the fluid outflow takes place; and second, a much more intensive “oscillatory movement” of the fluid that mixes the fluid of the channels with that of the cisterns. Due to its intensity, the oscillatory movement is superimposed on the slow circulation of the fluid. These morphological and functional factors obviously must play an important role in the spread of any blood that has penetrated into the subarachnoid space.

Experiment 1: Injection of Autogenic Red Cells Washed Free of Plasma into Cisterna Magna. Two to 8 cc of autogenic red cells washed free of plasma were injected into the cisterna magna of dogs while simultaneous observations of the surface of the hemispheres were made with a stereoscopic microscope. It was found that the red cells appeared first in the large channels of the Sylvian and ectoSylvian fissures, and later spread over the whole observable network of channels. When a small quantity of red cells was injected, they mixed with the cerebrospinal fluid, and a movement of separate red cells suspended in the fluid was observed. When a considerable quantity of red cells was injected, a large part of the fluid was promptly driven out of the system of channels due to the sharply increased pressure in the subarachnoid space, and was replaced by the spreading mass of red cells. At the beginning of the experiment, the movement of the red cells was in one direction. Later on, in connection with the equilibration of the pressure in the subarachnoid space, the uniform movement was reduced and replaced by oscillatory movements of the red cells, which were now moving alternately in opposite directions.

Experiment 2: Injection of Autogenous Whole Blood into Cisterna Magna. In another series of experiments, autogenous whole blood was injected into the cisterna magna. The preliminary investigation in vitro demonstrated that the blood coagulated in the cerebrospinal fluid, but clots of varying densities were formed depending on the ratio of the two ingredients. With small volumes of blood, loose clots were formed that absorbed only a negligible part of the red cells, while with large volumes of blood, dense clots were formed that absorbed the majority of the red cells. Thus, when 1 to 2 cc of blood were injected into the cisterna magna, a movement of free red cells was ob-
served in the channels of the hemispheres, and only rarely was the formation of separate loose clots seen on the walls of the channels. During the oscillations of the fluid, these clots were rapidly washed free of the red cells and appeared as a whitish network that finally sedimented into the fluid.

When 8 cc of blood were injected into the cisterna magna, the blood was seen to spread throughout the channels, ejecting its usual fluid. In 1 to 2 minutes, the blood coagulated in the channels, forming dense clots saturated with red cells. Isolated clots blocked the lumen of the channels at separate points, while continuous ones filled large sections of the channels.

At autopsy, similar clots were found in basal cisterns where they were obstructing the branching channels. The important point is that in all such cases dense clots interrupted communication between the cisterns and the channels, and this produced a cessation of fluid flow in the channels.

Experiment 3: Hemorrhage of Vessels of the Cisterna Magna. In the final series of experiments, we deliberately injured the vessels of the cisterna magna with a needle so as to imitate the natural conditions of a subarachnoid hemorrhage. Depending on the volume of blood drained into the channels, the same changes were observed on the cortical surface as were seen in the experiment involving injections of autogenous whole blood into the cisterna magna (Experiment 2). All of the phenomena noted in Experiments 1 and 2 were observed, beginning with the free movement of the red cells suspended in the channel fluid and ending with the formation of dense blood clots surrounding the artery that fully interrupted the communication of the channels with the basal cisterns.

Results

Comparison of Experimental and Clinical Data. The data of this experimental investigation of subarachnoid hemorrhages were compared with human autopsy material from cases in which there had been surgical intervention on the basal arteries of the brain or on arterial aneurysms with subarachnoid hemorrhages. Comparison proved that in man, as well as in dogs, the channels described are the main pathways for distribution of blood drained into the subarachnoidal space (Fig. 5).

Thus, we assume that in cases of spontaneous rupture of aneurysms the blood fills the corresponding cisterns and streams into the branching channels, literally flooding

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Fig. 5. Schematic drawing from human autopsy specimen showing blood clots in periarterial channels of the hemispheric convexity.
along the rich arterial tree. This correlates with observations made at the operating table indicating that any bleeding from a more or less large arterial trunk immediately spreads over a large area. As a result, even in areas of the brain rather distant from the ruptured aneurysm, the arteries are often surrounded with blood. This blood may be mixed with the cerebrospinal fluid, or may almost completely substitute for it. If the blood elements are suspended in the fluid, the blood remains liquid, and the communication of the channels with the basal cisterns is not disturbed. If the blood coagulates in the channels, the clots obstruct the channels and separate them from the basal cisterns.

