AFRRI SR74-31
DECEMBER 1974

AFRRI
SCIENTIFIC
REPORT

THE EFFECTS OF TRAUMATIC INJURY ON SPINAL CORD BLOOD FLOW

T. F. Doyle
A. I. Kobrine
A. N. Martins

ARMED FORCES RADIOBIOLOGY RESEARCH INSTITUTE
Defense Nuclear Agency
Bethesda, Maryland

AFRRI SR74-31

Research was conducted according to the principles enunciated in the "Guide for Laboratory Animal Facilities and Care," prepared by the National Academy of Sciences - National Research Council.

AFRRI SR74-31
December 1974

THE EFFECTS OF TRAUMATIC INJURY ON SPINAL CORD BLOOD FLOW

T. F. DOYLE
A. I. KOBRINE
A. N. MARTINS

D. O. CARPENTER
Chairman
Neurobiology Department

MYRON I. VARON
Captain MC USN
Director

ARMED FORCES RADIOBIOLOGY RESEARCH INSTITUTE
Defense Nuclear Agency
Bethesda, Maryland

ACKNOWLEDGMENT

This work was supported in part by the U. S. Army Medical Research and Development Command. The authors express their appreciation for the technical assistance of W. L. Stringfield.

TABLE OF CONTENTS

LIST OF FIGURES

FOREWORD
(Nontechnical summary)

Anesthetized rhesus monkeys were subjected to a direct spinal cord injury and then observed long enough to confirm that an injury of this severity results in permanent paraplegia. Using the hydrogen clearance technique, blood flow was measured in the lateral white matter and central gray matter of the spinal cord; at the site of injury (T8-T10), 1 cm above and 1 cm below, before and after the trauma described. Blood flow in the center of the spinal cord at the site of injury started to decrease within 1 hour after injury and continued decreasing for up to 4 hours. Blood flow in the lateral white matter more than doubled within 2 hours after injury and then fell to normal values where it remained for up to 24 hours. Because the axons which carry nerve impulses and whose dysfunction results in paralysis are situated in the lateral white matter, it is clear that the paralysis which ensues after trauma is not due to lack of blood supply and is probably unrelated to the hemorrhagic ischemia of the central gray matter.

ABSTRACT

Using the hydrogen clearance technique, the effect of direct crush injury on blood flow was measured in the lateral white matter and central gray matter of the spinal cord of the adult rhesus monkey. Three measurements were made: at the site of injury (T8-T10), 1 cm above and 1 cm below. After injury, blood flow in the central gray matter declined markedly. However, flow in the lateral funiculus increased 100 percent or more within 2 hours after injury, and then returned to normal range by 8 hours where it remained for at least 24 hours. These data contradict the prevailing theory of a progressive ischemia in the lateral white matter secondary to the development of a hemorrhagic infarct in the central gray matter as a mechanism in crush injury of the cord.

I. INTRODUCTION

The prevailing theory concerning the pathophysiology of experimental spinal cord crush injury centers about a progressive ischemia in the lateral white matter, secondary to the development of a hemorrhagic infarct in the central gray, possibly related to catecholamine release at the time of injury.[12] Earlier we used the hydrogen clearance method first described by Aukland et al.[1] to measure normal spinal cord blood flow (SCBF).[9] In the present study, we have used this method to measure focal blood flow changes in the lateral white matter and in the central gray in experimental spinal cord injury in an attempt to substantiate the premise of progressive ischemia as the primary cause of paraplegia.

II. MATERIALS AND METHODS

Twenty adult rhesus monkeys, weighing 3-4 kg and unselected as to sex, were used in this study. The animals were anesthetized with 0.5 ml phencyclidine HCl[13],* and 1 ml sodium pentobarbital. A femoral artery and vein were catheterized for monitoring arterial blood pressure and blood gases and for fluid maintenance with lactated Ringer's solution. The animals were intubated, curarized and artificially ventilated with N_2O and O_2 in a 2:1 mixture. The rectal temperature was monitored and maintained at 37° to 39°C with a heating pad. A standard dorsal laminectomy was performed on each animal between segments T7-T11. The traumatic injury consisted of a 16-g weight being dropped 37.5 cm onto an aluminum anvil, contoured to fit and resting on the spinal cord (Figure 1). The area of the anvil in contact with the spinal cord was 15.7 mm^2.

