The mechanism of spinal cord cavitation following spinal cord transection

Part 1: A correlated histochemical study

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Transection of a spinal cord is followed by massive accumulation of lysosomes and release of lysosomal hydrolases within both the rostral and the caudal spinal cord stumps. The lysosomal activity begins at 3 hours after cord transection, maintains its peak for 3 to 7 days, and declines at 14 days after transection. The process is associated with autolysis of the cord stumps and subsequent cavitation. Lysosomal accumulation is greatly diminished, and, paradoxically, superior wound healing is the result at the stumps of a 5-mm segment of isolated spinal cord produced by double cord transection.

Key Words □ spinal cord injury □ spinal cord necrosis □ spinal cord cavitation □ lysosome □ acid phosphatase □ nerve graft

Cavitation is a mode of wound healing unique to the spinal cord and the brain. Although a few authors have suggested that cord necrosis and liquefaction might precede cavitation, the exact mechanism of cord cavitation is still not fully understood. In 1928, Ramón y Cajal reported that, following transection of the mammalian spinal cord, a short segment of cord tissue immediately adjacent to both cord stumps became necrotic and spontaneously separated from the stumps. This phenomenon was called “spinal cord autotomy.” The segment of spinal cord that was separated from the stump was called the “preserved segment,” whereas the new end of the spinal cord stump thus formed was called the “metamorphic segment.” The metamorphic segment was characterized by axonal swellings and formation of terminal clubs. Electron microscopy of these terminal clubs showed that they were packed with numerous electron-dense bodies and other cytoplasmic organelles.

The consequence of such an accumulation of dense bodies at the axonal swellings and terminal clubs within the spinal cord stumps has not been reported. The dense bodies were defined by de Duve and Novikoff as “lysosomes,” which are now known to contain more than 50 enzymes, all hydrolytic and with acid pH optima. It is possible that dissolution of the terminal clubs and release of the lysosomal enzymes led to autolysis of cord stumps and subsequent cord cavitation. Although Ramón y Cajal originally reported spinal cord autotomy, he did not link the phenomenon to eventual cord cavita-
tion. Similarly, Davidoff and Galabov8 reported increased acid phosphatase (APase) at both the proximal and distal stumps of a rabbit's transected spinal cord, but did not correlate their findings with the eventual breakdown of the cord tissue at the cut ends of the stumps.

The purpose of this report is to clarify the topographical localization of enzyme activity within the spinal cord stumps and the relationship of enzyme activity to spinal cord autotomy and subsequent cavitation. Electron microscopic study provided information regarding the mechanism of enzyme release. In addition, the spinal cord was double-transected and wound healing of the isolated cord segment was studied in relation to the enzyme activity.

Materials and Methods

Surgical Procedure

Seventy-nine adult female dogs weighing between 20 and 30 lbs were anesthetized with Nembutal (pentobarbital sodium). Using sterile surgical technique, we performed subpial spinal cord transection as described previously17 at the T-10 cord level with the help of a Zeiss dissecting microscope. By this technique, the cord is transected without cutting across the pia-arachnoid tubing; thus hemorrhage is avoided and ischemic damage to the cord is reduced.

A complete subpial cord transection without grafting was done on 22 dogs. A group of 51 dogs underwent single cord transection with implantation of autografts into the gap; of these, 22 received brain autografts, seven nodose ganglion autografts, and 22 sciatic nerve autografts. The technique of grafting has been reported previously.17,18 Six dogs underwent double transection and double sciatic nerve autograft implantation. Following the transection at T-10, a second transection was performed 5 mm rostral to the first. A 5-mm segment of cord tissue was thus isolated from the rest of the spinal cord. The shape and position of the isolated segment of spinal cord were maintained within the intact pia-arachnoid tubing. Segments of autogenous sciatic nerve were then grafted into the gap above and below the isolated cord segment. The dura was closed with a continuous 6-0 black silk suture, and the wound was closed in layers.

Several dogs were sacrificed within a few hours of the operation. All the other dogs received penicillin, 300,000 units/day. The urinary bladder was catheterized. Spinal cords were obtained at times ranging from 1 hour to 2 years postoperatively.

