Special Review

The Pathophysiological Response to Spinal Cord Injury

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The pathophysiological response to spinal cord injury

The current status of related research

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In this review of spinal cord injury research, the author has selected contributions which in his opinion best represent modern experimental concepts regarding the mechanism and management of spinal cord injuries. He has placed special emphasis on the controversial issues appropriate to a new, stimulating, and competitive area of research.

KEY WORDS: paraplegia, spinal cord injury, hemorrhagic necrosis, spinal cord hypoxia, catecholamines, noradrenaline, dopamine, hypothermia, steroids, myelotomy, rhizotomy.

This is not a standard review of spinal cord management. Rather, we have tried to discuss the successes, failures, and conflicts in current research on the mechanism and treatment of spinal cord injury. The number of sound and provocative reports reflects the momentum of this rapidly expanding field of research.

Historical Background of Research

The contemporary chapter of acute spinal cord injury research and treatment actually begins in 1908, for it was then that Allen reported the first comprehensive clinicopathological study of human spinal cord injuries and emphasized the nature of central traumatic hemorrhagic necrosis. Allen also contributed a basic experimental model in the form of reproducible and graded spinal cord injuries produced by dropping specific gram-calibrated weights through a vented guide frame to strike the surgically exposed spinal cord. The magnitude of each injury could be expressed in gram-centimeters (gm-cm) representing the product of weight of mass and distance of fall. Little improvement has been made in Allen's injury model over the ensuing 60 years; contemporary investigators continue to use the same system with minor modifications (Figs. 1 and 2). His observation that 345 gm-cm causes moderate injury, 420 gm-cm spastic paraparesis, and 450 gm-cm lasting paraplegia are still accepted as reasonably accurate for larger mammals. For as yet unexplained reasons, rats and rabbits are severely wounded by 50 gm-cm; this represents a tenfold reduction in the
Courteous discrepancies appear in the recent reports of different investigators. Some workers report retention of hind limb function in a few animals after 500 gm-cm trauma, 24 while others believe this injury to be total and irreversible. 25,106 These variations are probably explained by a lack of standardization of the size of the impact (foot) plate. The expression of "gram-centimeters" relates to energy and not force. Force is defined as energy exerted per unit area; thus the area of spinal cord receiving the impact must be specified before injury results can be compared. For example, the forces are vastly different if the same weight-height formula is delivered through the broad head rather than the fine point of a thumb tack. With these factors in mind, Allen’s injury method should be reproducible within the limits of biological error. Even without standardization of force it appears that 400 gm-cm blows are irreversible for cat, dog, and monkey.

Concerning his observations on the results of the trauma, Allen wrote that “Either there is a destruction of axis cylinders consequent to the impact or else owing to the impact there is an edematous and hemorrhagic outpouring into the cord tissue, which by its pressure and chemical activity inhibits temporarily all conduction function or destroys permanently the spinal cord.” He continues, “In suggesting a possible treatment to aid and abet auto restoration, it is obvious that the hypothetical factor of direct injury to the axis cylinder by impact is beyond our reach, and that we should better confine our attention to the amelioration of the heightened intramedullary pressure.”

As a means of investigating this problem he injured five dogs with 540 gm-cm (30 gm at 18 cm) and subsequently made 1 to 1.5 cm longitudinal incisions at the impact level passing through the cord substance (mid-dorsal column); the elapsed time from trauma to cord cutting was not specified, but one gathers it was not great. All five dogs made an uneventful recovery and, although they were slightly spastic, they were still able to run and jump. Allen’s conclusions were “In case of fracture dislocation of the spinal column in the human subject, in which there exists the symptomatic picture of transverse lesions of the spinal cord, it were well to perform the operation of laminectomy at the earliest possible moment and if the cord be not completely severed to make a median longitudinal incision through the area of impact by means of a fine cannaliculus knife in order to drain the injured tissue of the products of edema and hemorrhage.” This dramatic therapy for severe and known “irreversible” spinal cord injuries was unfortunately either not widely acclaimed or denied by conservative advisors. At any rate, the use of myelotomy in the treatment of spinal cord injuries remained largely untried for several years until...
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repetitively reproused by McVeigh in 1923, Freeman and Wright in 1953, and Campbell, et al., in 1972. It is discussed in detail later in this review.

The next advance in cervical spinal injury treatment was Crutchfield's development of skeletal fixation and reduction of fracture dislocations by traction in 1936. Spinal cord compression due to misaligned cervical fractures could now be corrected without surgical intervention. The basic idea of skeletal traction has been widely accepted. Gardner has recently introduced skull tongs which are easily applied and have several desirable advantages.

The appropriate treatment for some spinal cord injuries can obviously be determined by the type of injury. Patients suffering from penetrating cord wounds or blunt injuries with attendant intraspinal bone fragments are undoubtedly best managed by surgery. The resulting debridement, removal of foreign materials, and local neural decompression has long honored support in principle and is logical in practice.

However, the treatment of the majority of spinal cord injuries is not so obvious. After closed fracture reduction, the need for decompressive laminectomy must be considered. For treatment purposes these injuries can be further subdivided into subtotal and complete neurological lesions. From a purely mechanical standpoint it seems reasonable to remove demonstrable mechanical neural obstructions; however, this logic approaches reality only when partial spinal neural loss and extra-axial compression coexist. This group of patients can be expected to experience some functional improvement after surgical decompression.

Our major treatment failures are related to blunt traumatic lesions with immediate and total sensory-motor loss below the injured level; in fact patients in this group rarely recover any neural function in spite of all available types of therapy. We cannot excuse our failures by assuming the spinal cord in these instances was anatomically transected and spinal realignment or laminectomy could not therefore have been beneficial. The truth of the matter is that the cord is physically tough and is rarely torn, lacerated, or transected even with massive fracture dislocations. Total spinal cord dissolution does follow severe injuries within 24 or 48 hours but this phenomenon is related to an inherent autodestructive process in the cord rather than to actual immediate physical disruption.

Because of the clinical failure of operative decompression, some neurosurgeons strongly advocate a conservative management routine; others prefer a middle ground and favor laminectomy for removal of extradural compressing lesions. Two major errors in surgical judgment are common. The first is in giving the patient a prematurely bad prognosis. This early fatalistic attitude may be devastating to the patient's morale, even if true; moreover, we have all seen a few patients who show the first signs of returning function as late as 3 weeks after injury. The other is the indulgence of "psychological surgery" performed to convince the patient and family that "everything possible has been done," although the surgeon has little or no faith in the efficacy of the treatment. Although opinions of this sort were formed on the basis of simplistic concepts relating mechanical pressure or distortion to continuing spinal paralysis, some have been reinforced by recent pathophysiological studies demonstrating chemical, neuronal, and blood flow alterations in the spinal cord which, once initiated, progress even without continued mechanical distortion. Since postinjury lesions are produced by an inherent spinal cord process (see below), laminectomy alone cannot be expected to benefit the severely wounded spinal cord.

Neuropathology of Experimental Spinal Cord Injuries

Microarchitecture

Light microscopy studies of spinal cords at intervals after standard experimental injury have revealed the progressive nature of the central lesions. There are usually a few small hemorrhages in the central gray matter 30 minutes after severe injury (500 gm-cm). The hemorrhages result from delayed rupture of thin-walled vessels with erythrocyte leakage into perivascular spaces. The small pетechial hemorrhages at this time are often restricted to the central gray matter adjacent
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Fig. 3. Sequential histopathological lesions following 500 gm-cm trauma. Left to Right: specimens from 30 minutes, 2 hours, and 24 hours after injury.

to the central canal or the anterior horns. The posterior gray matter is often free of lesion and the remaining microarchitecture is usually intact. Within 2 hours after the blow, the central petechiae enlarge while polymorphonuclear and microglial reactions become evident. The remarkable neuronal alterations that occur at this time include ghost cells, eosinophilic nerve cells with indistinct nuclei, "smudged" cytoplasm, and loss of Nissl bodies. The most striking microarchitectural change relates to the evolving hemorrhagic lesions within the central gray matter. The rapid progression from comparatively normal vessels to vascular congestion and blood extravasation emphasizes traumatic vascular reactivity (Fig. 3). At 4 hours this process has advanced to coagulation necrosis of up to 40% of the central gray and subadjacent white matter. At the necrotic margin, polymorphonuclear leukocytes and necrotic granular material can be seen. There is usually no glial cell reaction. Numerous retraction corpuscles appear in the myelin sheaths. Twenty-four hours after the injury the spinal cord is mainly composed of amorphous necrotic tissue and aggregated red blood cells with only a small rim of identifiable white matter.

Quantitative data analysis can be made from enlarged photomicrographs. The area of hemorrhagic necrosis (HN) can be accurately measured from the photograph with the compensating polar planimeter.* By relating lesion area to total cord area we found an average HN of 23.3% at 2 hours and 69.4% at 24 hours. Recent observations in our laboratory have shown time-based traumatic lesions spreading in a longitudinal as well as radial direction. Indeed longitudinal HN may extend several millimeters on either side of the trauma site and simulates dissecting hematomyelia (Fig. 4). As experiments on traumatic lesions and their treatment necessarily become more sophisticated, determination of cubic volume of HN as the product of cross-sectional and longitudinal areas will undoubtedly become necessary, and will more accurately reflect the true extent of lesion development.