* Sernylan, Bio-Centric Laboratories, Inc., St. Joseph, Missouri

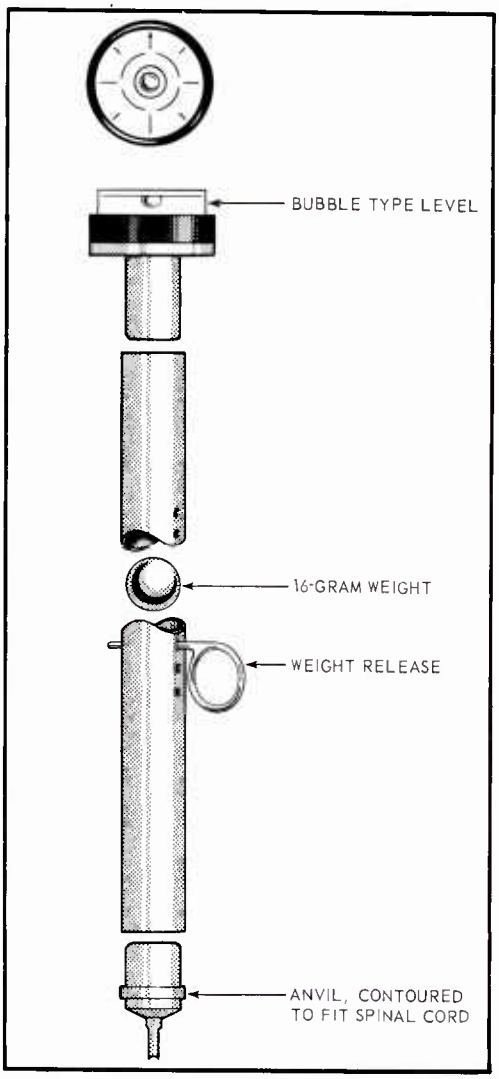

Figure 1. Type of apparatus used to deliver crushing injury to spinal cord. Ball is dropped a measured distance to top of lightweight aluminum anvil. The area of anvil in contact with spinal cord is 15.7 mm^2.

Blood flow measurement. One to three platinum electrodes, 250 μm in diameter, were placed into the spinal cord through the intact dura. The electrodes, approximately 1 cm apart, were positioned either at a point midway between the midline and lateral border to a depth of 2.0 mm for measuring flow in the lateral funiculus,[9] or in the center of the cord at a depth of 2.0 mm for measuring flow in the central gray matter.

The electrodes were placed 1 cm above, at, and 1 cm below the site of injury (T8-T10). These electrodes were maintained at +0.65 volts in reference to a stainless steel electrode placed in subcutaneous tissue. The circuitry for measuring hydrogen clearance is similar to that reported by Aukland et al.[1] but has been slightly modified as described earlier.[9,15]

Ten percent hydrogen gas was added to the inspired gases for several minutes until a satisfactory plateau was registered on the polygraph, at which point the hydrogen was turned off and the clearance of hydrogen from the spinal cord was recorded. The slope of the decay curve was analyzed by means of a least squares best fit. The flow, expressed as milliliters per minute per 100 g, is directly related to the slope of the decay curve. This technique, with the size of electrodes used, measures blood flow in a discrete volume of tissue less than 0.5 mm^3.[11]

The animals were divided into four groups.

Group A (four animals). These animals were prepared as above. After trauma, the wound was closed and the animals placed in restraining chairs. These animals acted as chronic controls to determine the clinical extent of the neurological deficit with this lesion.

Group B (seven animals). After laminectomy, platinum electrodes were placed in the lateral funiculus as described above. Blood flow was measured for 4 to 5 hours while the animals were maintained in a normocapnic, normotensive state. At the termination of the experiment, the animals were euthanatized and the spinal cord removed for examination.

