Development of a reproducible model of spinal cord injury has been the object of considerable research since Allen, (1911) first designed a technique for measuring experimental spinal cord trauma. According to many investigators, these models should consistently produce a threshold lesion (Allen, 1914; Kuchner, 1976), that results in permanent paraplegia without proper treatment.


Experimental spinal cord injury models should produce a type of injury similar to spontaneous accident cases and yet consistently produce uniform pathological responses in the spinal cord. Several models have been proposed to study the pathophysiological mechanisms associated with acute spinal cord trauma. The earlier techniques used to produce experimental spinal cord trauma were quite crude. In 1890, Schmaus
attached wooden boards to the backs of rabbits which were suspended vertically (Schmaus, 1890). After blows to the boards, he noted areas of degeneration and cavitation within the spinal cord.

The most frequently used method is the one proposed by Allen (1911) which was extended by Freeman and Wright (1953) and has become the standard injury model in many laboratories.

**Allen's Weight drop Model:** In this model, the actual apparatus for inducing injury to the spinal cord is a cylinder that is placed perpendicular to the dorsal surface of the spinal cord. The cylinder contains a loosely fitting plastic impounder which rests on the intact surface of the dura. The height of the cylinder is marked off in centimeters while a lead weight dropped through the cylinder for a determined distance until it makes contact with the impounder resting on the dural surface (De la Torre, 1975). Thus if the lead weight weighs 20 g and is dropped from a distance of 20 cm (20 x 20), 400 gm-centimeters of force (gcf) injury will have been delivered to the spinal cord.

With this technique, the force of impact on spinal cord can be determined and thus the intensity or degree of trauma quantified. One of the chief disadvantages of the Allen method of experimental trauma is that the most severe site of trauma
in spinal injuries (as seen in fractures, dislocations and disk protrusions) is on the ventral portion instead of the dorsal area of the cord (Ducker, 1971b; Balentine, 1978b). Ventral areas are vital for motor function and dorsal portions are largely sensory. Variability in the degree of injury like variations in magnitude of the weights used, and from the distance from which they are dropped on the cord and the area of the impounder that struck the cord may cause differing degrees of injury.

Balloon Method of Tarlov: In this method (Tarlov, 1957), a silastic balloon was placed on the duramater and held there with a metal cap in the bony defect. The balloon was inflated with compressed air to a pressure of 160 mm of Hg in 10 seconds. Pressure in the balloon was controlled with a Nullmatic pressure regulator and monitored continuously with an Allyn pneumatic pressure gauge. The pressure was maintained for 1 hour before the balloon was removed.

Spinal cord trauma was induced using a modification of the compression model. This method involved, placing a known weight extradurally on the spinal cord for a length of time. With this model, either reversible or irreversible paraplegia can be produced depending on the magnitude of the weight and the duration of compression. Methods designed to produce trauma to ventral areas of the cord include the balloon method
using steady pressure on the cord surface with weights
(Eidelberg, 1976) and introducing toxic substances into the
cord tissue (Kakari, 1973; Balentine, 1980). Circumferential
constricting balloons and modified aneurysm clips have been
used as additional trauma devices (Gelfan, 1965; Rivlin.
1978).

Techniques in Evaluating Experimental Spinal Cord Trauma:
Evaluation of recovery following Spinal cord trauma has
largely been based on return of functions such as sensory
perception, normal reflexes, voluntary motor movements,
urinary and fecal control and finally the ability to walk. The
neurologic evaluation as proposed by Tarlov (1957) is the most
generally used by most investigators with some modifications.
Other methods to assess neurologic deficits are to test the
motor function. An adequate methodology for assessing the
degree of functional neurologic impairment that follows spinal
cord injury are essential components of any model system.

For studies with rats, a modification of the Tarlov
scoring system and the inclined plane test of Rivlin and Tator
(1977) have been the most frequently used measurements of
function after spinal injury. Eidelberg et al., (1976)
developed a very good method of functional assessment of
ferrets with spinal cord injuries which utilizes inclined
plane. His technique requires conditioning of the animal and
motivation. Ferrets are trained and motivated by a food reward to climb the ramp prior to spinal cord injury, the motor index is then expressed based on the animals ability or inability to climb a given distance of the ramp at various degrees of elevation from the horizontal plane following cord trauma.