Light Microscopic Study

The spinal cords were fixed in situ by a perfusion technique using buffered 10% formalin.18 Blocks of about 7 cm containing the cord within the vertebral column were removed and placed in buffered 10% formalin for 10 days, at which time the spinal cords were removed from the canal. The spinal cord was cut into serial sagittal longitudinal sections, 10 μ in thickness. Various staining techniques were used as reported previously.17,18

Enzyme Histochemical Study

After administration of Nembutal anesthesia, the laminectomy wound was re-opened. The segment of cord from 3 cm above to 3 cm below the transection was removed in toto together with the dural tubing, and instantly frozen; fresh-frozen longitudinal sections 6 to 8 μ thick were cut on a cryostat at −20 °C. Acid phosphatase (APase) was stained using both the azo-dye method recommended by Zugibe24 and Gomori's technique as recommended by Barka and Anderson.3 Succinic dehydrogenase (SDHase) was also stained.24 Control sections were given identical treatment except those with specific substrates, which were substituted by corresponding buffer.

Electron Microscopic Study

At scheduled postoperative intervals, the dogs were again anesthetized with Nembutal and the femoral artery and vein catheterized. The spinal cord was fixed by retrograde perfusions of 2.5% buffered glutaraldehyde through the catheter in the abdominal aorta after the animal had been bled to death and the blood replaced by normal saline solution at normal physiological pressure. The laminectomy wound was then reopened and the spinal cord was flooded with 2.5% buffered glutaraldehyde in situ. The whole segment of cord from 3 cm above to 3 cm below the transection was removed.

The segment of spinal cord was then transferred to a container filled with buffered
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2.5% glutaraldehyde and a longitudinal myelotomy was made with the spinal cord bathed in the fixative. In the 1- to 7-day-old cord stumps, the tissue at the original cut ends of the stumps had become separated from the stumps and new ends of the cord stumps had formed. The separated tissues from these specimens and tissue specimens at 1, 2, and 3 mm from the new ends of the cord stumps were also obtained.

In the spinal cords studied 2 weeks or more after transection, the original cut ends of the stumps had been replaced by cavities. In these specimens, tissue was obtained at 1, 2, and 3 mm from the new end of the cord stump. These specimens were individually marked and left in fixative at 4°C for 2 hours. The tissue samples were then postfixed with 1% osmium tetroxide for 1 1/2 hours, dehydrated in graded ethanol, and embedded in epon. Thick and thin sections were cut with automatic ultramicrotome.* The thick sections were stained with toluidine blue and the thin sections with lead citrate. The thin tissue sections were examined with an electron microscope.†

Results

1 Hour After Transection

The spinal cord stumps at 1 hour after subpial microsurgical transection appeared clean (Fig. 1). Edema or contusion of the spinal cord was not conspicuous. Cord hemorrhage and laceration were not seen. Axons of the white matter could be seen at the cut ends of the spinal cord stumps.

3 Hours After Transection

Three hours after transection, a few polymorphonuclear leukocytes were seen at the cut ends of the spinal cord stumps. Moderately distended myelin sheaths were present near the area of transection. Already both APase and SDHase were seen in a small segment of axons 1 to 2 mm, or sometimes farther, from the cut ends of both rostral and caudal stumps (Fig. 2). Large fibers were more deeply stained than small. Each fiber stained more intensely at its tip, which ended abruptly 1 to 2 mm, or sometimes more, from the cut ends of the cord stumps. At 3 hours, most of these axonal tips were not yet swollen. The 1 to 2 mm of tissue at the ends of the stumps, however, showed no noticeable axonal APase or SDHase activities (Fig. 2).