Group C (five animals). These animals were prepared as described above with three electrodes placed in the lateral funiculus. After two control flow measurements were made, the middle electrode was removed, an injury as described above was delivered and the electrode was replaced in the area of trauma. Flow measurements were then made at hourly intervals for 4 to 24 hours. At the end of this period, the animals were euthanatized and the spinal cord removed for study.

Group D (four animals). These animals were prepared as above, but the electrodes were placed in the center of the spinal cord. After two control blood flow measurements were made, the middle electrode was removed, the cord was traumatized and the electrode was replaced. Flow measurements were then made for 4 hours, after which the animals were euthanatized and the spinal cord removed for study.

III. RESULTS

All of the animals in Group A demonstrated a flaccid paraplegia upon awakening from anesthesia. Two animals lived for 7 days following injury, and two lived for 14 days. Based on this observation and on reports of others,[7] we feel that this injury causes a permanent paraplegia 100 percent of the time.

The results from Group B were as follows. Based on 68 separate determinations from 12 electrodes, in seven animals, the overall mean flow as measured in the lateral funiculus at T8-T10 was 17.5 ml/min per 100 g $\pm$ 0.346 S.E.M. Four of these animals were allowed to awaken after the experimental period to undergo neurological examination, which was normal in all tested animals.[9] Microscopic examination of the cord revealed no lesions.

In the animals of Group C, at the level of trauma, blood flow in the lateral funiculus rose significantly within 1 hour following trauma to more than double the normal level ($p < 0.01$). Blood flow returned to normal by 8 hours and remained in the normal range for 24 hours. At no time did the blood flow in the white matter at the level of trauma fall below the normal range (Figure 2). Blood flow measured in the lateral funiculus 1 cm rostral and caudal to the level of injury followed a similar pattern, but to a somewhat lesser degree (Figures 3 and 4). Examination of the pathologic specimen of the cord showed a hemorrhagic lesion in the center at the level of injury, entirely replacing the gray matter. The segment of the cord 1 cm rostral and caudal to the trauma site appeared normal.