Recently, somatosensory evoked potentials (SEP) are introduced in the assessment of spinal cord trauma for both clinical and experimental use (D'Angelo, 1973; Martin, 1973; Perot, 1973; Cracco, 1975; Rowed, 1976; De la Torre, 1978). The SEP seems more practical in animal use. Somatosensory evoked potentials are based on the principle that when a subject's sensory system is stimulated, an electrical activity in a localized region of the brain will result. Either stimulation can be done cutaneously just above a peripheral nerve or electrodes can be attached to the nerve directly while the signals are recorded either by scalp surface electrode or by electrodes on to the skull overlying the somatosensory cortex. The former method is generally used in humans and the latter in animals. There appears to be a high correlation between the potential recovery of sensory motor function following cord injury and the summation of typical wave form recorded at the sensory cortex (Perot, 1973; Rowed, 1976).

Another electrophysiological approach following spinal
Fig. 1  Hypothetical chain of events in spinal injury (Taken from Demopoulos, 1980).
IMPACT INJURY

Physiological changes
- Loss of conduction
- Decreased circulation
- Ischemic hypoxia
  - Reduction of E\(^+\) transport and auto-oxidation of CoQ and FAD
    - \(O_2^-, H_2O_2, OH, O^-\)

Structural changes
- Vasospasm, rupture of capillaries
- Extravasation of cells and plasma
- Iron and copper from plasma and blood cells
- Metal catalyzed radical reactions

Graded pathologic free radical reactions in membranes

Neurons
- Inactivation of cytochrome oxidase and NAD:ATPase
- Permanent loss of conduction

Vessels
- Inhibition of prostacyclin formation in microcirculation
- Micro occlusions resulting in ruptured capillaries, less perfusion

Glia
- Peroxidation of cholesterol in myelin and other membranes
- Fragmentation of myelin

All cell types
- Peroxidation of lipids in lysosomal membranes
- Gradual dissolution of cell and tissue architecture
cord injury is the use of electrospinogram. This involves the
recording of spontaneous electrical activity from segmental
neurones in the spinal cord and measuring the amplitude and
frequency of the neuronal discharges in normal and traumatized
subjects (Morrison, 1975). Small bipolar electrodes have also
been used to record the spontaneous electrical activity of the
cells in the anterolateral column. This technique is useful
in studying arrangement and conduction velocities of various
fibre bundles in the spinal cord (Illingworth, 1974).

Pathophysiology of Spinal Cord Trauma: The pathophysiological
events preceding spinal cord injury (SCI) is not well
understood. Traumatic injury to spinal cord is associated with
a complex series of pathological events including both primary
and secondary components (Balentine, 1985; Fig 1). Both
clinical and experimental spinal cord trauma are characterized
by immediate paraplegia or paraparesis. Immediately following
spinal cord injury, paraplegia, loss of electrical conduction,
and shifts in electrolytes have been documented (Ducker, 1978;
Eidelberg, 1975; Kobrine, 1975; Young, 1982). There is
evidence that spinal cord injury in the acute phase results
from two separate mechanisms; the initial mechanical damage
and secondary changes due to vascular or biochemical effects.
The initial mechanical damage to the cord includes both the
impact force and any persistent compression by
intracanalicular space occupying lesions such as bone
Vascular Mechanisms and Spinal Cord Blood Flow: It has been reported that laminectomy alone reduces the spinal cord blood flow, which may be due to exposure of the dura to ambient air. Exposure of the dura results in a temperature induced vasoconstriction leading to reduced spinal cord blood flow (Anderson, 1978). Quantitative studies to determine the effect of trauma on spinal cord blood flow have been performed in experimental animals injured by the weight drop technique (Bingham, 1975; Ducker, 1971; Kobrine, 1975). Bingham et al., (1975) reported that there is a decrease of blood flow in gray matter while that in the white matter persisted. In most mammals, the arterial supply to the spinal cord is made up of one anterior and two posterior spinal arteries. The anterior and posterior spinal arteries are fed by a variable number of radicular arteries that span the length of the spinal cord. A similar venous system drains blood from the cord.

