CONTRAST MEDIUM INJURY TO THE SPINAL CORD PRODUCED BY AORTOGRAPHY

PATHOLOGIC ANATOMY OF THE EXPERIMENTAL LESION*

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The acute pathologic changes in the central nervous system produced by intracarotid injection of toxic doses of contrast media in experimental animals are well known. The mildest lesion consists of a transient breakdown of the blood-brain barrier, demonstrable only by the use of dye indicator technics, and unaccompanied by other structural changes. Reactions of greater severity are manifested by edema, vasodilatation and stasis, and by punctate hemorrhages. Anatomic evidence of neuronal damage has been sparse, only a single experimental study reporting a significant structural change. This effect, seen in acute experiments productive of severe disturbances in cerebral electrical activity and of the toxic manifestations listed above, consisted of an advanced hydropic cytoplasmic degeneration of neurones. Other than this report, there is no evidence from experimental studies to suggest that the contrast media are capable of producing an irreversible neuronal lesion.

Beyond the immediate and acute pathologic changes resulting from contrast medium injury in animals, virtually nothing is known. The reported experimental studies have made no attempt to follow the complete evolution of the lesion, or even to allow sufficient time for the necrobiotic and reactive changes secondary to irreversible tissue injury to appear. That negative results have been obtained in chronic studies merely indicates that an irreversible lesion was not produced in such experiments. The scarcity of chronic studies may reside in part in the general focusing of interest upon the initial stages of the reaction, and in part in the inability of the severely brain-injured animals to survive beyond the acute phase of the injury. Recently, however, a method has been developed for the production of a central nervous system injury by contrast media allowing extended survival of the injured animals and providing an opportunity for the functional and anatomic study of all temporal phases of the contrast medium lesion. The anatomic features of the cord injuries are described in the present report.

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These have been reported by us elsewhere, but it is necessary to summarize them in detail here.

The method of injury consisted of the rapid intra-aortic injection of 7 to 20 cc. (approximately 1 cc. per kg.) of a contrast medium into dogs. Except for a few studies made with 70 per cent Diodrast® (diethanolamine salt of 3,5-diiodo-4-pyridone-N-acetic acid) the contrast medium used was 70 per cent Urokon sodium® (8-acetyl-amino-2,4-6-triiodo sodium benzoate).* The injections were made at one of three levels: just below the renal arteries, above the superior mesenteric artery, or in the mid-thoracic aorta. An 18-gauge needle was used, pointing obliquely cephalad, and the injection was given over a 5 to 10 sec. period. In all injections, the animal was anesthetized with Nembutal and the aorta was surgically exposed. In the mid-thoracic injection, the animals were positioned on their right side; otherwise they were in a supine position. A total of 41 dogs was used in these experiments; the animals were sacrificed at periods varying from 5 hours through 27 days following the injection.

At the conclusion of each study, the animal was sacrificed by an overdose of Nembutal, and the vertebral column was removed. The entire cord was exposed by a dorsal laminectomy and fixed in situ for a few hours in isotonic neutral formalin, following which it was removed and fixation was completed with the cord suspended in a 5000 cc. cylinder. Most of the cords were sectioned transversely at 0.3 to 0.5 cm. intervals, but a few cords were sectioned longitudinally in a horizontal plane. The gross features of the lesions were recorded and in some instances photographed. Sections at 1.5 cm. intervals from the caudal 15 cm. of cord and from other levels with grossly recognizable lesions, and at 5 cm. intervals from the remainder of the cord were chosen for microscopic study. The materials were embedded in paraffin and sectioned at 6 microns. The sections were routinely stained with hematoxylin-eosin and with a modification of the Klüver-Barrera stain developed in our laboratory. This method, which allowed a study of the cell picture, the myelin sheath pattern, and the vascular bed in a single preparation, consisted of Luxol fast blue MBS (du Pont) followed by the periodic acid-Schiff reaction and a hematoxylin nuclear stain.

As a correlative study the acute phases of the cord injury were compared with lesions encountered in a previous study evaluating certain contrast media used for cerebral angiography and observed only in their early stages of development. The cerebral lesions had been produced by the following agents: Diodrast 35, 50, and 70 per cent; Neo-iopax® (3,5-diiodo-4-pyridoxal-N-methyl-2,6-carboxylic acid) 37.5 per cent; N-methyl nicotinamide hydrochloride 20 per cent, a normal body metabolite approaching the chemical structure of these agents; Urokon 30 per cent at pH 5.4 and 7.0; its non-iodinated homologue, 3 acetylaminobenzoic acid 20 per cent at pH 7.4; and the benzene derivative para-aminohippurate 20 per cent.