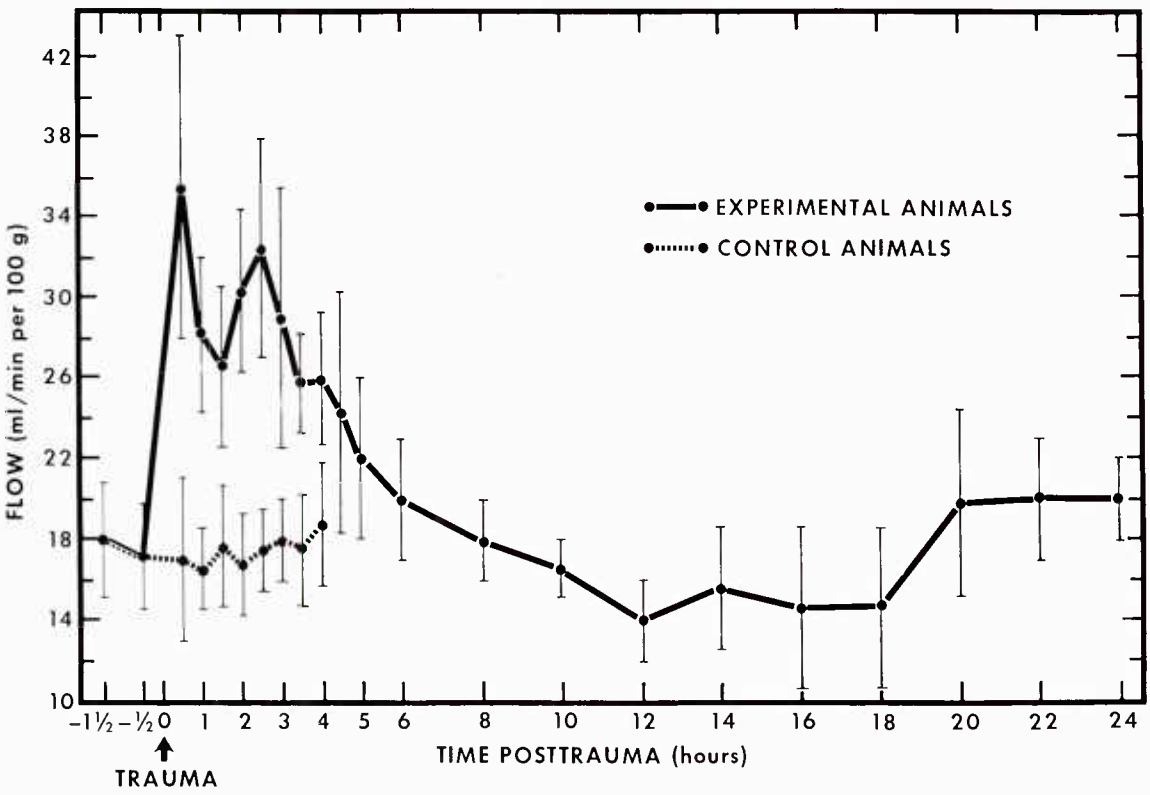

Figure 2. Blood flow measured in the lateral funiculus at the level of trauma (16 g dropped 37.5 cm onto an anvil with an area of 15.7 mm^2 resting on the spinal cord)

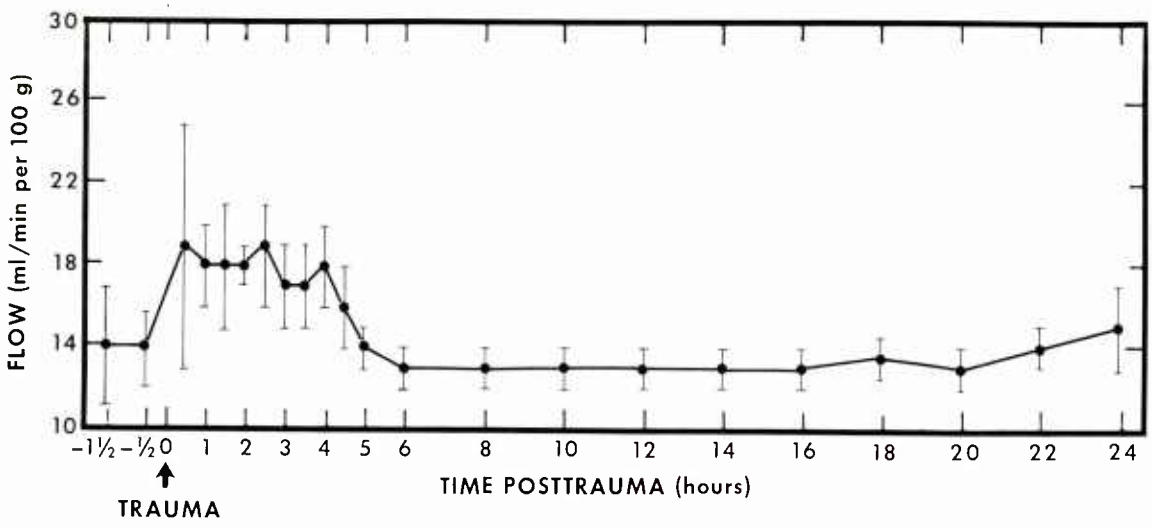

Figure 3. Blood flow measured in the lateral funiculus 1 cm rostral to level of trauma (16 g dropped 37.5 cm onto an anvil with an area of 15.7 mm^2 resting on the spinal cord)