Autoregulation of spinal cord blood flow (SCBF), has been documented by several investigators in uninjured dogs and monkeys (Griffith, 1973; Kindt, 1971; Kobrine, 1976). As with the brain, a severe injury to the cord tissue can result in loss of autoregulation and changes in the arteriovenous blood flow pattern (Senter, 1978; 1979).
There are various methods to measure spinal cord blood flow. The most commonly used methods for SCBF measurement are the hydrogen clearance and iodo-$^{14}$C-antipyrine technique. The hydrogen clearance method is based on the rate at which inhaled or injected $H_2$ is washed out of the spinal cord tissue. The second technique is an autographic method that measures spinal cord blood flow for the entire transverse section of the cord. Specifically this method discriminates between white and gray matter blood flow.

The progressive decline in spinal cord white matter blood flow is primarily a local event within the injured spinal cord segments, probably caused by an injury initiated molecular cascade involving massive intracellular calcium accumulation (Stokes, 1983; Young, 1982a), liberation of vasoactive prostanoids principally prostaglandin F2α (PGF2α) (Demediuk, 1985b; Jonsson Jr., 1976) and thromboxane A2 (TXA2) (Hsu, 1985) and microvascular lipid peroxidative reactions (Demopoulous, 1982; Hall, 1986). It has been reported that local trauma to the spinal cord may result in mechanical distortion of blood vessels, which will affect flow in areas near the site of injury (Wagner, 1969). Blood flow following spinal cord injury has been shown to decrease rapidly over a period of one hour in the central gray matter of the injured spinal cord. Mechanisms for decreased flow in gray matter have been examined ultrastructurally demonstrating that endothelial
damage with subsequent platelet thrombi is particularly responsible for microvascular occlusion (Goodman, 1979).

Microangiographic demonstration of the injured spinal cord vasculature has also contributed to a convincing body of evidence that post-traumatic ischemia is a significant pathophysiological component of spinal cord trauma (Dohrmann, 1971a, b; 1973; Fairhorm, 1971; Means, 1978).

Blood pressure shows a characteristic patterned response to major cervical cord trauma with an initial hypertensive peak followed by a prolonged period of hypotension (Guha, 1987). Young et al., (1980) attributed the initial hypertensive peak to a neuronally and humorally mediated sympathetic charge.

Histopathological Changes: The histopathological changes are noticeable immediately after the impact. The direct primary traumatic changes such as disruption of neurons, glial cells, myelin and vascular system are seen directly under the impact. Following primary traumatic changes the secondary pathological changes are seen at the site of injury. They are mainly characterized by hemorrhage and edema, which spread far beyond the site of the impact (Goodkin, 1969; Ducker, 1971; Yashon, 1973; Osterholm, 1974; Balentine, 1978a, b).
Various factors are involved in the necrosis of neural tissue in the spinal cord. The primary factor is the direct mechanical impact on the tissue. The secondary pathological changes are hemorrhage, edema and ischemia. Light microscopic studies showed that, ischemia, hemorrhagic necrosis, edema and inflammation progress from gray to white matter within hours and are clearly apparent by 4–8 hours. The edema that appears within minutes has a linear relationship of its extent to the degree of injury (Hsu et al, 1983b). Ultrastructurally, edema shows both vasogenic and cytotoxic criteria. Edema in the spinal cord may be due to a significant increase in the water content of tissue. Extensive necrosis of white matter tracts is a delayed event (Wagner, 1971; 1978).

Biochemical Changes:

Hypoxia: Regional hypoxia is believed to be a significant factor in spinal cord trauma. Hyperbaric oxygen has been advocated for treatment of SC injuries (Kelly, 1972; Holbach, 1975; Yeo, 1977). One of the earliest metabolic changes to occur following trauma to the cord is a linear decrease in tissue oxygen tension at the injury site that extends over several hours (Hayashi, 1980; Kelly, 1970). It has been postulated that a reduction in the delivery of oxygen to the injured cord leads to the dissociation of normally tightly coupled electron transport chain components. Such a disruption in the normal flow of electrons to molecular oxygen may result...
in the production of oxygen-free radicals within the membranes of cells and organelles and the subsequent peroxidation attack of unsaturated fatty acids within those membranes (Demopoulos, 1980; Hall, 1982).

Lactic acids: Locke et al., (1971) provided the first biochemical evidence of post-traumatic spinal cord ischaemia by showing that the lactate content of injured primate spinal cord rose significantly within minutes following trauma and remained elevated for 12-18 hours. Feldman et al., (1971) demonstrated that, following circulatory arrest, spinal cord lactate levels rose as blood flow to the cord decreased. Recently, Anderson et al., (1980, 1982) did not observe changes in spinal cord lactate content at two hours post-injury, but noted that the lactate content of the injured spinal cord as well as the lactate/pyruvate ratio was elevated at 8 and 24 hour after injury.