During these studies it was soon evident that anatomic features such as the blood supply of the spinal cord and its caudal position were of prime importance in determining the site and severity of the contrast medium lesion. Accordingly, a special study of these relationships was made in 14

* Kindly furnished by Mallinckrodt Chemical Works, St. Louis, Missouri.
of the dogs. The aorta was left attached to the vertebral column when it was removed, and the approximate level of injection was indicated by an India ink marker on the exposed dura mater. Following this, the arterial circulation was plotted under a dissecting microscope, with particular attention directed toward the distribution and relative size of the radicular arteries. The blood supply was found to be essentially similar to that of the human cord, with a relatively rich lumbosacral and cervical radicular supply and a poorer thoracic supply. It was also observed that the canine cord extended to the level of the 7th lumbar vertebra. Thus, a long stretch of the cord richly vascularized by short dorsal branches of the abdominal aorta was maximally exposed to the contrast medium. This exposure was graphically demonstrated by roentgenological studies made in selected animals, recording the position of the needle and the flow and distribution of the contrast medium during the terminal portion of the injection. The single roentgen-ray exposure made at the terminal phase of the injection showed only rarely the flow of the contrast medium into the spinal cord circulation. However, it did provide an adequate picture of the distribution of the injected material, particularly a retrograde flow extending rostrally the distance of one or two vertebral bodies, and a filling of the dorsal branches of the aorta. Examples of these studies correlating the level of the injection and the initial flow of the contrast medium with the blood supply and the site of the lesion may be found in our other communication. These topographic features are so intimately related to a consideration of the pathologic anatomy of the contrast medium lesion that they will be presented in detail below.

The modifying effects upon the lesion of variations in the amount and type of the contrast media and in the level of injection have been presented by us in detail elsewhere. The effects may be summarized as follows: Urokon was more toxic than Diodrast. A halving of the dose did not significantly modify the severity of the reaction. And with high thoracic injections, the site of injury was sometimes centered in the thoracic cord rather than in the terminal portion; the cord lesions tended to be less severe, and in some specimens the injury involved the thoracic white matter more than the gray matter.

While this work was in progress, another report appeared of experimental contrast medium injury to the spinal cord. This was an acute study in rabbits with the anatomic aspects limited to tests for a disturbance of the blood-brain barrier. One conclusion of interest drawn from this study was that an injection with the animal in the supine position favored dorsal filling and, hence, increased the chances of cord injury. This differential flow was explained on the basis of the specific gravity of the contrast medium being higher than that of blood. Accordingly, 6 animals were injected while in the prone position, with no paralyzing effects being encountered. These animals were not subjected to histologic studies.

A detailed description of the spinal cord lesion produced in our studies follows.
THE CONTRAST MEDIUM LESION

The functional effect of the contrast medium injection was expressed in the following characteristic manner: During the injection, a pronounced extensor rigor occurred, sometimes persisting as long as a minute. This reaction, considered to be comparable to the seizure discharges observed in experimental cerebral angiography, was succeeded by a state of hyperirritability of a few minutes' duration. These spinal convulsions invariably augured the development of a severe paraplegia, often with a pronounced spastic component, which was evident in the lower legs and back upon recovery of the animal from the anesthetic. The characteristic anatomic effect produced by the injection consisted essentially of a destruction of the gray matter of the lower portion of the spinal cord. The resultant lesions were classified according to an arbitrary system separating the injuries into clearly defined categories of progressive severity, designated as follows:

+ Sparsely scattered microscopic foci of destruction, affecting gray or white matter, present in one or more sections of spinal cord.
++ Multiple small (1-2 mm.) scattered foci of destruction of gray matter, with or without involvement of white matter or spinal nerve roots, distributed over 3 to 5 cm. of spinal cord.
+++ Massive focal discrete or confluent zones of destruction of gray matter with or without involvement of white matter or spinal nerve roots, extending over 5 to 10 cm. of spinal cord.
++++ Hemidestruction to complete devastation of gray matter, frequently extending deeply into the white matter and spinal nerve roots, involving from 10 to 18 cm. of spinal cord.