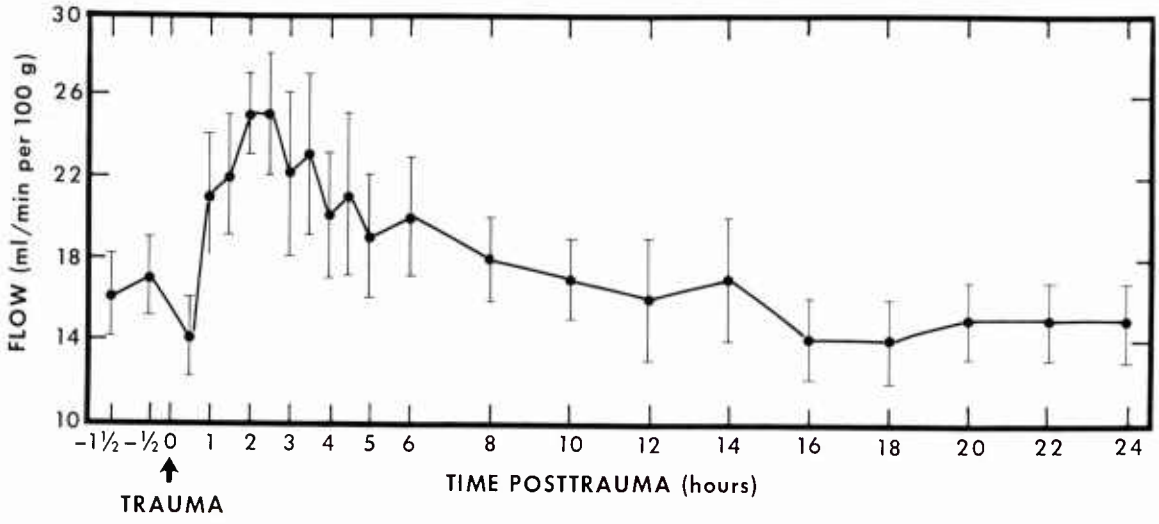

Figure 4. Blood flow measured in the lateral funiculus 1 cm caudal to level of trauma (16 g dropped 37.5 cm onto an anvil with an area of 15.7 mm^2 resting on the spinal cord)

The results from Group D were as follows. Normal blood flow in the center of the cord was 14 ml/min per 100 g ± 0.5 S.E.M. (N = 27). Blood flow in the center of the cord at the level of trauma fell within 1 hour after injury, and continued to fall

during the 4-hour experimental period (Figure 5). Blood flow in the central cord 1 cm rostral and caudal to the injury site remained essentially unchanged. Results of examination of the cords of this group were similar to those of Group C.

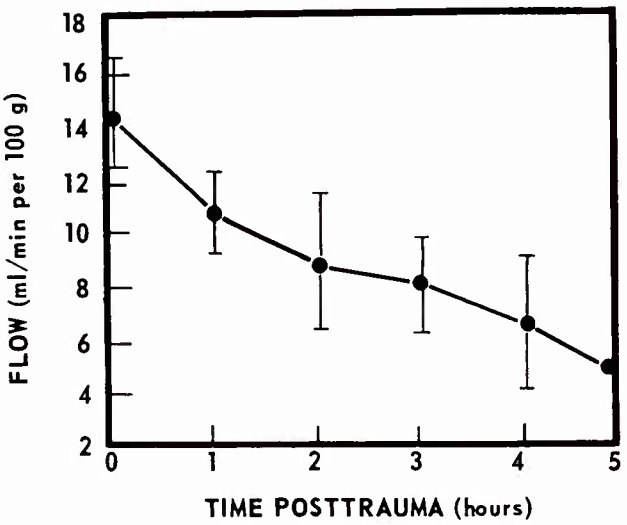

Figure 5. Blood flow measured in the center of the cord at the level of trauma (T10).

Systemic arterial blood pressure remained constant and in the physiologic range in all groups throughout the entire experiment except immediately after the injury. Within 30 seconds following trauma, there was a rise of 25 to 30 mm Hg in all injured animals, which lasted 60 to 90 seconds before returning to the normal range.

IV. DISCUSSION

In view of these results, we believe a reassessment of the popular pathophysiological theory stressing the importance of lateral white matter ischemia in experimental spinal cord injury is in order. Actually, there are other observed experimental phenomena to support this reassessment.