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* LKB ultratome III automatic ultramicrotome manufactured by LKB Instruments Inc., 12221 Park Lawn Drive, Rockville, Maryland 20852.
† RCA EMU-3C electron microscope manufactured by RCA, Camden, New Jersey 08101.
FIG. 3. Appearance of a spinal cord stump at the time of autotomy 3 days after transection. The end of the metamorphic segment (new end of rostral spinal cord stump, arrow a) is characterized by numerous irregularly shaped terminal clubs and segregated balls; however, many intact fibers are seen at the end of the preserved segment (arrow b). An extremely stretched, preserved fiber is shown (arrows). Bodian's stain, × 65.

4 to 6 Hours After Transection

At 1 to 2 mm from the cut ends of the spinal cord stumps, focal distention of myelin sheaths was more prominent and a few terminal clubs had begun to develop.

12 Hours After Transection

At 12 hours after transection, the spinal cord stumps were still grossly intact. On microscopic examination, however, the myelin sheaths were diffusely distended. In the area 1 to 2 mm from the cut ends of the stumps, the myelin sheaths became enormously distended; these distentions could be identified unequivocally as microcysts. This finding was identical at both rostral and caudal stumps. In silver stain preparations, each microcyst appeared as an elongated, oval, empty space around the tip of each terminal club (Figs. 3, 5, and 11). Microcysts occurred more frequently around the large myelinated axons and the unaffected small fibers around the microcysts were compressed and displaced. Electron microscopic study and slides stained for myelin showed that these microcysts were due to the accumulation of transuded fluid between the terminal club and the myelin sheath, which was distended like a bag.

1 to 3 Days After Transection

By 1 to 3 days after transection, the 1 to 2 mm of cord tissue at the cut ends of the stumps separated at the site where the microcysts were most abundant (Fig. 3). In hematoxylin and eosin preparations, the separated preserved segment appeared pale, poorly stained, and necrotic. In silver stains, however, many axons were seen; they appeared astonishingly intact (Fig. 3) and were of medium or small caliber fibers. They showed no swelling, and formed no terminal clubs. They were abundant near the original cut ends of the spinal cord, but became fewer farther from the cut ends. At the area where spinal cord autotomy took place, these fibers were extremely stretched (Fig. 3).

When the preserved segment was just separated from the metamorphic segment, many voluminous, bizarre-looking terminal clubs and segregated balls could be seen at the end of the metamorphic segment. Their shapes were extremely irregular, coniculated, frequently vacuolated, and rarely smooth or round (Fig. 3). Microcysts were frequently formed around each one of these terminal clubs and segregated balls. The neighboring tissue, however, was devoid of cellular infiltration or hemorrhage, and apparently bore no causal relationship to the development of the microcysts.

The day after the cord transection, when numerous terminal clubs were formed and autotomy of the cord stumps began to take place, APase and SDHase were seen at the terminal clubs (Fig. 4). At higher magnification, two types of APase stain could be iden-
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Fig. 4. Appearance of a spinal cord stump 1 day after cord transection, stained for acid phosphatase, shows axonal swelling and terminal clubs at a distance from the cut end of the stump (arrow b). Terminal clubs occur at end of metamorphic segment (arrow a). Gomori's stain, × 65. Inset: Densely stained and sharply delineated terminal clubs are seen. A halo of diffusely stained APase activity is seen around each terminal club. Gomori's stain, × 260.

1 Week After Transection

One week after transection, separation of the preserved segment from the metamorphic segment was unmistakable. The separation was augmented by numerous cysts formed at the edge of the metamorphic segment by coalescence of the microcysts. They eventually became quite large and were visible even to the naked eye (Fig. 5). The terminal club itself, the boundary of which was sharply delineated, contained heavily-packed droplet-form APase activity. A second type of APase activity was diffusely stained, and was seen as a halo around the densely-packed stain droplets. The boundary of the diffuse APase activity was poorly defined and the stain gradually faded into the surrounding tissue (Fig. 4).