*Direct Contact of Hemorrhagic Blood with the Arterial Adventitia.* Hemorrhage from a ruptured aneurysm is practically a “bleeding into the system of channels.” This results in an unusual pathological situation that is highly specific for cerebral arteries, for the blood comes into contact with the total widespread surface of adventitia of the main arterial branches. By comparison, in injuries to the peripheral arteries of the body located in dense layers of connective tissue, this external washing of the arteries with blood does not occur.

The adventitia of brain arteries is known to be rich in nerve elements. It contains two nerve plexuses, ganglion cells, and various forms of receptors.15,18,19 How deeply these nerve elements were imbedded in the adventitia, however, has remained obscure up to the present time. Since microtome sections proved inadequate for the solution of this problem, we obtained pellicle preparations of the adventitia with its nerve elements by impregnation after the methods of Campós7 or Gross-Bilshovsky-Lavrentjev.30 These preparations revealed the endothelial sheath of the artery covering the adventitia, and easily distinguished the nuclei concentrated in typical groups. By focusing the oil immersion lens on these endothelial nuclei, it became clear that the nerve fibers and receptors were in the same layer. In other words, the nerve elements are located not only in the depths, but also on the very surface of the adventitia. Only a thin endothelial membrane a few microns thick separated the nerve elements from the cerebrospinal fluid (or blood) in the lumen of the channels.

One more fact is essential; there is a rich network of vasa vasorum, also located on the surface of the adventitia under the endothelial sheath, as seen on the film preparations of the adventitia. The branches arising from these vasa vasorum penetrate into the muscle layer of the artery, where the capillary network develops.

Hence, the intimate contact between hemorrhagic blood in the channels and the arterial adventitia may result in a direct effect upon the nerve elements located on the surface of the adventitia. Some blood components may even penetrate into the vasa vasorum also located on the surface, and by way of these vessels reach the muscular elements of the arterial wall and thus stimulate constriction in a manner comparable to that of physiological mediators penetrating the muscular layer of the artery.

*The Significance of Mechanical and Chemical Factors of Hemorrhagic Blood in the Pathogenesis of the Spasm of Cerebral Arteries.* The data of many authors make it evident that spasm of cerebral arteries in cases of ruptures of aneurysms is caused by both mechanical and chemical factors.10,17,20,23

The basis of a mechanical irritation is formed by the rupture of an arterial wall in the area of an aneurysm and the release of a jet of blood directed from the artery into the basal cisterns and the connecting channels under a pressure significantly higher than that of the cerebrospinal fluid. Large quantities of blood may cause deformations and displacements of the arteries in these channel spaces. However, this in itself does not cause the spasm. The spasm develops as a result of a mechanical irritation of the nerve elements located on the surface of the adventitia. This irritation may be caused by the direct hemodynamic action of the blood jet. However, indirect irritation of the adventitial nerve elements via connective tissue chordae that stabilize the position of the artery in the channel deserves special consideration. The blood spreading through the channels strikes the chordae crossing the lumens of the channels. The chordae are strained, and may even rupture in cases of extreme filling and dilatation of the channels with blood. Since the chordae merge with the arterial adventitia and come into intimate contact with its
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nerve elements, the strain or rupture of the chordae causes an intense mechanical irritation of the nervous elements of the arterial wall.

The chemical irritation causing the arterial spasm is effected by the action of highly active substances released in the process of blood coagulation. It should be mentioned that until recently the problem of blood coagulation in the cerebrospinal fluid remained obscure. Even such outstanding neurosurgeons as Polenov, Rowbotham, and Walton believed that blood does not coagulate in the cerebrospinal fluid and no clots are formed in it. We have demonstrated that this conviction is no longer justified. In normal humans and dogs, blood coagulates in cerebrospinal fluid in dilutions as low as 1:100. This was observed in in vitro experiments, and in dogs in vivo in the experiments already described when autogenic blood was injected into the cisterna magna. Thus there is no doubt about the formation of blood clots in the cisterns and channels in cases of subarachnoidal hemorrhages. It is known, that in the process of coagulation the decaying platelets release serotonin (5-hydroxytryptamine) and other potent vasoconstrictors. In experiments in rats, Zucker observed spasm of the mesenteric arteries under the effect of serotonin released during blood coagulation, while Raynor, et al., produced spasm of the cerebral arteries in cats by dripping a serotonin solution onto the surface of the hemispheres. It is clear that blood clots may be the source of chemical stimulation of spasm of cerebral arteries.

In our experiments with injection of suspensions of washed red cells into the cisterna magna, we noticed no arterial spasm. Neither was there spasm after injecting washed red cells through a thin needle directly into the channels. On the contrary, in experiments with autogenous whole blood injected into the cisterns or directly into the channels, arterial spasm was observed in several cases near a blood clot in the lumen of the channel. Within 10 to 20 minutes after the formation of such a clot, a distinct local arterial spasm developed in the form of a purse string or hourglass. Some time later the spasm spread in both directions and beyond the clot. Such spasms persisted for 2 to 3 hours of observation.