In 36 of the 41 animals tested there were cord lesions graded as follows:

+ ............ 5
++ ............ 9
+++ ............ 8
++++ ............ 14

In the description to follow, attention will be focused on injuries of the two most advanced grades.

The initial phases of the contrast medium injury were studied in 4 dogs, sacrificed 5 to 10 hours after the injection. The early stages of the injury were manifest in two forms. One of these was a massive hemorrhagic necrosis, rather sharply limited to the gray matter (Fig. 1A) observed in a dog sacrificed 10 hours following the injection. The terminal 10 cm. of cord was involved by this reaction. The parenchyma within and bordering the hemorrhage was strikingly edematous, and far advanced cytolytic changes had affected the neurones. The second type of early change was unattended by significant hemorrhage, and appeared as a profound edema. This change was observed in 2 dogs, sacrificed at 5 and 6 hours after the injection. In one, the alteration was so severe that the gross topographical features of
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Fig. 1. (A) Lumbosacral segments of spinal cord 10 hours following Urokon injury. Massive hemorrhagic necrosis.

(B) Lumbosacral segments of spinal cord 6 days following Urokon injury. Early myelomalacic changes are confined essentially to gray matter. See Fig. 2B for microscopic appearance.

the sectioned cord were obscured over the caudal 15 cm. In microscopic preparations, a selective involvement of gray matter and a sparing of white matter were clearly demonstrated (Fig. 2A). Virtually all the neurones in the edematous zone had undergone a severe hydropic degeneration. The Nissl substance was lysed and the cytoplasm was honeycombed with vacuoles (Fig. 3A). The nuclei were less severely affected by karyolytic changes. Oligodendroglia exhibited a balloon-like swelling. At this stage the myelin network, even in the most severely involved areas, remained unaffected. The basement membrane of capillaries was still intact, but the small vessels of the cord were strikingly bloodless. No thrombotic features were observed, and larger vessels were not structurally altered. These early lesions were comparable to the most advanced changes produced by the various agents used in the previous contrast medium study. Both of these sets of lesions presented a gross edema, severe hemorrhagic manifestations, and an advanced degree of cytolytic change in neurones, featured by hydropic degeneration and chromatolysis.
The continued development of the contrast medium injury was observed in 32 animals sacrificed at periods of 2 to 27 days following the injections. One animal studied at 2 days showed an extensive advanced edema and cytolyis. In a dog sacrificed on the 4th day, the cord was involved by a hemorrhagic necrosis which wiped out the gray matter of the caudal 13 cm. (Fig. 6B).

Fig. 2. (A) Lumbar cord 5 hours following Urokon injury. There is advanced edema involving entire gray substance and sparing white matter. Details of this lesion are shown in Fig. 3A. The normal density of gray matter may be seen in the right half of the cord in Fig. 4B. Modified Klüver-Barrera stain.

(B) Sacral cord 6 days following Urokon injury. Myelomalacia affects virtually all of gray matter; scattered degenerative changes are present in white matter. Modified Klüver-Barrera stain.
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Fig. 3. (A) Gray matter 5 hours following Urokon injury. Note advanced cytolytic changes with hydropic degeneration of anterior horn cells and interstitial edema. The fiber network and capillary bed (arrows) appear structurally intact at this stage. For a colored plate of this figure see Fig. 5 of Margolis and Pickett. Modified Klüver-Barrera stain, ×319.

(B) Main trunk of anterior sulcal artery just beyond point of entrance into spinal cord. Fibrinoid necrosis and secondary thrombus formation, 6 days following Urokon injury. Hematoxylin-eosin stain, ×219.
Virtually all the white matter in the segment of cord infiltrated by hemorrhage was bloodless and necrotic. In the remainder of the animals, studied at 6 days or longer following the injections, progressive disintegrative changes with resorption of the necrotic material and cavity formation constituted the outstanding features. As early as 6 days, the injured regions of the cord had become softened and spongy. The distribution of these changes, with the lesion being confined at a gross level to gray matter (Fig. 1B) was remarkably similar to the topography of the lesions studied at earlier stages.