Fig. 5. Detail of a spinal cord stump showing evolution of the microcysts in a dog sacrificed 7 days after cord transection and sciatic nerve autograft. When the microcysts first appeared at the end of the metamorphic segment (arrow a), they frequently contained a terminal club formed at the end of an axon (Cyst 1). A short distance distal to this region, the cysts were considerably larger, and frequently contained a segregated ball separated from its axon (Cysts 2 and 5). The thin septa formed between these cysts showed disruption and the cysts became confluent (Cysts 2, 3, 4, and 5). Eventually larger cysts were formed (Cysts 6 and 7). Cyst 7 appears to be compressing the preserved segment, and Cyst 6 appears to be compressing Cyst 7 from behind. Arrows indicate the vector of the force. A few preserved fibers are still visible at the end of the preserved segment (arrow b). Bodian's stain, × 66.
FIG. 6. Distribution of enzyme activity 7 days after cord transection and sciatic nerve autograft. The grafted nerve segments are seen between arrows b and c. Note the cystic cavities that have formed with the stumps. Intense enzyme activity is seen at the ends of the metamorphic segments (arrows a and d). Within the cystic cavities, enzyme droplets are seen as if suspended in the tissue fluid. Gomori’s stain, × 65. a: new end of the rostral spinal cord stump; b: original cut end of the rostral spinal cord stump; c: original cut end of the caudal spinal cord stump; d: new end of the caudal spinal cord stump. Inset: Acid phosphatase-positive droplets are seen accumulated in a terminal club. Azo-dye method, × 260.

FIG. 7. Electron micrograph of a portion of terminal club seen in a specimen obtained 2 mm from the new edge of cord stump, 1 week after cord transection. The terminal club contains numerous dense bodies, mitochondria (m), and dense core vesicles (dcv). Disintegration and autophagy of dense bodies are shown. 1: Fairly intact dense body; 2: floccular dense body; 3: early breakage of a dense body with no identifiable membrane; 4: further break down of a dense body surrounded by vacuoles; and 5: a dense body containing a mitochondrion and a dense core vesicle (autophagy). × 20,000.

clubs and segregated balls in this segment were oval or round, and there were fewer of them than in the previous specimens. Frequently there were distended microcysts which contained no terminal clubs or segregated balls (Fig. 5). The preserved fibers were generally much shorter than those seen in Fig. 3 and were not stretched any more (Fig. 5). With the enlargement of the cystic cavity, the preserved fibers became progressively shorter and those at the very end of the original cord stumps were the last to disappear.

Figure 6 shows the enzyme activity at the peak of spinal cord autotomy 7 days after cord transection. Both APase and SDHase showed an identical distribution. If the spinal cord was simply transected and no graft was placed in the gap, the degraded preserved segments of the rostral and caudal stumps became mixed in the gap and transformed into a semifluid custard-like material. There were maximum concentrations of both APase and SDHase at the end of the spinal cord stump that was the metamorphic segment. Within the gap, enzyme droplets were mixed with the necrotic tissue.

If the gap was grafted with segments of autogenous sciatic nerve, the intense APase and SDHase activity could be unequivocally localized within the metamorphic segment (Fig. 6). By this time, cystic cavities had
FIG. 8. Electron micrograph showing four denuded segregated balls without myelin sheaths at the edge of the metamorphic segment 1 week after cord transection. The segregated balls are lined with a single plasma membrane and packed with numerous dense bodies and mitochondria. The plasma membranes of the segregated balls are disrupted at several points (arrows) and the contents of the terminal clubs are being discharged to the extracellular space. The dense bodies within the segregated balls also show disintegration. × 10,500.

developed between the metamorphic and preserved segments. Within the cystic cavities enzyme droplets were seen as if suspended in the tissue fluid.

The change of APase from droplets to diffusely scattered could also be appreciated within a single specimen at the 1-week study. The terminal clubs or segregated balls located at the end of the metamorphic segment usually contained diffuse APase, whereas those at a distance from the end of the metamorphic segment contained APase only in droplet form.

Electron microscopic examination showed ruptures of terminal clubs and dissolution of segregated balls. Dense bodies and other organelles once contained within the terminal clubs and segregated balls were then released to the extracellular space (Figs. 7 and 8).