We must assume that direct contact of the blood clot with the arterial adventitia is not at all necessary for the development of an arterial spasm. If the serotonin washed by the spinal fluid from the clot spreads through the channels in sufficient concentration, it may cause an arterial spasm distant from the clot. In our experiments, we injected 0.05 cc of a pure serotonin solution (1:1,000 to 1:100,000) through a needle directly into the channels; spasm developed almost instantaneously, and immediately occluded whole arterial trees (Fig. 6). In some experiments we observed a simultaneous blanching of the hemispheres in the zone served by the channels injected.

Discussion

The extremely different, often paradoxical manifestations of arterial spasm in various patients have already been mentioned. Spasm may develop immediately after the rupture of an aneurysm, or after longer intervals, such as 6 days after the operation in one of our cases. Brawley, et al., on the basis of experimental investigations, emphasize the two-phase character of the spasm, a short initial and a prolonged late phase. The same point of view has been expressed by Podgornaja, et al., in their clinical observations.

The delayed development of spasm in cases where a recurrent subarachnoid hemorrhage is definitely excluded may be conditioned by retention of serotonin during the impairment of fluid flow along the channels. In this connection the data of Zucker and Borrelli deserve attention, since they dem-

![Fig. 6. Arterial spasm on canine hemisphere convexity induced by injecting serotonin solution directly into the channels. Left: Before injection. Right: After serotonin injection.](image-url)
Proven that in the process of blood coagulation only half of the serotonin absorbed by the platelets is released during their decay. The other half of the serotonin is released during several succeeding days. It means that decaying platelets release serotonin continuously and thus support the arterial spasm for a long time.

Strangely enough, the investigations of spasm in cerebral arteries do not adequately account for the fact that, along with the release of serotonin, blood coagulation may result in impairment of spinal fluid flow. According to our data, injection of autogenous whole blood into the fluid causes the formation of dense blood clots obstructing the channels arising from the cistern. This excludes the possibility that products of hemorrhagic blood decay concentrated in the basal cisterns might penetrate into the channels. Under such conditions, serotonin and other highly active vasoconstrictors produced by blood decay do not spread along the channels from the sites of their formation. However, our experiments in dogs showed that 3 to 4 days after blood coagulation the initially continuous clots fall into small retracting parts with intervals appearing between them. At the same time fluid flow is restored along the channels, as proved by the rhythmic oscillations of the red cells suspended in the fluid of the channels. This results in a new situation providing for the delayed spread of serotonin and similar vasoactive products of decay (including the products of fibrinolysis of clots) with the flow of spinal fluid from the cisterns into the channels. It is now evident that blood contains, in addition to serotonin, other components that cause the arterial spasm. This was convincingly shown in the papers of Kapp, et al. They separated a polypeptid from blood capable of causing very active spasm of an artery. We have blocked serotonin-reactive structures of cerebral arteries with an antagonist of serotonin, tipendol (β-dimethylaminoethyl ester 1,3,4,5-tetrahydrothiopyrano (4,3-b)-indol-8-carbonic acid). This experimental model also convinced us of the presence of other active vasoconstrictive components in whole blood. We have made these studies the subject of another report.

It should be stressed that, independent of the moment of spasm onset, the local mechanical and chemical factors of the drained blood are aided by vasomotor reflexes that primarily provide for spread of the spasm over large sections of the arteries. Evidently it is these reflexes that explain the development of a spasm in arteries not surrounded by blood.

In conclusion, it should be noted that all the facts mentioned simply clarify separate links in the pathogenic chain of the spasm of cerebral arteries. The problem as a whole, however, is still far from solved.

**Summary**

In canine experiments utilizing operating microscopy of the hemispheres, and in human autopsy material, we have studied the mechanism for distribution of hemorrhagic blood into the basal cisterns of the brain and hence along the connecting system of channels surrounding blood vessels. Through these channels, the blood and spinal fluid directly bathe the adventitia of the arteries, located, as a rule, in the lumen of the channel.

The strain and rupture of the chordae suspending the arteries with the lumen of the channels, as well as the superficially located nerve elements in the arterial adventitia, play an important role in the pathogenesis of arterial spasm following the rupture of an aneurysm.

Washed autogenic red cells produced no vasospasm. Arterial spasm was produced experimentally in cases where there was blood clot formation in the blood and CSF mixture within the lumen of the channels, or by injection of serotonin into these channels.

**References**

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