Ultrastructure

Recent electron microscopic studies by Dohrmann, et al., 41,43 have shown the microvasculature to be the most trauma-sensitive tissue in the cord. Dramatic fine structural alterations occur primarily in the gray matter after moderate (300 gm-cm) experimental injuries to the spine. Within 5 minutes, postcapillary venules become distented with erythrocytes. Red cells actually penetrate the

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*Polar planimeter Model No. 620015 manufactured by Keuffel and Esser, 565 Virginia Drive, Fort Washington, Pennsylvania 19034.

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Fig. 4. Longitudinal section of cat thoracic spinal cord 24 hours after a 500 gm-cm blow. The traumatic lesion has effectively transected this specimen.
injured vascular endothelium within 15 to 30 minutes and are found within the perivascular spaces of postcapillary and muscular venules. This is apparently due to endothelial gaps and ruptures in the walls of the muscular venules. Such ruptures are first detected within 15 minutes after contusion but increase in number and size thereafter (see Neurotransmitter). Vacuolation and swelling, hallmarks of ischemic endothelial injury, were found at 4 hours in the endothelium of capillary and postcapillary venules throughout gray and white matter.

The white matter also undergoes characteristic traumatic ultrastructural alterations. After 5 minutes after a 300 gm-cm injury the myelinated fibers resemble those of a control animal. After 15 to 20 minutes, however, some fibers develop moderately enlarged periaxonal spaces. Further changes at 1 hour consist of altered myelin sheaths, splaying of myelin lamellae, and greatly enlarged periaxonal spaces. One-fourth of the 4-hour fibers have broken myelin sheaths, denuded axons, and some axonal degeneration.

From these detailed ultrastructural studies it becomes apparent that microvascular changes are characteristic of spinal cord injury, while various neuronal degenerations are secondary to profound vascular changes and subsequent hypoxia. The vascular alterations clearly precede those in other tissues. They also accelerate faster. These facts will be further interpreted and extended below in discussions relating to traumatic blood flow retardation, hypoxia, and actions of certain central neurotransmitter substances following trauma.

Blood Flow in the Spinal Cord

Blood Supply

The vascular supply of the spinal cord has already been reviewed by Turnbull and will only be summarized here. DiChiro and Wener's review details the angiographic anatomy so extremely important to clinical blood supply interpretations. The cord is nourished by the anterior and two posterior spinal arteries. They are supplied by an inconstant number of anterior and posterior radicular arteries. There are usually more of the latter (between 10 and 23) than the former (between 6 and 10). The anterior spinal artery forms an anastomotic channel which is fed by the various anterior radicular arteries, and extends the entire length of the spinal cord. It serves the anterior two-thirds of the spinal cord while the small ramifying and at times discontinuous posterior arteries supply the posterior third. Small branches ramify over the surface of the cord from the larger named vessels to form a pial arterial plexus. The spinal cord parenchyma is penetrated by central branches from the anterior spinal artery that supply the central third of the cord. Branches from the pial arterial plexus irrigate the outer half of the cord, while the remaining central intermediate zone is overlapped by both systems. Terminal arteries give rise to an extensive capillary network, more dense within the gray than in the white matter (Fig. 5).

Spinal Cord Blood Flow

For normal spinal cord microcirculatory flow and function, the cord arterial system must be perfused by pressures greater than 30 mm Hg at the distal end of the intercostal arteries. Killen and Adkins reported that experimental intercostal ligation regularly resulted in paraplegia when distal intercostal pressures fell below this critical level. Of course perfusion depends both on the perfusing pressure head and the...
number of anastomotic channels. When either factor is sufficiently disturbed, the cord circulation will be embarrassed. These factors are well known clinically in terms of aortic surgery, dissecting aneurysms, and hypotension. Under normal physiological states, blood flow in the spinal cord is known to be primarily reactive to arterial pCO₂ pressures, and poorly responsive to topical or intraarterial vasoactive substances (see under Neurotransmitter). Ducker and Perot found the normal spinal cord blood flow in dogs was 15.2 ml/100 gm/min, increased to 19.4 ml/100 gm/min by hypercarbia, and fell to 11.1 ml/100 gm/min with low arterial CO₂. They also found that spinal cord blood flow was independent of perfusing pressures over a fairly wide range. The available evidence and present thinking strongly favor a blood flow autoregulation within the spinal cord, which is quite analogous to that identified for cerebral vessels.

Spinal Cord Hypoxic Lesions

A relationship between slowing of spinal blood flow and traumatic cord lesions can be inferred from the work of Wilson, et al., and others. In their studies of cervical spinal ischemia induced by multiple radicular artery ligations, they produced hemorrhagic central cord lesions. Their histopathological photographs and descriptions closely parallel those described for traumatic central gray hemorrhagic necrosis. In some instances, purely hypoxic lesions could not be distinguished from those of the same stage of development resulting from blunt trauma (Fig. 6).

Posttraumatic Tissue Oxygenation and Microcirculatory Changes

Since hypoxia alone can produce central hemorrhagic necrosis of the cord, the characteristic pathological lesion of trauma, it obviously was important to test the role of this factor. During the course of direct cord oxygen measurements in acute trauma, Kelly, et al., found a dramatic fall in tissue pO₂. One hour after experimental injury, oxygen tensions dropped below normal tissue requirements; once severe hypoxia developed it continued for hours. Assenmacher and Ducker observed the spinal microcirculation by magnification of the exposed cord. After irreversible wounding (500 gm-cm), they found subcortical hemorrhages in 30% of the acute lesions; however, all tissues showed hemorrhage in the subacute stage. Vascular stasis occurred in only 5% of acutely injured animals but progressed to 30% in 30 minutes, 65% in 1 to 8 hours, and 100% at 5 days.

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Fig. 6. Hemorrhagic central gray necrosis resulting from multiple radicular artery ligations. Compare with traumatic lesions shown in Fig. 3. (Wilson, et al.: Experimental cervical myelopathy. II. Acute ischemic myelopathy. Arch Neurol 21:571-589, 1969. Reproduced by permission of the publisher.)
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and Goodkin performed microangiograms on injured spinal cords which exquisitely demonstrated nonfilling of most small vessels within the central gray and white matter lying beneath (Fig. 7). Using particulate fluorescent dye, Dohrmann, et al., also documented these vascular changes. The fact that small vessels did not fill strongly suggested the presence of localized retardation or arrest of blood flow.

Following these qualitative studies, Duck- er and Perot measured local spinal cord blood flow directly by sophisticated xenon 133 desaturation curves after microintra-medullary isotope injections. The rate of blood flow fell from 15.2 to 9.3 ml/100 gm/min at 1 hour; 2 hours after a 500 gm-cm trauma it fell to 6.1 ml/100 gm/min. The flow calculations compare well with companion polarographic tissue oxygenation measurements. Tissue oxygen tensions were depressed from a normal level of 39 mm Hg to 24 mm Hg 2 hours after trauma, and 17 mm Hg in 3 hours. A further tissue pO2 decline occurred at 4 hours when the oxygen tension fell to 13 mm Hg, or one-third normal value. Although the authors do not state the minimal values for central cord blood flow and tissue pO2 compatible with cord integrity, we can extrapolate from the known large central hemorrhagic appearance at 2 hours; thus, the reduction of flow by two thirds (15.2 to 6.1 ml/100 gm/min) and of pO2 by one third (39 to 24 mm Hg) would be below the critical requirements of central gray matter. It is of considerable interest that they found spinal cord blood flow to be only 30% to 45% of brain blood flow on a weight basis, yet the tissue oxygen levels are essentially the same in both organs, namely, 35 mm Hg as compared to 39 mm Hg. This suggests that the cord, which seems to be more reactive and sensitive to injury, has a naturally low capacity flow system. Perhaps because of this factor, the spinal cord has a relatively minimal capacity to adapt to minor vaso-spastic phenomena by means of increased flow from anastomotic areas.

Biochemical Confirmation of Traumatic Spinal Cord Hypoxia

Posttraumatic spinal cord ischemia as biochemically determined through lactate tissue accumulation has been reported by Locke, et al. The lactate content of the spinal cord rose from a control value of 3.64 mm/kg tissue to 5.50 mm/kg after experimental injury, and the acid metabolite continued in supranormal concentration (4.07 mm/kg) for up to 40 hours. Using a circulatory arrest model to stop local spinal cord blood flow, these authors established that the tissue lactate rose as the blood flow in the cord decreased. Totally anoxic spinal cord tissue lactates were elevated 10 minutes after circulatory arrest (14.33 mm/kg) and continued at that level throughout a 30-minute observation period. By correlating rising lactate levels in circulatory arrest with those of spinal trauma, the authors feel their data support the hypothesis of localized cord ischemia and hypoxia as the genesis of posttraumatic parenchymal cord lesions. Lactate accumulates during tissue ischemia from a conversion of aerobic to anaerobic metabolism and from inadequate washout of the metabolite due to poor tissue perfusion.