Dense bodies within the terminal clubs, and in the extracellular space underwent a lytic process which was characterized by floccular appearance of the electron-dense substance and fragmentation of the lysosomal membrane. Later, vacuolation and dissolution of the electron-dense substance took place (Figs.
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FIG. 9. Enzyme distribution 7 days after double cord transection and double sciatic nerve autografts. The specimen is distorted due to difficulty in fixation. The site of transection is indicated by the grafted nerve segments (b–e and f–c). Maximum enzyme accumulation is again seen at the ends of the rostral and caudal metamorphic segments (a and d). The preserved segments (a–b and c–d), grafted nerve (b–e and f–c), and the stump of the isolated cord segment (e and f) show no enzyme activity. The gray matter of the isolated cord segment (A), however, shows enzymes within the nerve cells. Gomori's stain, × 5.

7 and 8). Autophagy was also observed as the dense bodies occasionally contained vesicular profiles or even a mitochondrion (Fig. 7).

2 Weeks After Transection

The 2-week-old spinal cord wound was dominated by macrophages (gitter cells). The remaining portions of the preserved segment were then invaded by macrophages and fibroblasts. A few broken preserved fibers were seen between these scavenger cells. Within the metamorphic segment, the number of terminal clubs was greatly reduced, and the activity of APase and SDHase also declined remarkably. The blood vessels of the dissolved preserved segment, however, resisted the autolysis and remained. They were seen as longitudinally elongated structures crossing the cystic cavity. Some of them were dilated and contained many red blood cells.

3 Weeks After Transection

By the end of the third week, two cavities were clearly formed, one on each end of the spinal cord stumps. The end of the stump seen at this time was not the original cut end of the stump at transection, but was actually the end of the metamorphic segment. Within the metamorphic segment, resorption of terminal clubs and segregated balls continued. When these structures were removed, many empty microcysts remained and gave the meta-

FIG. 10. Paraffin preparation of a spinal cord 7 days after double transection and double sciatic nerve autograft. The isolated cord segment e–f shows minimal degradation at either end; its approximation to the grafted nerve b–e and f–c is far superior to that between the spinal cord stumps and the grafted nerve a–b and c–d. Note the honeycomb appearance of the spinal cord stumps due to numerous microcysts, whereas within the isolated cord segment such a change is minimal. Areas a and e are shown further magnified in Fig. 11. DeMyer's stain, × 5.
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Morphologic segment a honeycomb appearance. Enzyme histochemistry study showed only occasional droplet type APase activity within the remaining terminal clubs and no diffuse APase.

The histological appearance at any time after 3 weeks was essentially the same as in the 3-week-old specimen except that the cavities formed above and below the grafted tissue were cleaner and devoid of tissue debris or macrophages.

Our electron microscopic examination of a spinal cord transected 2 years previously was in agreement with that of Lampert; a few terminal clubs containing dense bodies were still present. However, there was no evidence of breakdown of either dense bodies or terminal clubs.

Double Transection Study

The result of double cord transection study further emphasized the correlation of lysosomal activity and cord cavitation (Figs. 9-11).

Figure 9 shows enzyme activity of the spinal cord 7 days after double cord transection and double sciatic nerve autograft. Massive accumulation of APase and SDHase was demonstrated at the metamorphic segments of the rostral and caudal stumps whereas in the cut ends of the isolated 5-mm segment of the cord only very scanty enzyme activity was seen. The APase droplets that accumulated in the cut ends of the isolated cord segment did not conglomerate as did the APase droplets in the rostral and caudal stumps and were therefore visible only at high magnification.

Figures 10 and 11 demonstrate the histological differences between the cord stumps and the isolated segment of cord. Autotomy had taken place at the end of both the rostral and caudal stumps. A cystic space dissected them into preserved and metamorphic segments. Numerous axonal swellings, terminal clubs, and segregated balls were seen at the metamorphic segment.

On the contrary, only minimal degradation occurred at either end of the isolated 5-mm cord segment. The cord tissue at its ends appeared closely approximated to the grafted nerve with minimal separation by the cysts. Healing between the isolated cord segment and the grafted nerve was far superior to the healing between the cord stumps and the grafted nerve.