Lactic acidosis has a negative effect on glucose and oxygen consumption since it decreases these substances in tissue during metabolic acidosis (Patel et al., 1973). Neuronal or glial membranes may be damaged by free radicals, excessive lactate production from continued supply of substrate for anaerobic glycolysis may lead to excessive tissue acidosis and enhance tissue damage (Siesjo, 1984).
Monoamines: The hypothesis of norepinephrine (NE) metabolism alterations in experimental spinal cord injury, first proposed by Osterholm and Matthews (1971) remains controversial. The conflicting results may be due to differences in the method of producing the injury, in analyzing the content of monoamines and in species used in experimental models (Bingham, 1975; Eidelberg, 1976; Hedeman, 1974; Hinwood, 1980). Released norepinephrine (NE) impairs the neuronal cell membrane by induction of lipid peroxidation. Levine and Moskowitz (1979) have stated that, stimulation of arachidonic acid metabolism occurs through NE mediated α or β-receptors. The nonenzymatic lipid peroxidative mechanism may be propagated when the released NE is metabolized by degradative enzymes, monoamine oxidase and catechol-O-methyl transferase (COMT). Quinone, one of the degradation products, is considered to produce free radicals (Kurihara, 1985). Many studies have been performed on the role of monoamines in the pathogenesis of spinal cord injury. Osterholm and Matthews (1971; 1972) postulated that hemorrhagic necrosis in the central gray matter following spinal cord injury was produced by vasoconstrictive action of released norepinephrine. It has been proposed that the deleterious metabolic progression of events that occurs, secondary to physical injury to the central nervous system involves the spasmogenic or other effects of NE, (Osterholm, 1972; Lavyne, 1975), dopamine (Hedeman, 1974; Naftchi, 1974) or 5-Hydroxytryptamine.
Various studies of the effect of impact injury on spinal cord monoamine content have been performed in cats, dogs, monkeys and sheep and the results are in variance. These variations may be due to species differences, differences in the generation of spinal cord injury and the discrepancies in monoamine analytical methodology.

**Lipid Peroxidation and the generation of free radicals:**

Lipid peroxidation seems to be one of the earliest biochemical events detected in injured spinal cord tissue (Demopoulous, 1979; 1980; 1982; Hall, 1982; Anderson, 1985a; 1985b; Demediuk, 1985a). In spinal cord injury, the initiation of pathologic free radical reactions is probably mediated by the initial extravasation of blood in the central gray matter and perhaps by coenzyme Q (CoQ) autoxidation when spinal cord ischemia (hypoxia) occurs (Demopoulous et al., 1979; Ransohoff et al., 1980). Kurihara (1985) found that spinal cord tissue lipoperoxides were increased 30 min after injury. Other studies report that impact injury causes membrane disruption, release of intracellular contents and the generation of lipoperoxides. Some of the products of lipid hydrolysis such as free fatty acids, lysophospholipids and diacylglycerols are known to perturb the integrity of biomembranes (Allan, 1978). Arachidonic acid was shown to be increased in the cat spinal
cord by 5 min after compression injury (Saunders, 1985). The metabolic degradation of arachidonic acid leads to the liberation of prostaglandins, free oxygen radicals, thromboxane and leukotrienes. Prostaglandin levels were increased at the site of injury in spinal cord trauma (Jonsson Jr., 1976). Among the vasoactive prostanoids, thromboxane (TXA2) and prostacyclin (PGI2) are two of the most potent substances affecting hemostasis and vascular integrity (Harlan, 1981). TXA2 stimulates platelet aggregation and vasoconstriction (Moncada, 1979). Lipid hydrolysis with subsequent eicosanoid production is an early pathochemical event in the injured spinal cord (Anderson, 1985a). The enzymatic lipid peroxidation may be initiated by the intracellular increase in Ca^{2+} (Pryor, 1976).