Summary of Experimental Blood Flow Data

At the time of this writing the available evidence strongly favors the hypothesis that trauma provokes a microvascular response that causes significant localized retardation.
of blood flow. Since this reaction is progressive, lethal hypoxia develops within hours. In this context, extrinsic mechanical pressure becomes an unrelated factor because the injury was produced by an immediate, direct blow without protracted neural deformation. Traumatic cord autodestruction depends on an inherent process which, when activated, can proceed without axial tissue distortion. These basic facts help explain the failure of decompression laminectomy to influence the functional outcome of severe injuries that leave the cord in continuity.

Vascular Versus Neurovascular Traumatic Hypoxia

Two separate theories have arisen concerning the precise mechanism of traumatic microcirculatory failure in the spinal cord. Some investigators favor a direct theory wherein wounded vascular smooth muscle shortens and contracts to narrow the lumen, increase resistance, and retard blood flow. This theory fails to explain why direct traumatic vasospasm increases with time, or why the presumably more fragile neurons are not more deranged.

The other hypothesis is that spinal cord catecholamines are responsible for the vascular changes, since there is a large supply of these amines at vascular receptor sites. Under this hypothesis delayed hemorrhages are explained by the necessary lag in metabolic time before neurotransmitters can be produced in toxic concentrations.

Both theories arrive at the same end point, but differ significantly in pathophysiological mechanism. Therapeutic considerations make elucidation of this problem important. Since in the ultra-acute stage severe blunt trauma usually spares the long white pathways, effective antivasospasm therapy should prevent progression and subsequent autodestruction.

Effects of Spinal Cord and Dorsal Root Sectioning on Traumatic Central Lesions

To differentiate neurotransmitter from direct smooth muscle vascular injury in traumatic hemorrhagic necrosis (HN), the author established experimental spinal cord and root interruptions prior to the application of trauma.

Spinal Cord Transection. One week after transection of the cord at T-1 in cats, the T-8 thoracic segments were removed for histological study. Since this material was microscopically normal, we assumed that a section of the cord at T-1 does not interfere with the local mid-dorsal circulation. A further group of 10 cats were similarly transected, and 7 days later were injured at T-8 (500 gm-cm). Two hours after the blow, the tissues at T-8 were removed; several specimens were moderately edematous, but few had central hemorrhages. In this group, the traumatic lesions occupied less than 1% of the cord area, a highly significant reduction from the expected 23% standard injury lesion size (p < 0.001). When Brown-Séquard hemisections were created at T-1, 7 days before T-8 injuring, definitive traumatic lesions (hemorrhagic necrosis) developed within 2 hours in tissues contralateral to the surgical cut. There were only minimal lesions in wounded tissue below the hemisection. Since total or partial high spinal sectioning so significantly altered the location and magnitude of traumatic HN, it seems logical to postulate that descending neuronal pathways influenced central traumatic cord lesions.

Dorsal Root and Posterior Column Sections. In acutely injured animals under light anesthesia, myoclonic jerks often occurred distal to the site of injury; these were of sufficient magnitude to throw an unrestrained animal from the table. This phenomenon continued spontaneously for 3 to 5 minutes, and could be reinitiated by distal sensory stimuli (pain or touch) implying afferent involvement in the injury process.

To test local afferent influence on HN, four pairs of dorsal roots, T6-9, were sectioned prior to severe cord wounding between T7-8 at the middle of the rhizotomized cord. Two hours after injury, some of the histopathological specimens were edematous but there were no hemorrhages. Midline dorsal myelotomy extending over two segments rostral to the experimental injury site also reduced the otherwise predictable central lesions.

Thus both procedures indicate involvement of the dorsal root-posterior column
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axis in posttraumatic tissue changes. We interpreted the combined ablation-injury experiments as demonstrating the necessity for intact afferent-efferent spinal cord and root pathways in traumatic spinal cord autodestruction. Since integrity of either system seems requisite for the full development of HN, a neurotransmitter-vascular alteration seems more likely than direct traumatic vascular disruption.

The issue of cord pathways, as they may relate to cord injury lesions, is further discussed under the catecholamine heading in terms of the ipsilateral descending norepinephrine (NE) bulbospinal fiber system. The issue of cord pathways, as they may relate to cord injury lesions, is further discussed under the catecholamine heading in terms of the ipsilateral descending norepinephrine (NE) bulbospinal fiber system.

Catecholamine Theory of Traumatic Hemorrhagic Necrosis

Based on the intense traumatic vascular reaction associated with a time-based progression of traumatic spinal lesions, we undertook metabolic studies of naturally occurring cord neurotransmitter substances with documented vasospastic capabilities. Our experimental hypothesis was that trauma may induce an excessive or perverted neuronal metabolic response, leading to large elaboration and tissue release of transmitter substances. Provided access to spinal cord smooth muscle vascular receptor sites in toxic concentrations, these materials might produce vasospasm, hypoxia, and subsequent tissue necrosis.

High Catecholamine Concentration in Spinal Cord After Injury

Chemical Studies. After 500 gm-cm mid-thoracic injuries in cats, a fluorescent tissue product was isolated and identified with the technique described by Fleming, et al.; the concentration of this product increased fourfold within 1 hour. The material remained in supranormal concentration until necrosis was practically complete at 4 hours, and thereafter it decreased. The material had the excitation (410 m\(\mu\)) and emission (520 m\(\mu\)) spectra of authentic norepinephrine (NE).

Histofluorescent Studies. Using the histochemical reaction of Falck-Hillarp, catecholamine (CA) can be identified by characteristic yellow green fluorescence. When tissue is viewed with the ultraviolet microscope, the microanatomical CA position can be seen and semiquantitative concentration estimates made.

Synaptic fluorescent granules of CA are sparsely seen throughout gray matter and upon small vessels in normal spinal material. However, Irvin found that the CA pattern and intensity had changed dramatically 1 hour after severe injury (500 gm-cm). A brilliant CA fiber collection fanned into the gray from the intermediolateral gray matter, while a profusion of CA synaptic endings now ringed most gray neurons (Fig. 8). Small vessels often had many more densely fluorescent CA dots (Fig. 9). Rated on a semiquantitative scale...
for the combined features of numbers of CA granules and individual synaptic intensities, controls were 1+ and injured tissue 3+ or 4+. Trauma not only increased CA fluorescence in its normal anatomical location (gray matter) but introduced CA into the white matter, where it is not found in normal tissues.

Vise, et al., in an independent recent study, found that injured tissue samples prepared by formol-saline technique contained more yellow green (CA) fluorescence than controls. The fluorescent intensity (increased CA concentration) was greatest 1 and 2 hours after wounding. An example of the superb quality of Vise's material is shown in Fig. 10 and the cover illustration. There can be no doubt concerning definitive semiquantitative CA increases in this study. We differ only in our interpretation of the mechanism of CA accumulation, for Vise believes the material concentrates in wounded tissues from blood sources as a consequence of blood-brain barrier disturbance within gray matter. This issue cannot be resolved until detailed neurochemical and surgical studies have been performed that clearly delineate CA contributions from the peripheral and central nervous systems.

Lesion-Producing Capability of Catecholamines

The capability of a given material to reproduce traumatic lesions must be established if it is to be designated a pathogenic agent. Since injected NE (levophed) is known to cause hemorrhagic sloughing of many body tissues, this action was tested within the intact spinal cord. Under rigidly controlled conditions (micro-injection of 10 μl/5 min, with 35 and 100 mg NE as base), NE caused lesions of a size 4.6% and 8.0% of the cross-sectioned cord area respectively. Controls injected with saline were lesion-free. Areas of hemorrhage and necrosis localized about the needle tip (35 mg) and spreading 2 mm over gray matter (100 mg) were always found in specimens injected with NE.

Majno and Palade confirmed the devastating tissue changes produced by neurotransmitter materials; histamine, serotonin, and bradykinin all produced distinct ultrastructural changes in 3 to 4 minutes. When these endogenous mediators were injected into tissues they increased vascular permeability by causing gaps to appear between endothelial cells; postcapillary venules were especially susceptible. The gaps presumably resulted from endothelial contractions that made a sieve of the vascular wall; these

Fig. 10. Formol-saline histofluorescent preparation of the traumatized thoracic cord of a dog (300 gm-cm). Yellowish fluorescence can be seen on either side of a small gray vessel which has been sectioned longitudinally. For color reproduction see cover illustration. (Published through the courtesy of Dr. W. M. Vise.)

Fig. 11. Histofluorescent preparation of thoracic spinal cord (T-8) in the cat after severe untreated injury. An intense accumulation of catecholamines (arrows) can be seen at the edge of the developing necrotic zone (HN) which appears as a blank region to the right. X 84.
vascular clefts became large enough to leak red cells into the perivenular spaces. It is noteworthy that chemically-induced endothelial gaps occur prominently in the same structures (venules) which first become "leaky" after spinal cord injury. The effect of injected NE on vascular epithelium must still be established. Figure 11 illustrates this concept by a dense accumulation of CA about the edge of a developing zone of central necrosis soon after severe injury. This massive flooding of vascular receptor sites with amines is thought to produce vasospasm, endothelial clefts, and subsequent hemorrhagic necrosis.