The histological difference between the cord stumps and the isolated segment of cord was striking (Fig. 11). The metamorphic segment of the cord stumps contained multiple microcysts that gave a honeycomb appearance as demonstrated by the silver stain. Terminal clubs or segregated balls were seen within the microcysts. No such microcysts were formed at the isolated cord, and the cord tissue appeared undisrupted. Irregular axonal swelling was seen within the isolated cord segment; however, few small terminal clubs or segregated balls were found.
Discussion

Lysosomes are a class of cytoplasmic organelles defined by de Duve and Wattiaux. They form part of an intracellular system that involves the endoplasmic reticulum and Golgi apparatus, and are of fundamental importance for intracellular digestion, secretion, phagocytosis, and autolysis. It is often assumed that when acid phosphatase is present, other hydrolases are also to be found. The histological demonstration of acid phosphatase activity by Gomori's or azo-dye methods and the electron microscopic demonstration of the organelle are the most reliable standards at present for the identification of tissue lysosomes. Excellent reviews of lysosome in the nerve cells are available.

Our study shows that the spinal cord autotomy described by Ramón y Cajal is linked to the unique lysosomal cellular lytic process. This is a local reaction of cord tissue to injury and differs from the well known remote effect of Wallerian degeneration. It occurs at the rostral and caudal stumps simultaneously. Peculiarly enough, the lytic process does not start at the cut ends of the cord, but at some distance from the cut end within the spinal cord stumps. It then advances toward the cut end and leaves a cystic space behind. This explains the presence of intact axons, the preserved fibers, at the very end of the original cord transection when the cellular lytic process had already developed within the spinal cord stumps. Bailey and Holmes have also described the presence of such preserved fibers within the necrotic tissue in human spinal cord specimens obtained shortly after trauma.

The identical pattern of APase and SDHase stain is probably related to the simultaneous accumulation of lysosomes and mitochondria within the axon. In sciatic nerve transection, ligation of the nerve proximal to the proximal stump interfered with the accumulation of SDHase in the stump. This evidence strongly favors the concept of a proximodistal transport of axoplasm. However, it does not explain that accumulation of APase and SDHase and swelling of axons can also develop in the distal stump of a transected nerve or cord or even in the stumps of an isolated segment of nerve more than a few millimeters in length. Friede attempted to explain these phenomena by the development of a local injury current that caused redistribution of axoplasm in a manner similar to electrophoretic movement. Absence of such enzyme activity in an isolated segment of nerve a few millimeters long was thought to be due to the absence or scarcity of polarized tissue between the cut ends of the isolated nerve segment.

The diminished autolysis at the stumps of the 5-mm isolated cord segment was probably due to diminished lysosomal accumulation. All other possible parameters interfering with wound healing, such as severity of injury, interruption of blood supply, anoxia, and local acidosis are the same as in the rostral or the caudal stumps, if not worse. Yet the healing at the ends of the 5-mm isolated cord segment is paradoxically far superior to that of its counterparts at the spinal cord stumps.

Since lysosomes and mitochondria are present in the nerve fibers long after autotomy has ceased, a second factor must be present in the wound which gives rise to the release of the lysosomal enzyme. De Duve's concept of autolysis deals with lysosomal rupture and subsequent intracytoplasmic or extracellular release of acid hydrolases, which causes further tissue injury and degradation. The causes for lysosomal rupture are still not fully understood. Lysosomal rupture probably has several forms. The type of lysosomal rupture that we observed in the transected cord is identical to the process described in sebaceous glands. The process is associated with a conversion of APase from droplets to diffusely scattered as revealed by histochemical staining.

Since electron microscopy revealed the localization of lysosomes within the nerve fibers and terminal clubs, it is unlikely that the APase originated from the circulation. We therefore propose the concept that the lysosomes that accumulated in the cord stumps following cord transection originated within the nervous system. It is also likely that these lysosomes are mobilized from some distance within the nervous system, rather than synthesized locally at the site of cord injury. The fact that lysosomes are greatly diminished at the ends of the isolated 5-mm segment of cord supports the above concept.