**Changes in Ca^{2+}**: Central nervous tissue maintain a remarkable calcium ion gradient between intracellular and extracellular compartments. Under normal conditions, the cell membrane is a very effective barrier to extracellular Ca^{2+}, maintaining a low intracellular Ca^{2+} level. Ischaemic or traumatic insults to the central nervous system results in reduction of cellular Ca^{2+} balance (Schanne, 1979) and decrease in extracellular calcium. This decrease may be due to increase in cell membrane permeability and influx of Ca^{2+}, which result in decreased extracellular calcium (Nicholson, 1976; Sonjen, 1980). Contusion, mechanically disrupts cells particularly in
the gray matter where breakage of blood vessels and cells is histologically evident during the first hour after injury (Wagner, 1971; Means 1976; Balentine, 1978a; 1980; Ducker, 1978). This may result in release of intracellular Ca\(^{2+}\). Mass movement of water vascular space may also dilute extracellular Ca\(^{2+}\) (Green, 1973, Griffiths, 1974).

The entry of calcium into cells has diverse pathological consequences. Several studies have reported that excessive Ca\(^{2+}\) influx into axons, degrades neurofilaments (Schlaepfer, 1977a, b; Pant, 1980) resulting in local axonal transport block and accelerated degeneration of axons (Banik et al., 1979). These changes take place hours after trauma (Balentine, 1980). The immediate effect of intracellular calcium is an increase in membrane permeability to other ions, intracellular acidosis, uncoupling of glial and neuronal cell-cell communication channels and disruption of metabolic activity (Young, 1982a). Deshpande et al., (1987) have recently demonstrated that calcium accumulates before cell necrosis occurs implying that loss of calcium homeostasis is an early event and not an epiphenomenon of cell injury. Accumulation of calcium in intracellular space is thought to activate phospholipase A and C, which will attack membrane phospholipids resulting in the production of free fatty acids (Siesjo, 1981; 1984). This loss of membrane phospholipids will increase permeability of neuronal and mitochondrial membranes, which will further alter
calcium homeostasis with additional detrimental effects on oxidative phosphorylation.

**Endogenous opioids:** Endogenous opioids have been implicated as one of the autodestructive factors in spinal cord injury. Pharmacological studies show that, the opiate receptor antagonist naloxone improves physiological variables and/or functional recovery after such injury (Faden, 1981; 1981a; 1982).

**Enzyme changes:** Some of the products of lipid hydrolysis such as free fatty acids (FFA), lysophospholipids and diacylglycerols are known to perturb the integrity of biomembranes (Allen, 1978). Demediuk et al., (1985a) postulated that the plasma membrane is a primary site of cellular damage after spinal trauma, leading to changes in membrane bound enzyme activity. Na⁺, K⁺, ATP-ase is associated with the plasma membrane and its main task is to participate in the energy requiring translocation of sodium and potassium (Jorgensen, 1982). Clendenon et al., (1978) reported that the activity of this enzyme decreased as early as 5 min after spinal cord impact injury in dogs. Recently, Braughler & Hall (1982a, 1982b) also demonstrated the relationship between the inhibition of activity of this enzyme and lipid peroxidation following spinal cord injury. Na⁺, K⁺, ATP-ase is an integral membrane protein with an absolute requirement for
Fig. 2. Schematic diagram of the localization of AChE in a CNS neuron showing possible loci and mechanisms of release: I, dendritic; II, axonal; and III, terminal release. The two major localizations are the endoplasmic reticulam in the cell body and the cell membrane. From the site of synthesis in the cell body, the enzyme is transported to the axonal and dendritic process.
phospholipids for activity (Decaldentey, 1979). So changes in membrane phospholipids may change this enzyme activity.

Traditionally, AChE has been considered to be located on the surface of cholinergic terminals, where it serves the purpose of hydrolysing ACh (Tauc, 1977). AChE hydrolyses the neurotransmitter acetylcholine after its release from presynaptic membranes. Histochemical localization of AChE indicated that the synthesis and release of AChE are attributable to neurons (Fig. 2). AChE could have a role other than that of inactivating ACh [Dray, 1979; Silver, 1974]. AChE is associated primarily with cells, which are involved in cholinergic synaptic transmission. Although it is found in a variety of other neuronal and non-neuronal cells (Silver, 1974; Rosenberry, 1975), AChE activity in the spinal cord is located in the gray matter.