In order to avoid lesions caused by the trauma of injection, the microinjection method established by Sinha, et al., must be carefully followed. If more than 0.1 ml/min is delivered, internal trauma results in histopathological changes similar to those following blunt injury; the injection of 10 μl/5 min of saline caused no microscopic lesions and is the method we recommend for intramedullary drug testing. Failure to reproduce these results depends primarily on technical factors concerning needle size, excessive injection rates or volumes.

Modification of Injury Response by Anti-CA Therapy

The third and final requirement for proof of CA involvement in spinal cord injury is the ability of specific anti-CA therapy to produce unequivocal improvement in traumatic lesions. Several such agents have fulfilled this criterion in our hands. Alpha methyl tyrosine, reserpine, FLA-63,* and phenoxybenzamine all significantly minimize the size of the lesion 2 hours after controlled wounding of the spinal cord (p < 0.001). Black agrees with us on the efficacy of reserpine, while Hedeman and Shellenberger's best recorded pretreatment for preserving walking ability was phenoxybenzamine, a highly specific NE receptor blockade. This material is discussed further in the treatment section of this review.

CA Studies from Other Laboratories

Two separate groups of investigators have recently found posttraumatic metabolic alterations in spinal cord dopamine (DA). Within 15 minutes after moderately severe trauma to the spinal cord of dogs, Hedeman and Shellenberger observed a sharp increase in the DA content of the cord; 45 minutes after injury they recorded a peak seven times the control level, and by 90 minutes the DA had declined to nearly the control level. Naftchi, et al., employing a similar CA assay procedure, found a twofold increment in DA concentration 1 hour after less severe spinal cord trauma in the cat. On the other hand, simultaneous norepinephrine (NE) assays on the same wounded tissues indicated that compared to controls, the injured cords contained normal or somewhat lower NE levels at 45 and 60 minutes and nearly 50% less NE at 3 hours. Several of these differences from control were difficult to validate statistically.

At first glance, these reports stand in

*FLA-63 is manufactured by AB Biotec, Chemical Department, Maria Skolgata 83, S-116 52 Stockholm, Sweden.

†In this discussion context CA refers to either norepinephrine (NE), dopamine (DA), or both amines.
direct conflict with our original work regarding injury CA. We found acutely increased NE and slightly lower DA in injured cat cords, in other words, a mirror image of Hedeman and Shellenberger's time curve of DA-NE content. Both observations cannot be totally correct, yet in the context of the following discussion a harmonious compromise may be reached.

Although different species and CA extraction procedures were used, these technical variations cannot explain the discrepant results. We believe Shellenberger and Gordon's chemical assay method to be a reliable and sensitive procedure for DA analysis, and have recently adopted it as routine in our laboratory. No doubt the assay method used by Naftchi, et al., is equally reliable. At present, we must accept the neurochemical DA results as being valid for their experimental injury systems and conditions. Nonetheless several vitally important questions concerning experimental methodology, control values, and conclusions about spinal CA fibers in traumatic HN, will be discussed in the context of the total available knowledge. We will develop specific arguments about NE in the wounded spinal cord, show how DA is involved within this specific system, and hopefully unify the available data.

Differences in Experimental Methods

Operative Technique. As noted by Hedeman and Shellenberger, the dopamine content of the spinal cord is extremely sensitive and reacts to injury within 5 minutes. The norepinephrine reaction is perhaps even more delicate. We performed laminectomies on uninjured animals, and after detailed evaluation of them in comparison with intact animals, we realized that the NE values in our "uninjured" laminectomized controls were supranormally elevated and therefore invalid for comparative baseline purposes. Minor surgical mishaps elevate tissue NE content by as much as 200% within 1 hour. The experimental operative technique cannot be considered valid for CA studies until NE levels in the laminectomized-uninjured cord approach those found in unoperated animals. When this obtains the manipulative errors are nil; the procedure and changing amine levels will reflect metabolic response to the experimental trauma alone.

A suspicion of this experimental error appears in Naftchi's study, in which a 16% differential was observed in NE measured rostrally to caudally over 3 cm of laminectomized (but non-injured) cord in the mid-thoracic region. NE content varies somewhat between cord regions, but significant differences within so small an anatomical confine have not been observed in our studies or, to our knowledge, in any other laboratory. In a similar vein, tissue NE levels in Hedeman and Shellenberger's controls (3 animals) also appear abnormally high. Their NE values at 3 hours after injury were recorded as subnormal (50%); however, NE is, in our experience, still elevated at this time and approaches control, but never subcontrol values 4 hours after injury. If true NE control value is less than that 3 hours after injury, then their postinjury NE data become similar to ours.

Experimental Injury Forces. Experimental injuries have customarily been expressed by gram-centimeters. As discussed earlier, however, the area impacted must be specified before wounding forces can be interpreted from laboratory to laboratory. In our injury system 500 gm-cm of impact energy is applied to a 7.06 mm² cord area (severe injury). By employing a larger footplate (19.81 mm²) and only 370 gm-cm energy, Naftchi, et al., made a moderate injury. Hedeman and Shellenberger also applied less force per unit area than we do. In order to reproduce our injury forces per unit area with the larger footplate, such as that used by Naftchi, et al., 1400 gm-cm of impact energy would be required. By simple calculations then (1400/370), our injuries carry nearly four times as much energy as those studied by the other investigators. The validity of comparing metabolic injury data collected from such disparate sounding systems must be seriously questioned.

Collection and Storage of Tissue. Catecholamines of the spinal cord are rapidly destroyed by enzymatic action if they are not removed within minutes of death, if excessive tissue manipulation occurs during dissection, or if the specimens are not immediately frozen. The tissue must not be
stretched, deformed, or squeezed, as such manipulations cause rapid CA changes. Somewhat more tissue should be collected than is required for analysis so that the ends, which are traumatized by forceps during collection, can be atraumatically removed. Small tissue bits for histofluorescent study may be frozen on dry ice, but specimens for neurochemical analysis should be frozen more rapidly, as, for instance, in liquid nitrogen or methanol refrigerated by an acetone-dry ice mixture stored at -80°C and assayed within 48 hours. The surgery involved in tissue exposure and removal is so critical to success of biochemical studies that this author refuses to delegate these tasks.

Experimental Interpretations and Conclusions

Absence of Dopamine Fibers and Receptor Sites in the Spinal Cord. There is extensive literature on neuropharmacological and neurochemical studies of the CA of the spinal cord. Much of the work is from Sweden, under the leadership of Andén, Carlsson, Falck, Hillarp, Dahlstrom and Fuxe. They specifically chose the spinal cord for central NE studies because unlike the brain, it uniquely contains a single and pure NE fiber system. The only CA fibers found in the cord are noradrenergic, and the spinal CA receptor sites are definitely NE-specific. Based on several exquisite investigations over the last decade, the consensus of these authorities clearly is that there are no DA fibers in the spinal cord.

Thus, when Hedeman and Shellenberger suggest that the increased DA in injured cords may be causally related to traumatic HN, they fail to recognize or explain their divergence from a large and solid body of literature on spinal cord CA. A more likely interpretation is that moderate injury increases DA synthesis so that it saturates the available dopamine B-hydroxylase (DBH) enzyme in NE neurons, and so leads to a DA pile-up. As a consequence, and providing DBH activity was not compromised by trauma, NE synthesis and release would be substantially increased and the toxic effect of NE thereby realized.

The conspicuous absence of spinal cord DA receptor sites also argues against cord lesions being caused by DA. It is, however, theoretically possible for trauma to so disrupt NE terminals that axoplasmic DA flows from the wounded fibers. The free amine, differing from NE only by a hydroxyl moiety, might bind to NE receptors and mimic the physiological or toxic response of actual NE activation. Andén, et al., have studied and discarded the likelihood of this possibility. In experiments with spinalized rats, they reduced NE storage by reserpine, and administered L-dopa. They found that the consequent relatively small NE formation had much greater functional significance in NE receptor activation than in the larger DA formation. When NE synthesis was prevented by FLA-63 in this system, they found only slight NE receptor stimulation by massive DA presence. From these results, Andén and Fuxe concluded that NE was 20 to 100 times more efficient than DA in activating spinal cord NE receptors. In carefully controlled experiments, we have shown that DA infusions into the spinal cord can induce small lesions (hemorrhagic necrosis), perhaps via the NE receptors; however, at least 70 times more DA than NE is required for an equal response.

We believe that since the cord has no DA fibers or receptor sites and since DA is itself an extremely weak spinal cord NE receptor activator, DA should be more properly considered a metabolic precursor of NE than an etiologically active substance in spinal cord injury.