Regardless of the length of the cord segment, lysosomal accumulation within it probably will not be completely abolished.
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Fig. 12. A proposed mechanism of wound formation in spinal cord injury. Left: If immediately after injury a small gap or no gap is created (1), then at 1 week the preserved segments are in close approximation with each other and seal off connective tissue invasion (2); therefore, at 3 weeks, when the preserved segments are completely dissolved by autolysis, only a single cyst is formed which is lined with astroglial cells (3). Right: If a gap is produced at injury (1), the preserved segments act as a mold to cast the shape of the connective tissue scar at 1 week (2); at 3 weeks, when the preserved segments are dissolved and replaced by cavities, the edge of the connective tissue scar indicates the exact position of the original cut end of the spinal cord stump at transection (3). Wallerian degeneration is not shown in the drawing for the purpose of simplicity.

Unlike the segments of isolated peripheral nerve a few millimeters in length, an isolated segment of cord always contains nerve cell bodies within its gray matter. Therefore, a certain amount of cytoplasm and lysosomes are always provided within the cord segment no matter how short it is.

Lysosomal spinal cord autotomy bears no resemblance to catecholamine hemorrhagic necrosis of the cord, since the entire process of cord cavitation is not accompanied by any histological evidence of hemorrhage. Furthermore, local anoxia alone cannot explain this mechanism of cavitation, because within the preserved segments destruction is least at the end, which would be most severely affected if anoxia were the cause.

In subpial microsurgical cord transection, there is a sharply limited end point of trauma to the cord. Only in this experimental model can the conclusion be clearly established that lysosomal spinal cord autotomy develops within the intact spinal cord at a distance from the end point of trauma. Additional grafting to the cord stump provides further valuable information. When a segment of cord tissue is lost by cavitation, the cut end of grafted nerve remains and marks the position...
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of the original cut end of the cord.\textsuperscript{18} No other experimental technique can provide this information.

Although a transection model is used in the present study, judging from light microscopic reports of contused cords\textsuperscript{1,7,13,14,22} especially the report by Ramón y Cajal\textsuperscript{22} that terminal clubs also form at a distance of cord contusion, it is likely that lysosomal spinal cord autotomy also occurs in the contused cord at a distance from the end point of injury, leading to further destruction of cord tissue and subsequent cavitation of the contused cord. The fact that in human pathological material, an injured cord, regardless of mode of injury, forms either a single cavity or a dense connective tissue scar surrounded by cavities, can then be explained by the size of the gap created at injury.

When there is a small gap of cord tissue or none, and the preserved segments of the rostral and caudal stumps come in close contact, the gap seals off connective tissue invasion (Fig. 12 left). By the end of the second week, when the preserved segments are completely dissolved, there is nothing but a single cavity between the edge of the metamorphic segments of the rostral and caudal stumps.

If the preserved segments of the stumps are separated, the gap is filled with tissue exudates, red blood cells, and polymorphonuclear leukocytes and fibroblasts, which then form the collagenous connective tissue scar (Fig. 12 right). In the beginning, the end of the preserved segments and the pia-arachnoid tubing mold the shape of the collagenous connective tissue. Since the very end of the preserved segment is the last to disappear, there is ample time for the collagenous connective tissue to mature and solidify within the mold made by the ends of the preserved segments. By the end of the second week, when the preserved segments are completely liquefied and replaced by cavities, the collagenous connective tissue scar is then surrounded by the cavities. In a sense, the collagenous connective tissue scar is simply a "casting" molded by the original ends of the spinal cord stumps. Although it is surrounded by cavities at the third week, the very end of the collagenous connective tissue scar is in fact in the exact position of the original end of the spinal cord stump produced at trauma.

In a transected spinal cord, a gap frequently occurs between the rostral and caudal stumps. It is therefore likely that the type of wound containing both cavities and collagenous connective tissue scar occurs more frequently than that causing a single cavity.\textsuperscript{18} In a contused spinal cord, since no gap is created, a single cavity at the site of contusion is frequently formed.\textsuperscript{3}

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