Fig. 4. (A) Lumbar cord 14 days following Urokon injury. Massive bilateral myelomalacia destroying all of gray matter and extensively involving white matter. Modified Klüver-Barrera stain.
(B) Sacral cord of same animal. Unilateral lesion involving supply zone of an anterior sulcal artery.
At a microscopic level, the destructive changes were centered upon gray matter (Fig. 2B) but not so sharply limited. Injury of the white matter was observed in the form of involvement of the lamina propria, scattered focal destructive changes, broad areas of extension into white matter closely approaching a transecting lesion (Fig. 4A), and focal destruction of spinal nerve roots.

The severe edema in all the early lesions and the few examples of massive hemorrhage are adequate indicators of a severe vascular injury. However, the structural integrity of the vascular network was preserved to a greater degree than the other fixed tissue elements. As indicated above, the capillary basement membrane appeared intact at a time when the neurones were irreversibly injured. At 5 to 6 hours most of the lesions appeared ischemic, but no thrombi were observed. At 2 days, the capillaries appeared generally intact, except for the presence of infrequent thrombi having the appearance of agglutinated platelets. In the material studied evidence of anatomical lesions in the vessels of the pia was rarely observed. In lesions at 4 days and later, a fibrinoid necrosis and associated thrombosis was occasionally observed in the largest intrinsic arteries of the cord, particularly the anterior sulcal artery just beyond its point of penetration into the cord (Fig. 3B). In the fully developed cystic lesions, a loose network of vessels spanned the cavities.

The histologic features of these fully developed lesions associated with cavity formation were characterized by the destruction of virtually all tissue components, including neurones, glia, and the vascular network as described above. The zones of destruction were sharply bordered, with an abrupt transition to normal tissue at their margins. Swarms of activated microglia, distended with lipids and other cellular debris, occupied the cavities. In the bordering tissue, a variable astrocytic proliferation was observed.

The topographic features of the lesions demonstrating the intimate relationship between the level of the injection, the initial distribution of the contrast medium, and the anatomical position and arterial supply of the spinal cord are graphically illustrated in Figs. 5, 6, and 7, correlating these studies in a single dog. Shown particularly well is the manner in which the cord injury following an injection into the abdominal aorta uniformly extended higher than the level of the injection, a distribution closely corresponding to the initial retrograde flow of the contrast medium in the aorta. Also clearly demonstrated is the low anatomical position of the canine cord which renders it so susceptible to injury in these procedures. The virtually selective involvement of gray matter may be explained in part by the differential vulnerability of this tissue and the richness of its blood supply. However, this localization also corresponds closely to the primary distribution of the sulcal branches of the anterior spinal artery, a feature suggesting that the injury may be the result of the heaviest and most concentrated flow of contrast medium through this pathway. Support for this
concept is found in further topographic features of the lesions. In some cords, the injury had a remarkably unilateral distribution (Fig. 4B), and occasionally alternate sides were affected at different levels. Such lesions could be most readily explained on the basis of a direct injury to an anterior sulcal artery or its primary branches, or by the sweep of a substance of noxious character through this vascular network. Although thrombotic and necrotizing lesions were observed in this vascular bed, such lesions were infrequent.

Fig. 5. Lateral roentgenogram showing distribution of Urokon at terminal period of injection. Features to be noted include the retrograde flow and the filling of the dorsal branches of the aorta. However, it is clearly evident that the major portion of the contrast medium is destined for the circulation of the extremities.
In a few animals, distinctly demarcated zones of nearly complete destruction of gray matter were separated by a region with minimal involvement. No vascular maps enabling a precise correlation between blood supply and the site of the lesion were available in this group. In some cords, sharply focal lesions in gray matter again suggested an injury based primarily upon a

**Fig. 6.** (A) Dog with spinal cord exposed to demonstrate anatomic position. Twelve cm. of cord are situated below the level of T13. Four days previously this animal had been injected with Urokon into the aorta at a level of the 6 cm. below T13 (arrow indicates level).

(B) Longitudinal horizontal section through low thoracic lumbosacral cord. Massive hemorrhagic necrosis involving terminal 18 cm.
direct effect upon the vascular bed. The preponderance of white matter involvement in the thoracic cord lesions pointed to the possibility of entry of the contrast media along posterior root radicles in this zone.18

**DISCUSSION**

The contrast medium lesion produced in these investigations is so far beyond the grade of injury previously observed in experimental studies of the effects of these substances that it compels a re-evaluation of the toxic potential of these agents. On the basis of these observations it is evident that the concept of the effect as a transient vascular disorder, exemplified by the statement of Broman and Olsson8

“... the injury caused by [Umbradil forte and Ioduron] being manifest solely as a... completely reversible disorder of the vascular permeability without any attendant signs of edema, stasis, or hemorrhages... (It is conceivable that this effect may be of therapeutic value in certain diseases.)"
is no longer valid. It is evident from comparative studies of the acute phases of the spinal cord lesion and of previously observed experimental angiographic injuries of the brain that the reaction encountered in these studies is not to be considered as a new order of injury. Rather it is the natural evolution of the maximal contrast medium injury, followed through its complete developmental stages, observable only because the site of injury was compatible with extended survival of the experimental animals.