Common Pitfalls in Interpreting Tissue Neurotransmitter Concentrations. All published CA spinal injury chemical data have been collected from simple tissue amine concentrations measurements. The CA neurotransmitters are said to be responsive to injury if the cord concentrations vary significantly from control at some time after wounding. Such tissue content experiments evaluate only steady-state neurochemical concentrations ("stores") at a single study time. Major interpretive errors can be made from such data if the neuronal study system is rapidly or irregularly discharging and/or synthesizing its neurotransmitter material. Even under normal dynamic neuronal activity states, which may vary

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from moment to moment, tissue amine content is no more than a gross reflection (the algebraic sum) of the difference between release rate and new neurotransmitter formation. Spinal cord CA neurons, like all neurons, operate by processing their individually characteristic neurochemical instead of merely containing it. Neurotransmitter content analysis is therefore a relatively poor method of determining neuronal activity at a given point, and even less indicative of a neural function over a time span.

In this context, supranormal spinal cord DA levels associated with normal or low NE concentration at some point after wounding can be theoretically predicted. If it is assumed that post-wounding NE release exceeds synthesis, then neuronal amine stores would become partially depleted. To compensate the lowered NE should trigger increased synthesis, via elevated tyrosine hydroxylase activity, with resultant increase in L-dopa and DA. These metabolic adjustments may provide more DA per unit of time than can be enzymatically converted to NE and supranormal DA levels may thus result. The relative DA and NE spinal tissue concentrations would certainly vary with the stage at which this dynamic, intraneuronal process was observed. The true magnitude and meaning of any observed CA changes can only be determined by detailed, differential CA turnover studies, and these are now in progress.

Role of NE in Hemorrhagic Necrosis after Spinal Cord Injury

Neuropharmacological probing adds another dimension to our knowledge of the neuronal network which mediates the toxic sequelae of spinal cord injury. With known drugs we can block specific receptor sites, selectively inhibit synthetic enzymes, and either stabilize, release, or prevent neuronal re-entry of specific neurotransmitters. Hill and this author have investigated these various neurochemical mechanisms by testing the effects of each drug category upon traumatic hemorrhagic necrosis. The relation of some of these investigations to NE-DA spinal cord injury roles is summarized below.

NE Synthesis Inhibition (DBH)

In one study, cats were treated before injury with FLA-63* and tissues were examined 2 hours after injury; hemorrhagic necrosis of the spinal cord was essentially nonexistent. This marked protection (90%) was highly significant, compared to control injuries (p < 0.001). As used in this study, FLA-63 selectively and completely inhibits the intraneuronal enzyme dopamine B-hydroxylase. By blocking this enzyme, FLA-63 prevents DA hydroxylation and therefore NE synthesis in the descending noradrenergic neurons of the spinal cord. Further, the ability of FLA-63 to protect the injured cord from acute HN indicates that continued NE neuronal synthesis is necessary for the spread of the central, injury-induced lesions. The results of this experiment strongly argue against a separate role for DA in spinal cord injury, since DA accumulates within noradrenergic neurons after FLA-63 treatment and is, in this system, incapable of producing significant lesions.

NE Receptor Blockade

The only other possibility for a direct (e.g., non-precursor) DA spinal injury involvement would seem to require the presence of specific cord DA receptors. If such receptors were present (unknown to this time) and activated in response to excessive DA, and were also responsible for lesion development, then timely pharmacological DA receptor inactivation should ameliorate cord damage. Pimozide and haloperidol are potent, highly selective inactivators of central DA receptors, as shown by a convincing variety of test procedures. Pretreatment with either drug completely failed to protect cords from acute central hemorrhagic necrosis from injury. In fact, the cords of cats pretreated with pimozide (the most selective DA blocker) appeared to be more severely damaged at injury than injured control cats.

*FLA-63, or bis(4-methyl-1-homopiperazyl thiocarbonyl) disulphide, is manufactured by AB Biotec, Chemical Department, Maria Skolgata 83S-116 52 Stockholm, Sweden.
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animals. These results show that unlike inactivation of NE receptors, central DA receptor blockade does not ameliorate traumatic lesions.

Compelling support for the presence of NE receptor sites upon spinal microvasculature has been provided by Hartman. Using an extremely sensitive and definitive immunofluorescence DBH technique, he found numerous NE synapses upon small vessels in the monkey. A highly purified DBH antibody is used in these studies, and the presence of DBH is this synaptic-receptor position identifies the CA fiber as noradrenergic. In this regard the vascular innervation of brain and spinal cord are similar. Hartman speculates that a common brain stem NE fiber system may autoregulate blood flow to both organs (see below).

In summary, neuropharmacological studies support the following findings: 1) there are no spinal cord DA fibers; 2) in spite of intensive study spinal cord DA receptors have not been found; 3) DA in the spinal cord only weakly activates NE receptors, and is 70 to 100 times less efficacious than NE in this regard; 4) when DA to NE conversion in the spinal cord is arrested by FLA-63, central wounding lesions are markedly diminished in spite of massive DA pile-up; 5) specific NE receptor blockade by phenoxybenzamine greatly attenuates hemorrhagic necrosis of the spinal cord; 6) specific DA receptor blockade by pimozide or haloperidol does not diminish the size or progression of wounding lesions; and 7) synaptic innervation of spinal cord microvasculature is NE-specific.

Spinal Cord Catecholamine Fibers

Much confusion has arisen concerning the nature and origin of the catecholamine fibers of the spinal cord. We have long been accustomed to associating the NE fibers solely with the peripheral sympathetic nervous system. The catechol-spinal cord fiber system is, however, another unique and extensive nervous plexus and is anatomically quite distinct from the vegetative nervous system.

The NE fibers in the spinal cord descend from cell bodies in the reticular medulla. In normal states the NE fiber ending can be seen by histofluorescence as multiple punctate dots in synaptic relationships within the spinal gray matter (neurons and vessels). These minute fluorescent spots are visualized because the CA, highly concentrated in synaptic storage vessels, forms an intensely fluorescent formaldehyde reaction product. By the same token CA fibers (versus synaptic terminals) are not ordinarily seen since diluted non-aggregated axoplasmic CA materials are below the level of technical sensitivity. Following transection of the spinal cord, however, the proximal cut CA axon stumps become bulbous and engorged with CA-fluorescent material. Under these experimental conditions the anatomical position of amine fibers can be mapped. In our laboratories, Irvin has found innumerable descending catechol fibers diffusely spread in the lateral and ventral white matter. CA fibers are characteristically absent in the posterior columns and only occasional fibers are seen in the spinal roots. At all spinal levels, some amine fibers congregate in the intermediate gray matter as a dense band prior to distribution, mainly through the ipsilateral gray matter, but with a small contribution to the other side. CA fibers terminate upon small vessels in the cord (Fig. 9), and on gray neurons (Fig. 8). We have seen amine terminals on almost every central gray neuron, although these connections are more extensive upon anterior than posterior horn neurons.

Sparse CA fluorescence dots can be seen on normal spinal cord vessels, but the quantity is small and CA is poorly shown and at times is unconvincing. After traumatic injury or certain drug treatments, however, there is an abundant distribution of fluorescent amine materials in synaptic relationship with the central microcirculation (Fig. 9). Trauma causes increased brilliance of these endings as well as the appearance of many more synapses than are ever seen in controls. Therefore, the study of traumatized material portrays the extent and complexity of spinal vasomotor CA innervation more accurately.

In their descent from hind brain, CA fibers are enmeshed with other descending white matter amine fibers. One week after high spinal section all fluorescent materials
disappear from the parenchyma of the distal cord. The only fluorescent materials seen in chronically transected material are the discrete fluorescent synapses upon the large pial vessels. Perhaps these vessels are innervated by the peripheral sympathetic system via recurrent radicular fibers. Large vessel CA fibers do not follow the vessels into the cord parenchyma and are therefore distinct from the microcirculation amine system.

Norepinephrine, the active transmitter material in this system, is synthesized within spinal cord neurons from tyrosine, which easily passes the blood-brain barrier. Tyrosine is converted successively into dopa and then to dopamine. NE is finally formed by the action of dopamine beta hydroxylase at the synaptic vesicle where the transmitter is stored and protected from enzymatic degradation. The synaptic granules are transmitted down the catechol fibers to accumulate at synaptic terminals. Coincident with neuronal electrical activity a quantum of NE is released from the granule and freed from the fiber. This response has been chemically documented; increasing amounts of free NE are detected in fluid bathing the electrically stimulated and isolated spinal cord.

The physiological action of NE upon synaptic dendrites in the spinal cord is a type of membrane hyperpolarization which effectively blocks further synaptic or anterograde electrical invasion. When the authentic amine is electrophoretically applied to gray neurons there is a rather consistent depression of electrical activity. NE may therefore qualify as a natural inhibitory transmitter substance within the spinal cord. Synaptic transmission is also profoundly inhibited by administration of the NE precursor dopa. Presumably this results from rapid synthesis of NE, although a direct dopa neuronal response cannot be excluded.

**Spinal and Cerebral Blood Flow Autoregulation**

From the above discussion of the histofluorescent and immunofluorescent CA microvascular system, it is apparent that small spinal parenchymal vessels derive rich CA fiber innervation via the bulbospinal system. Since blood flow autoregulation in the spinal cord must occur at small vessel level, the intricate CA vascular innervation of these structures should be highly significant. Hartman and Udenfriend, using DBH immunofluorescence, demonstrated in monkeys a similar CA fiber system upon both spinal cord and cerebral vessels. They proposed that this neurovascular system be considered the controlling mechanism underlying cerebral autoregulation. Perhaps this is so. Brain and spinal cord vessels are known to autoregulate in essentially the same manner, and perhaps both are controlled from a single brain stem CA center with fibers ascending to the brain or descending to the cord.