In all experimental designs, animals injured with a force sufficient to render them paraplegic are rendered so immediately at a time when minimal change can be observed in light and electron microscopic examination of both the central gray and lateral white matter.[3,14] Also evident at this time is the total inability of the spinal cord to conduct impulses, as evidenced by the absence of sensory evoked potentials.[2] Studies correlating the clinicopathologic changes seen in varying degrees of trauma have shown an inverse temporal relationship[4] between function and pathology. Those animals injured with a force causing transient paraplegia demonstrated a worsening of the central lesion as they were clinically improving. Hedeman and Sil,[8] who were unable to demonstrate any rise in norepinephrine levels of injured spinal cord, also found no correlation between the size or evolution of the central lesion and the return of neurological function of treated improved animals. Therefore, evidence exists that the well-known and easily observed central ischemic lesion may in effect be coincidental and unrelated, caused either by the initial trauma or the release of some as yet unknown substance, but having no causal relationship with the devastating neurological deficit.

Locke et al.[10] have demonstrated an increased lactate level in the injured segment of spinal cord and considered this to be further evidence of spreading ischemia. However, since the entire segment was utilized in the lactate determination, the elevated level could represent changes in the metabolism of cells only in the central lesion rather than metabolic changes in the peripheral white matter. Our data from Group D are not inconsistent with a significant ischemia and elevated lactate levels in

the central lesion following severe injury, since this and hyperperfusion of the white matter could occur concomitantly.

Previous attempts at measuring blood flow in the spinal cord by the direct injection of xenon into the parenchyma of the cord,[5] or by the washout of argon as measured by a probe 2 mm in diameter placed into the cord,[6] either in themselves create a lesion in the tissue in which flow is being measured or are unable to differentiate between flow in the lateral white matter and the central lesion.

The marked rise in spinal cord blood flow measured in the lateral funiculus after traumatic paraplegia could be explained as hyperperfusion in response to an increased metabolic demand, or more likely as a "luxury perfusion" state, with loss of autoregulation and subsequent vascular dilatation as a direct result of trauma to the lateral funiculus itself or secondary to the effects of nearby necrotic tissue in the center of the cord. We, therefore, suggest a possible alternative to explain the permanent neurological dysfunction seen in severe experimental spinal cord trauma.

Because of the hyperperfusion which develops in the lateral funiculus, we suggest that ischemia does not exist in this area following severe spinal cord trauma, and, therefore, plays no role in the associated pathophysiology. We suggest that the initial trauma causes an immediate and permanent functional disruption of the cell membrane of the axons in the lateral white matter by either interfering with the selective permeability of the membrane to sodium and potassium or, in some other way, interfering with the ability of the axonal membrane to conduct an action potential. We further suggest that the lesion which evolves in the center of the injured segment, whether caused by direct trauma or the release of some as yet unknown substance, probably

plays no role in the pathogenesis of the lateral white matter dysfunction. We also suggest that the return of function seen in experimental transient paraplegia is probably based on the return of functional integrity of the cell membrane rather than related to changes in blood flow.

REFERENCES

1. Aukland, K., Bower, B. F. and Berliner, R. W. Measurement of local blood flow with hydrogen gas. Circulation Res. 14:164-187, 1964.

2. Campbell, J. B., Segel, J., DeCrescito, V., Tomasulo, J. and Ransohoff, J. Bioelectric prediction of permanent post-traumatic paraplegia. Presented at the Annual Meeting of the American Association of Neurological Surgeons, Houston, Texas, April 1971.

3. Dohrmann, G. J., Wagner, F. C. and Bucy, P. C. Transitory traumatic paraplegia: electron microscopy of early alterations in myelinated nerve fibers. J. Neurosurg. 36:407-415, 1972.

4. Ducker, T. B., Kindt, G. W. and Kempe, L. G. Pathological findings in acute experimental spinal cord trauma. J. Neurosurg. 35:700-708, 1971.

5. Ducker, T. B. and Perot, P. L., Jr. Spinal cord oxygen and blood flow in trauma. Surg. Forum 22:413-415, 1971.

6. Ducker, T. B. and Perot, P. L., Jr. Experimental spinal trauma: I. Blood flow and tissue oxygen in acute paraplegic dogs (in press).

7. Green, Barth (personal communication).

8. Hedeman, L. S. and Sil, R. Studies in experimental spinal cord trauma. Part 2: Comparison of treatment with steroids, low molecular weight dextran, and catecholamine blockade. J. Neurosurg. 40:44-51, 1974.