The objection may be raised that the injury encountered in these experiments is not comparable to that observed in other reported studies. Particularly, the argument may be advanced that factors such as size of dose, concentration of the medium, elevated intraluminal pressure associated with the rapid injection, and a differential gravitational flow of the contrast medium resulting from the supine position of the animals during the tests may have heavily weighted these studies in favor of a toxic effect far beyond that possible to achieve with other methods. The test dose, of approximately 1 cc. per kg. body weight, is comparable to that used in clinical angiography. Furthermore, it is clear from a study of the angiograms (Fig. 5) that only a small fraction of the injected material reaches the circulation of the spinal cord.

Our own experience with the lesions produced by 30 per cent Urokon clearly demonstrates that the concentration used in these studies is far in excess of the critical level toxic for the nervous system. This observation is firmly backed by clinical studies. No attempt was made to measure the degree of dilution of the contrast media in our studies. Information available in the literature points to a rapid dilution under such circumstances. Idbohrn and Jacobsson reported a maximum concentration of 17 per cent in the contralateral femoral artery following the retrograde femoral injection of 60 per cent Umbradil (20–50 cc. in 2 to 3 sec.) in rabbits. Farinas reported that the intra-aortic concentration following the injection of a small amount of 70 per cent Diodrast (20 cc. in 2.5 to 3 sec.) in man was 8 to 10 per cent. Idbohrn and Berg found that 50 per cent Umbradil (3 cc. per kg.) injected into the carotid artery of rabbits was diluted to 19 per cent or less in the femoral artery. This high dilution factor may be used to justify the use of 70 per cent concentration of contrast media in clinical aortography. Yet Idbohrn and Berg reported renal injury by Umbradil at a critical level between 10 and 17.5 per cent.

The factor of increased intraluminal pressure is minimized by the large vascular bed into which the injection is made. Studies in our laboratories have demonstrated no rise in intra-aortic pressure with these injections. Stirling has demonstrated a rise of 8 mm. Hg in the aorta and 2 mm. Hg in the renal artery following the injection of 18 cc. of contrast medium in less than 1 second into the aorta of man.

It is an undeniable fact that the supine position during injection favors the production of spinal cord injury by a contrast medium. The radiographic studies of Hol and Skjerven indicate that such a position favors filling of dor-
sal branches of the aorta. However, Greitz,15 elaborating on the work of Lindblom,20 Kjellberg,22 and Ribbing23 has convincingly demonstrated that such a phenomenon is not the result of a differential gravitational flow based upon a specific gravity of contrast media higher than that of blood. By studies on glass and rubber tube models, and by observations during phlebography in man, he observed that the high viscosity of contrast media favored layering rather than ready mixing with blood. He confirmed the observations of Lindblom that a laminar flow was accentuated in horizontally oriented vessels and eliminated by placing these vessels in a vertical plane. In his examples the contrast medium usually flowed beneath the layer of blood. But where vessels curved, he sometimes encountered, as did Kjellberg, a splitting of the layer of contrast medium, with one lamina following the superior wall of a vessel. With an upward flow, a direction that may be compared to a retrograde injection, he noted that a laminar flow could be produced in vertically oriented tubes. In test tubes he was able to layer Umbradil over blood, or vice versa, depending upon the order of introduction of these materials into the tubes. It is difficult to estimate how applicable these observations, made in vessels under conditions of low pressure and comparatively slow flow, are to the arterial system with its high pressure and rapid flow. Certainly, the demonstration by McDonald25 of a turbulent flow in the rabbit aorta indicates that conditions are unfavorable for laminar flow in this animal, and that the interpretations of Hol and Skjerven may be an oversimplification of the situation. Most studies in dogs have indicated that laminar rather than turbulent flow conditions prevail. Direct studies of circulatory dynamics in the canine aorta have not been made, but McDonald and associates17 have failed to demonstrate turbulence in vessels the size of the femoral artery. Further, McDonald,28 using dye-coagulation injection methods, was able to show a streamline flow in the basilar artery of dogs. Smith and associates,2,5,37 by following the localization of experimental emboli and by injecting plastic materials of different colors into the great veins, have demonstrated a stream-flow that remains discrete while passing through the right heart and pulmonary artery of dogs. In cats, observations of such streamlining of contrast media in the systemic circulation were recorded photographically by Browne and Stern10 in the pial veins following intracarotid injections. In our own aortograms, no laminar flow was observed. However, none of our studies used high-speed sequential radiographic technics, necessary for adequate visualization of streamline flow. Inasmuch as two examples of severe spinal cord injury in man resulting from aortography in the prone position6,44 are known to us, it is certain that the supine position is not an essential condition for this injury.