Conclusive controversy arises when spinal or cerebral autoregulatory mechanisms are discussed in terms of nervous control. This is because experiments with neurotransmitter materials have often been inconclusive and the results even disparate. For example, when purified amines are injected into the spinal arteries they seem to have no predictable control over local blood flow. Under these conditions NE does not usually cause vasoconstriction, and may, under some experimental conditions result in vasodilation. Undoubtedly this is true, for it has been long known that the CNS vasculature is little affected by blood-borne catecholamines. These observations neither prove nor disprove a CA fiber regulating influence, but rather confirm the fact that intravascular vasoactive amines such as NE and epinephrine are metabolically excluded from CNS entry by the active brain-spinal cord barrier system. If the mediating substance cannot gain access to its physiological receptor site, no response will occur, and the experimental testing model is, for flow regulation purposes, invalid. For perhaps similar reasons, irregular vascular responses have also been obtained with topical or subarachnoid catecholamines. When placed in the spinal fluid, the amines may not be able to penetrate tight tissue junctions throughout the brain to reach the controlling microvasculature receptor sites. An added complication arises in subarachnoid studies because of duality of large versus small vascular...
Review of current research on spinal cord injury innervation. The large pial vessels are supplied by peripheral sympathetic CA fibers (if they are the same as the cord), while parenchymal vessels are separately innervated by the brain stem CA system. The function of each network may be quite different. Subarachnoid amines should have more influence on the larger CSF bathed vessels; misleading inferences may be drawn if data are extended to include the microvasculature system. If these objections to intravascular or subarachnoid transmitter test routes are confirmed, more discrete study will be required. We propose direct microtissue CA injections in conjunction with adjacent microcosm flow studies as perhaps the only method of getting the amines into an active position, and determining their ability to modulate central regional blood flow.

Current Diagnostic Methods for Determining Spinal Cord Conduction

**Sensory-Evoked Potentials**

In 1954, Dawson introduced an objective electrographic technique for evaluating spinal cord conductivity. From a single peripheral nerve shock he was unable to induce a visible evoked potential over the cortical sensory area; however, when repetitive nerve stimuli were delivered 1/sec and 20 such cortical records superimposed, definitive changes in the sensory-evoked potential (SEP) occurred in the appropriate sensory area of the brain for half a second or longer. By developing an electronic signal averaging device, he improved the sensory evoked potential visualization. This technique is now commonly replaced by the standard memory storage oscilloscope or computer signal averaging devices.

In 1960, Gilbin reported an SEP study on seven patients with spinal lesions involving the posterior column. He could not produce cortical SEP's from distal nerve stimulation, and concluded that the spinal SEP pathway lies in the white matter of the posterior cord. Halliday and Wakefield further documented this observation in the Brown-Séquard syndrome with unilateral position sense loss. Normal evoked brain responses were recorded from the cortex contralateral to the normal side but SEP's were characteristically diminished or absent from the abnormal half of the body. They also described four patients with reduced and delayed SEP's. Even when the position sense was recovering, SEP's remained minimal.

The conventional pain pathways are not necessary for SEP; patients with only loss of pin prick sensation showed evoked responses that could be readily produced by stimulation of either side of the body. Morin found a supplementary spinal pathway in the cat whereby cutaneous stimuli were rapidly conducted up the posterior ipsilateral dorsal funiculus. Should this system be documented for man it would suggest that cutaneous sensory shocks traverse the posterior ipsilateral spinal cord and that their cortical arrival rather accurately predicts integrity of that quadrant. Bilateral normal SEP's should indicate functional, and probably structural, integrity of the posterior half of the spinal cord.

Donaghy and Numoto found that recovery of SEP within 4 hours of severe spinal cord injury indicated a good prognosis for acutely paraplegic dogs. Campbell, et al., also defined the usefulness of bioelectrical studies in acute spinal cord trauma since they could, on the basis of SEP's, make reasonably accurate predictions concerning functional recovery in the experimental animal. If after a graded blow, the averaged evoked cortical potential response to contralateral peroneal nerve stimulation returned within 3 hours of impaction, it could be anticipated that the animal would regain walking ability in 6 weeks. On the other hand they observed that the continuing absence of SEP's 3 hours after spinal cord contusion was always followed by lasting sensory-motor paralysis.

Gelfan and Tadov reported electrophysiological measurements made across a standard spinal cord compression. A pressure of 200 mm Hg about a 5-mm cord segment by an encircling cuff caused failure of impulse transmission. In order to determine the role of mechanical compression versus anoxia upon nonconductivity in the spinal cord they compared the cuff data to that obtained after anoxia induced by administration of intratracheal nitrogen or
by ascending aorta ligation. They concluded that the effects of cord or peripheral nerve compression resulted solely from mechanical neuronal distortion. This assumption was made because the patterns due to electrical inactivation by compression are directly opposite to those attending generalized hypoxia. No oxygen tension measurements were made in the region of cord compression to support their experimental conclusions.

The electrical inactivation pattern of generalized ischemia to the entire complicated spinal cord system may be quite different from that for localized or segmental cord anoxia. It seems illogical that local tissue compressive forces above systolic blood pressure would not arrest blood flow in the tissue. If this is true, they may have been led to an erroneous conclusion by their experimental design. The evidence already presented supports a hypoxic mechanism after blunt spinal cord injury, at least for progressive hemorrhagic necrosis, and this assumption should be valid for severe spinal cord compression as well.

Unfortunately the prognostic significance of SEP may differ with the site of injury. Cervical cord injuries seem to produce SEP’s that differ from those related to thoracic trauma. Campbell interpreted the absence of SEP 3 hours after injury as functionally irreversible for the thoracic cord. However, Singer, et al., reported return of SEP 24 hours after severe mechanical distortion injuries of the cervical cord, but evoked activity within the reticular formation remained absent throughout the 6-week study period. Reticular SEP’s should be more thoroughly evaluated in light of this observation, as they may be a more sensitive indicator of small traumatic cord lesions than cortical responses.

Croft, et al., recently reported that SEP’s were useful in assessing intraoperative spinal cord conductivity. They recorded cortical evoked potentials in anesthetized cord of sufficient magnitude to provoke reversible blockade of potential. Motor responses were also evaluated by stimulating electrodes stereotaxically placed in the cerebral peduncles. Motor and sensory potentials were simultaneously abolished by a 38-gm weight applied to the exposed cord for 20 minutes. In this experimental setting, motor and sensory conduction blocks were parallel and invoked by similar compressive forces. The study suggests the value of SEP in predicting the results of decompression of the spinal cord.

Unfortunately bioelectric techniques without direct electrode insertion have not yet been perfected to evaluate corticospinal function in spinal cord trauma. It was anticipated that caloric stimulation of the eighth nerve would influence the tonic motor activity of distal musculature and thereby predictably change the averaged electromyographic (EMG) response in normally innervated systems. By inference then, some diagnostic change in the caloric-EMG response might occur with vestibulospinal tract injuries. In pilot human experiments this technique has thus far proven unreliable. Objective electrographic assessment of descending spinal cord function is needed for better objective evaluation of human cord trauma.

The “H” reflex has recently been advocated by VanGilder as a useful measurement of spinal gray integrity. He believes that the absence of this segmental reflex after trauma indicates considerable disruption of the central internuncial pool by traumatic hemorrhage.

The most detailed available human SEP study has just been reported by Perot. He found a maximal cortical evoked response after 128 repetitive stimuli to the peripheral nerve recorded over 2 minutes. His study of 47 patients led him to believe that somatosensory evoked potentials have a definitive role in patient management since they provide a sensitive and early indication of incomplete spinal cord lesions. This technique will also provide valuable monitoring during treatment of spinal cord injuries.

Current Experimental Treatment of Spinal Cord Injuries

Partly because of the original impetus given spinal cord injury treatments by Albin, et al., several laboratories in this country and Canada have developed major research programs in spinal cord injury over the last 10 years. This has been due in part to frustration with present clinical methods but
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also because the spinal cord presents an ideal study model. Unlike the brain, where severe experimental injuries are complicated by multiple support factors, animals with injured spinal cords survive with minimal care, and the efficacy of treatment is more easily assessed. Experimental treatments are usually surgical, metabolic, or a combination.

Surgical Treatment

Midline Myelotomy. As originally suggested by Allen, midline myelotomy has often been proposed as a useful early treatment for severe cord injury. Three human cases were treated in this fashion at Allen's insistence in 1914. The first patient had suffered an ascending neural loss from hematomyelia which responded favorably to cord incision, but he unfortunately died in the subacute phase from intracranial hemorrhage. A second myelotomy was done in a patient with total sensory motor loss from thoracic injury. Four days postoperatively there was return of distal deep pressure and position sense. The third case was reported to be gradually improving after 1 year.