9. Kobrine, A. I., Doyle, T. F. and Martins, A. N. Spinal cord blood flow in the Rhesus monkey by the hydrogen clearance method. Surg. Neurol. 2:197-200, 1974.

10. Locke, G. E., Yashon, D., Feldman, R. A. and Hunt, W. E. Ischemia in primate spinal cord injury. J. Neurosurg. 34:614-617, 1971.

11. Meyer, J. S., Fukuuchi, Y., Kanda, T. and Shimazu, K. Regional measurements of cerebral blood flow and metabolism using intracarotid injection of hydrogen, with comments on intracerebral steal. In: Brain and Blood Flow, Proceedings of the Fourth International Symposium on the Regulation of Cerebral Blood Flow, London, September 1970, Ross Russell, R. W., editor, pp. 71-79. London, Pitman Medical and Scientific Publishing Company Ltd, 1971.

12. Osterholm, J. L. The pathophysiological response to spinal cord injury: the current status of related research. J. Neurosurg. 40:3-33, 1974.

13. Popovic, N. A., Mullane, J. F., Vick, J. A. and Kobrine, A. Effect of phencyclidine hydrochloride on certain cardiorespiratory values of rhesus monkey (Macaca mulatta). Am. J. Vet. Res. 33:1649-1657, 1972.

14. Wagner, F. C., Jr., Dohrmann, G. J. and Bucy, P. C. Histopathology of transitory traumatic paraplegia in the monkey. J. Neurosurg. 35:272-276, 1971.

15. Willis, J. A., Doyle, T. F., Ramirez, A., Kobrine, A. I. and Martins, A. N. A practical circuit for hydrogen clearance blood flow measurement. Bethesda, Maryland, Armed Forces Radiobiology Research Institute Technical Note TN74-2, 1974.

UNCLASSIFIED
Security Classification

DOCUMENT CONTROL DATA - R & D

(Security classification of title, body of abstract and indexing annotation must be entered when the overall report is classified)

1. ORIGINATING ACTIVITY *(Corporate author)*
Armed Forces Radiobiology Research Institute
Defense Nuclear Agency
Bethesda, Maryland 20014

2a. REPORT SECURITY CLASSIFICATION
UNCLASSIFIED

2b. GROUP
N/A

3. REPORT TITLE

THE EFFECTS OF TRAUMATIC INJURY ON SPINAL CORD BLOOD FLOW

4. DESCRIPTIVE NOTES *(Type of report and inclusive dates)*

5. AUTHOR(S) *(First name, middle initial, last name)*

T. F. Doyle, A. I. Kobrine and A. N. Martins

6. REPORT DATE	7a. TOTAL NO. OF PAGES	7b. NO. OF REFS
December 1974	16	15

8a. CONTRACT OR GRANT NO.	9a. ORIGINATOR'S REPORT NUMBER(S)
b. PROJECT NO. NWED QAXM	AFRRI SR74-31
c. Task and Subtask C 912	9b. OTHER REPORT NO(S) *(Any other numbers that may be assigned this report)*
d. Work Unit 22	

10. DISTRIBUTION STATEMENT

Approved for public release; distribution unlimited

11. SUPPLEMENTARY NOTES	12. SPONSORING MILITARY ACTIVITY
	Director Defense Nuclear Agency Washington, D. C. 20305

13. ABSTRACT

Using the hydrogen clearance technique, the effect of direct crush injury on blood flow was measured in the lateral white matter and central gray matter of the spinal cord of the adult rhesus monkey. Three measurements were made: at the site of injury (T8-T10), 1 cm above and 1 cm below. After injury, blood flow in the central gray matter declined markedly. However, flow in the lateral funiculus increased 100 percent or more within 2 hours after injury, and then returned to normal range by 8 hours where it remained for at least 24 hours. These data contradict the prevailing theory of a progressive ischemia in the lateral white matter secondary to the development of a hemorrhagic infarct in the central gray matter as a mechanism in crush injury of the cord.

DD FORM 1 NOV 65 1473

UNCLASSIFIED
Security Classification