In the past, the experimental observations characterizing the contrast medium injury as a benign, reversible process have been in conflict with evidence produced by complications of cerebral angiography in man. Permanent neurological defects1,12,31,32,40 have been observed clinically and in-
farct-like lesions have been demonstrated in postmortem studies. Of particular value on a comparative basis is the report of Utterback and Haymaker. They studied 4 fatal cases of contrast medium injury to the brain, with deaths occurring at 40 hours, 3 days, and 10 days (2 cases) following angiographic studies. In all of these cases massive infarction, focused particularly on cortical gray matter, was encountered. Necrobiotic changes in vessels, particularly arterioles, and secondary thrombus formation were a prominent feature in the 2 cases of shortest duration, and were noticeable in the other 2 cases. The close correspondence of these changes with those encountered in our experimental material indicates that the toxic manifestations in humans and animals are essentially identical. On this basis it would appear that there is no longer a need to implicate such extraneous factors as pre-existing vascular or parenchymal disease or clot emboli to account for the severe irreversible contrast medium injuries encountered in man.

The sharply marginated malacic lesions, closely corresponding to specific blood supply zones, are best explained as the result of the primary sweep of a toxic concentration of the contrast medium through the spinal cord circulation. This exposure is exceedingly brief, lasting no more than a minute, even when severe disturbances of flow are produced by the contrast agent. Yet the fully developed lesion exceeds in severity the ischemic cord changes produced by acute aortic compression of 1 hour’s duration. An irreversible vascular injury, as well as widespread thrombosis, could produce such a lesion, but there is little evidence to support the latter possibility. The involvement of all tissue components argues strongly against a simple angiospastic effect. The immediate convulsive reaction, which stands in sharp contrast to the delayed functional effects of hypoxia on the cord, indicates a direct toxic action upon neurones, and that the injury is not entirely the result of ischemia. However, it is likely that all of the irreversible effects follow the vascular injury. For example, the early stages of the neuronal changes show a close similarity to neuronal alterations secondary to ischemia and hypoxia, both in their cytologic features and in their rate of development. Whether functional alterations of vascular dynamics, thrombotic phenomena, or vasonecrotizing effects are of greater importance in the production of the disruption of circulation is difficult to determine in an essentially two-dimensional anatomical study such as this. The relative roles of these mechanisms and the precise locus of the vascular obstruction are currently under study by additional technics.

From these studies it is evident that the canine spinal cord is an ideal site for the testing of the toxic effects of contrast media upon the nervous system. In its structure and blood supply, it closely resembles the human cord. Its low anatomical position renders it especially accessible to agents injected into the aorta. Finally, the site of injury allows extended survival of the experimental animal, and an opportunity to study all developmental phases of the contrast medium lesion.
SUMMARY

The pathologic anatomy and topographic features of experimental contrast medium injury to the spinal cord, produced by aortographic procedures, have been investigated. A severe destructive effect productive of extensive myelomalacia has been encountered. These findings indicate that the previous concept of the contrast medium injury as a transitory disturbance of the blood-brain barrier is inadequate. This extension of our knowledge has been possible, because the site of injury has allowed extended survival of the experimental animals, and an opportunity to study the complete evolution of the lesion. The cord is recommended as a test site for measuring the relative toxicity of contrast media.

The histologic material was prepared under the direction of Mr. J. Phillip Pickett, and the photography was supervised by Mr. Carl Bishop.

REFERENCES

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