The myelotomy issue was experimentally reevaluated by Freeman and Wright in 1953. They applied midline cord incisions after 500 gm-cm injuries in the dog. Unoperated animals universally failed to regain distal neural function after this blow while three of nine treated animals were able to walk. A similar result was obtained by Campbell, et al., in 1972; early myelotomy led to successful restoration of motor function in three of ten animals.

Allen and contemporary investigators ascribe the efficacy of myelotomy to mechanical cord decompression and removal of noxious blood elements. Campbell, et al., feel heme and heme copper complexes from blood decomposition may initiate structural deterioration of spinal cord myelin and perhaps other formed cord elements.

We found that when myelotomy was done four segments above a subsequent injury site, the injured cord was protected against hemorrhage; there were some minor areas of necrosis but the lesions were significantly smaller than those that followed untreated wounding. At the cord site below the myelotomy, but above the injury, there was a definite and qualitative reduction of NE histofluorescent varicosities. Thus we feel that myelotomy modifies both the neurotransmitter and HN injury response. In terms of the chemical theory of HN, fiber sectioning alters the traumatic chemical response and this, rather than mechanical decompression, may be the protective factor.

Rhizotomy. As noted, a posterior root-dorsal column system appears to be the afferent loop for traumatic HN. A bilateral two-segment section of the dorsal root on either side of a future injury protects against traumatic lesions. The histofluorescent catecholamine pattern more closely resembles normal than that in the untreated injured cord.

We believe there is a definite therapeutic place for immediate myelotomy or dorsal root sectioning in the management of acute spinal cord injuries. Both procedures interrupt the hemorrhagic afferent loop system. Until systemic antimetabolic or other effective therapy is fully tested and developed for human use, these techniques are sound and some functional preservation may be gained by their use. The myelotomy effect should be accentuated in combination with steroids or hypothermia as elaborated below. When myelotomy is undertaken we urge that it be done at the injury site and extended proximally two segments. The rationale for proximal cutting comes from our observations that important inputs to the autodestructive system stem from at least two proximal root pairs. Although myelotomy can probably be safely done at any level in the cord, rhizotomy must be restricted to the thoracic region. In either case careful attention must be given to preservation of even the smallest spinal cord vessel and magnification techniques are essential. These procedures are best applied within the first few hours to patients with total sensory-motor loss.

Nonsurgical Treatment

Urea. Since injured spinal cord tissues are edematous, dehydration therapy may lessen neuronal destruction. Joyner and Freeman
Jewell L. Osterholm

treated experimentally injured animals with urea. As would be expected from moderate 375 gm-cm injuries, almost half the untreated animals regained walking ability over a period of 4 months of observation. Many of them walked imperfectly. By comparison, all animals treated with urea walked without obvious neural deficit in half this time. In spite of this encouraging initial report, we are unable to find subsequent experimental or clinical documentation concerning the efficacy of urea. A hypertonic therapy does not usually pose excessive risk, it should be reinvestigated either singly or in combination with other presently available methods.

**Hypothermia.** Albin, et al., have widely published and acclaimed hypothermia as an effective treatment for spinal cord injury. In addition to this major scientific contribution they were the first to suggest the justification for a guarded optimism regarding the reversibility of the results of spinal cord injury. By thus removing the existing hopeless attitude toward all spinal injury treatment, their work inspired renewed interest in research leading to major breakthroughs.

Deep hypothermia (7°C to 20°C) was tried because it slows neural enzymatic processes and reduces cellular metabolic rates and oxygen requirements. In their initial experiment, Albin, et al., rendered 13 control monkeys irreversibly paraplegic at T-10 by a 300 gm-cm force impact, and failed to demonstrate neural recovery after 1 month. On the other hand, 14 injured monkeys treated by local hypothermia from 4 to 7 hours after injury had excellent return of function in a similar time. The only real criticism to be made of this work is that the injury forces are now known to be moderate and function should return in some untreated animals. It would be much more impressive if similar results were obtained after 400 to 500 gm-cm blows. Their results, however, suggest the value of this treatment for moderate spinal cord wounding.

In their most recent report, White, et al., applied laminectomy and hypothermia to acute human cervical injuries. Of five treated patients, three achieved some functional return in the legs. If we can be assured that a total sensory-motor loss paralysis existed prior to hypothermic treatment, the results even in this small series must be considered impressive.

Other investigators have presented experimental data to confirm the efficacy of local hypothermia in the treatment of spinal injuries. In a critical review Ducker and Hamit found that animals treated with hypothermia achieved significantly better functional results than untreated controls after standardized experimental injuries. In our hands experimental cord injuries in animals treated by irrigation with 4°C saline 15 minutes after wounding until sacrifice 2 hours postinjury significantly retarded HN. We do not have data on long-term functional recovery after cold-treated injuries, but hypothermia definitively does alter the acute phase of central cord lesions.

The efficacy of extravascular surface injury cooling has been questioned by Howitt and Turnbull. They found this method of no clinical benefit in 17 rabbits injured with 50 gm-cm blows. At sacrifice there were no histological or microangiographic differences between the spinal cords of the treated and control animals. Black and Markowitz cooled monkeys with 300 gm-cm cord injuries for 4 hours and found a somewhat slower recovery rate than for untreated controls. They believed some deleterious effect may follow dural opening since swollen cord tissues can possibly herniate through the defect prepared for surface cooling. Selker cooled three patients with penetrating cord injuries and one with a closed injury; he reported no functional recovery in the 1-year follow-up. This series was heavily weighted by a preponderance of penetrating injuries which are more likely to lacerate cord tissues, and may not be a valid answer to the effect of hypothermia on blunt spinal cord injury.

Hypothermia exerts a profound influence on amine metabolism in the injured spinal cord. We found NE concentrations in injured tissues treated with hypothermia significantly reduced in comparison to untreated traumatized segments. The cooled tissues contain half the amine found in untreated wounded tissues (control tissue contains 0.46 μg/gm amine; injured tissue 1.2 μg/gm; injured hypothermic 0.67 μg/gm).

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\(\mu g/gm\). As NE levels were depressed by cold toward normal, there was a diminution in central hemorrhagic necrosis. Half the specimens had only minor histological alterations while the others had small gray hemorrhages. Untreated cords at this time characteristically have sizeable hemorrhages (23\% of total cross-sectioned area). In terms of the catecholamine injury hypothesis, hypothermia may confer injury protection through the ability to influence hyperaccumulation of NE after injury.

Since hypothermic treatment for spinal cord injury has shown variable and indecisive results from laboratory to laboratory, the technique requires further documentation. It may be naïve to assume that HN can be stopped by short term cooling. If HN is due to an inherent metabolic change, the process may continue for hours or days. After short treatments metabolic HN response suppressed by hypothermia may be reactivated with warming. A true and maximal hypothermic benefit can only be established through formal time-response curves. As closed nonoperative cold perfusion techniques can be developed, they should be experimentally applied for measured times and the optimal cold treatment schedule thereby defined.

**Hypothermic versus Normothermic Perfusion.** Recently Tator and De creeke\[189\] evaluated the results of spinal cord injury in monkeys perfused with cooled and noncooled Elliott’s B Solution (10 comparable animals in each group). Both treatments offered significantly better functional restoration than was found in similarly wounded non-perfused animals. Although the differences could not be substantiated statistically, the grade of neurological recovery after normothermic perfusion seemed consistently better than with hypothermia. This is a most striking observation. As to the mechanism of protective effect, they suggest perfusion dialysis of some noxious, injury-related, chemical material from the wounded cord. Their thesis is in harmony with much of this report. The authors have recommended normothermic perfusion treatment of selected patients with spinal cord injuries.

**Steroids.** Wide experience with high dosage steroid treatment for intracranial edema makes it clear that the glucocorticoids reduce intracranial hypertension and neurological deficits.\[92,95\] Steroids apparently maintain vascular integrity after injury, protect cellular membranes during hypoperfusion states, and support lysosomes.\[19\] In this context Ducker and Hamit\[49\] used glucocorticoid treatment 3 hours after 375 gm-cm standard spinal injuries. Four of 12 dogs recovered nearly normal function with intramuscular dexamethasone treatments continued for 1 week. Their treatment results were significantly different from the controls. Animals treated by intrathecal depomethylprednisolone also improved, although not as significantly as the intramuscular steroid group. They felt that the difference in treatment groups is based on a profound vascular influence by systemic steroids. Black and Markowitz confirmed the efficacy of steroid treatment in the experimentally injured monkey; they found that the rate of neurological recovery after 300 gm-cm injuries was statistically enhanced by intramuscular dexamethasone continued for 14 days.\[22\]

Glucocorticoids depress postinjury catecholamine metabolism and accumulation. Systemically administered hydrocortisone was more effective in this regard than topical subarachnoid steroids.\[112\] NE was 1.2 \(\mu g/gm\) in injured controls, 0.88 \(\mu g/gm\) in injured tissue treated with hydrocortisone, and 0.98 \(\mu g/gm\) in injured tissue treated with subarachnoid depomedrol. The intravenous medication lowered NE tissue concentrations 30\% while subarachnoid steroids induced a 20\% depression. Steroidal NE depression was less striking than that observed with hypothermia. Although hemorrhagic necrosis occurred in three-fourths of the steroid treated cords, the lesions were consistently smaller in number and size than those found in untreated controls. A major steroid characteristic is its remarkable stabilization of white matter.

It can be concluded that steroids do influence postwounding hemorrhagic necrosis of the spinal cord. Their potency in this regard, however, may not be great. The published studies relate only to moderate wounding, and although some treated animals improved, others remained paralyzed. Our clinical impression is that severely wounded patients do not fare much better.
with steroids than without. The final answer to this question awaits the creation of a severe injury steroid-dose-response curve. Since these drugs have known benefit, are easily administered, and usually cause no major complication (save gastrointestinal hemorrhage) their continued use in human injuries is justified.

Antifibrinolytic Therapy. Campbell, et al., recently described antifibrinolytic therapy in acute experimental injuries. The rationale for applying Amicar (aminocaproic acid) stems from its known action in bleeding disorders with active fibrinolysis. Amicar lessens bleeding by inhibition of plasminogen activator substance plus a lesser anti-plasmin activity. Thus a fibrin clot once formed may be somewhat more stable as the fibrin-destructive system is held in abeyance by treatment. Since hemorrhage is a major factor within acutely injured spinal cord tissues, the logic of clot stabilization and hopeful arrest of further bleeding is obvious. Although the influence of Amicar alone has not been reported, Campbell and his co-workers believe the combination of steroids, Amicar, and myelotomy are additive and more effective than the individual treatments alone. Three of five cats so treated for 400 gm-cm injuries regained walking ability.

Hyperbaric Oxygen. Kelly, et al., found that the spinal cord pO2 rapidly declined to near zero within 30 minutes after 400 gm-cm injuries. Although ventilation with 100% oxygen and more dramatically by an oxygen-carbon mixture resulted in increased cord tissue pO2 in normal animals, no such favorable effect was observed after wounding. Injured tissue pO2 could only be raised to supranormal values by local 2 or 3 atmospheric hyperbaric treatments. Twenty-five of 30 dogs had a significant functional recovery with hyperbaric treatment; thus another potentially useful treatment modality has been introduced.

Anti-Serotonin Therapy. Misra, et al., found increased serotonin (5 hydroxytryptamine) levels after spinal cord trauma. Based on this observation and the known distribution of the vasoactive amine in the spinal cord, Howitt and Turnbull treated wounded rats with methysergide, a serotonin antagonist, but were unable to show beneficial results. We are in agreement with this observation as tissue serotonin in the spinal cord is probably not increased by trauma. The situation is quite different for brain, however, for serotonin rapidly increases after trauma to brain stem and cerebral tissues and simultaneously appears in the spinal fluid.

Catecholamine Treatment

Alpha Methyl Tyrosine. Treatment of acute and chronic spinal cord injury in animals with alpha methyl tyrosine (AMT) (anti-synthetic NE agent against tyrosine hydroxylase) was first reported from this laboratory. AMT is highly effective in preventing acute NE hyperaccumulation, and when given 15 minutes after injury (500 gm-cm), protects against hemorrhagic necrosis. Two hours after severe experimental injuries, saline-treated animals have significant hemorrhagic necrosis (HN) of the spinal cord which on the average occupies 23.3% of the total cross-sectioned cord area. Alpha methyl tyrosine reduced the HN area by a factor of eight; the 14 treated cords averaged only a 2.9% area of necrosis (p < 0.001). We concluded that the development of acute posttraumatic HN requires the continued synthesis of a catecholamine neurotransmitter.

In a preliminary study, we allowed 15 cats to survive after severe injury and treatment with AMT. Five of them began walking within 2 to 10 days and three recovered completely. Eight animals were left with mild or moderate paraparesis; they vigorously withdrew tail and limbs in response to pain and regained some coordinated hind limb movements, but failed to walk. Two animals remained severely paraplegic.

The most effective AMT anti-HN dosage for cats was 200 mg/kg; however, renal shutdown and anuria followed this treatment in more than half the animals. We have been unable to reduce this toxic reaction by water loading or slow infusions.

Why AMT is so effective during the acute phases of injury while subacute and chronic injured and treated cords often become severely degenerated remains an unanswered question. Hedeman and Shellenberger
were unable to detect any protection from single treatments of AMT in chronic dog studies. We agree that many animals remain paraparetic, although in our hands there are real differences from untreated controls. Perhaps their relative failure with AMT relates to a necessity for retreatment. Other routes of administration are under investigation as we seek to sustain the initial beneficial effect and reduce toxicity.

We tested 18 drugs or drug combinations with known anti-NE synthesis, storage site depletion or receptor site blockade in the standard injury system. The treatment effects were compared by neurological assessment and histopathological cross-sectional tissue studies to results achieved in animals infused with saline 24 hours after standard 500 gm-cm force injuries. These are discussed below in descending order of anti-HN drug potency.

Reserpine. Reserpine, administered intramuscularly in doses of 2.5 to 5 mg/kg 15 minutes after injury and repeated in 12 hours has proven most effective in preventing hemorrhagic necrosis. On the average, 93% of cord structure is intact 24 hours after reserpine-treated injury. This compares to 30.6% viable remaining tissue with saline infusions. Black believes it is the best available agent in doses of 1 mg/kg initially, and 0.5 mg/kg in 24 hours; monkeys treated with reserpine did better than those treated with steroids, decompression, or hyperbaric oxygen. Reserpine is known to deplete catecholamines in the peripheral and central nervous systems, and to interfere with dopamine transformation to norepinephrine at the storage granule site.

Levodopa. Levodopa (75 mg/kg) was found to be surprisingly effective against traumatic cord lesions. The material was originally given to gain support for the NE hypothesis, as precursor loading should aggravate traumatic lesions. The anticipated result was not found, and paradoxically L-dopa stabilized the injured cord. Treated cords had 10% areas of necrosis while untreated cords were 70% destroyed. Anti-NE L-dopa action is not known for it induces orthostatic hypotension in the peripheral vessels by depleting sympathetic catecholamine stores and inhibits by diminishing tyrosine hydroxylase activity. Alpha Methyl Dopa. Alpha methyl dopa (AMD) given intravenously in doses of 40 mg/kg to 800 mg/kg, is a commonly used antihypertensive agent. The average area of necrosis 24 hours after injury with AMT treatment was 10%, a sevenfold reduction from the size of an untreated lesion.

Phenoxybenzamine. Andén, et al., reported that treatment with phenoxybenzamine (20 mg/kg) in combination with AMT (50 mg/kg Lf form) was superior to either drug alone. AMT renal toxicity may be overcome by diminishing the effective dosage by 75% in this combination. Three of four injured cords were almost totally preserved by this treatment. Dibenzyline is a known noradrenergic alpha blocking agent. Disulfiram. Disulfiram administered 7.2 mg/kg prevented traumatic hemorrhages and saved 53% more total cord area than saline alone. The drug specifically acts against dopamine beta hydroxylase (DBH), the final enzyme in NE synthesis.

6-Hydroxydopamine. Continuous epidural infusions of 6-hydroxydopamine in doses of 10 to 50 mg/kg first depleted catecholamines and then selectively destroyed the fibers. This chemical eradication of spinal cord NE is theoretically desirable. The efficacy of 6-hydroxydopamine by this route is demonstrated by 80% of the injured cord tissue being saved with treatment compared to 30% in the untreated group. Apparently there is very poor dural penetration, for major NE depletion follows microgram infusion via the subarachnoid route. We are currently testing this administration method since, if effective, the drug could easily be instilled percutaneously.

Other Anti-HN Drugs. Other drugs with anti-HN activity that have been screened are fusaric acid and FLA-63. These DBH inhibitors saved 79.5% and 78.0% of the injured spinal cord respectively. Guanethidine and bretylium produced 78.2% and 77.0% normal cord as compared to 30.6% remaining cord tissue 24 hours after injury.

From analysis of the 88 animals in this subacute pharmacological screening series we concluded that all anti-NE treatments have distinct cord-saving capabilities. The drugs differ mainly in the degree of protection which ranges from 11.4% to
62.4%. Eleven drugs were highly significant in this regard. From analysis of our entire drug data, 75% of all anti-NE treated animals (68 of 88) retained sufficient cord substance 24 hours after injury to predict future walking ability. This applied of course only if the HN was arrested and did not continue thereafter.

Summary

From the combined investigative efforts of several spinal cord research laboratories considerable progress has been made over the last 10 years. The nature of progressive hemorrhagic necrosis after injury has been emphasized by sequential microstructural studies. This process may be primarily responsible for chronic functional loss after severe blunt injuries, since the microarchitecture of the cord is converted from an early intact to a totally necrotic state in hours. The mechanism of the necrosis seems to be profound local hypoxia. Definitive microcirculatory slowing and blood flow failure attend severe injury, while vessels and tissue unable to tolerate protracted hypoxia become necrosed. Either direct vascular injury or toxic neurotransmitter-vascular reactions are proposed as explanations for traumatic microcirculatory arrest. Various surgical and drug treatments have been advanced. Many of these show promise but all are still in the experimental stage. We are encouraged by the conclusion that guarded optimism may before long become a realistic attitude toward the treatment of severe spinal cord injuries.

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