Acid hydrolytic enzymes released from their normal intracellular location within lysosomes by cell injury may participate in extending the injury throughout the neighbouring tissues by their hydrolytic action on cellular constituents. The lysosomes contain a variety of acid hydrolases and any membrane damage to this organelle will result in the release of lysosomal enzymes into the cytosol (Allison, 1969).
Neuronal degeneration and tissue necrosis may occur early and even precede ischemia, but are generally regarded as results of the profound and early vascular changes (Assenmacher, 1971; Dohrmann, 1971, 1971a; Kajihara, 1973). Lysosomal enzyme release has been implicated in the pathogenesis of late phases of spinal nerve tract damage in feline experimental spinal cord injury (Kakari, 1974). Lysosomal enzymes are certainly affected by spinal cord injury, but release of these enzymes into the cytoplasm or extracellular fluid does not appear to play a role in the early phases of the pathophysiologic process.

Acute Treatment of Spinal Cord Injury:

Corticosteroids: Corticosteroids are widely used in the treatment of spinal cord injury, the rationale for which rests almost entirely on animal experiments. The majority of animal studies report improvement in functional outcome after steroid treatment (Ducker, 1969; Black, 1971; Campbell, 1973; 1974; De la Torre et al, 1975; Eidelberg, 1976). Some investigators failed to observe any beneficial effect in spinal injury (Kajihara, 1973; Hedeman, 1974). The resulting controversy has led to debate regarding the optimal dose range and type of steroid preparation. Recently very large doses of methyl prednisolone (30-60 mg) have been proposed, due to the relatively short lived effect of methyl prednisolone (Braughler, 1983). The list of demonstrated cerebroprotective
mechanisms of methyl prednisolone (with in the context of the injured spinal cord) includes inhibition of post traumatic lipid peroxidation (Demopoulous, 1982; Hall, 1982; Anderson, 1985; Kurihara, 1985), reversal of intracellular calcium accumulation (Young, 1982), prevention of neurofilament degradation (Braughler, 1984), inhibition of arachidonic acid release and vasoactive prostaglandin F2α and thromboxane A2 formation (Anderson, 1985) and enhancement of neuronal excitability and synaptic transmission.

Experimental evidence suggests that use of high dose corticosteroids may lead to enhanced morbidity and mortality (Faden, 1984). High dose dexamethasone was found to be more effective in spinal cord compression (Delattre, 1989). It has been recently shown that dexamethasone is effective in lowering prostaglandin production in the brain (Weidenfeld et al., 1987). Beneficial effect is controversial and their mechanism of action is not clear.

Hyperbaric Oxygen: Hyperbaric oxygen (HBO) treatment prevented severe tissue necrosis and reduced cavitation formation. (Yeo et al., 1977). It is reasonable to assume that the beneficial results of HBO therapy in spinal cord injury are due in large measure to increased levels of O2 supplied to ischaemic neural tissue adjacent to the lesion. Studies on HBO also show that this treatment can increase the collagen
formation in the damaged cord (Gelderd et al., 1980). This treatment has not been widely adopted owing to conflicting results and the various claims that the $O_2$ at high pressure can induce pulmonary toxicity and CNS manifestations.

**Hypothermia:** Nervous tissue metabolic requirements are materially reduced by temperature reduction, a series of experiments were undertaken to cool the locally traumatized spinal cord with saline irrigations at a temperature of $4^{\circ}$C. Another controversial approach to the treatment of SCI is hypothermia. The basis for using this is its ability to lower metabolic and $O_2$ requirements of nerve cells (White, 1973). Studies using hypothermia experimentally show that the procedure may act to slow down the degree of swelling by shrinking the neural tissue and by vasoconstricting vessels near the site of injury, a process that could also reduce tissue volume (Albin, 1966). There is no general agreement on how long and at what temperatures, cooling of the cords will be more beneficial. Cooling improves the microcirculation and may also block the metabolic acidosis resulting from trauma (Tsubokawa, 1975). The beneficial effects of hypothermia in spinal cord injury have been challenged by other investigators who could not find any beneficial effect from this treatment in their experimental animals (Selker, 1971; Tator, 1973).

**Calcium Antagonists:** In view of the evidence indicating $Ca^{2+}$
toxicity associated with the migration of Ca$^{2+}$ from the extracellular to the intracellular space, it is reasonable to consider the use of pharmacological agents that specifically block this ionic shift. The recent development of Ca$^{2+}$ antagonists (slow channel blockers; Nayler, 1983), provided a new class of potential therapeutic agents as well as the means of examining the potential role of Ca$^{2+}$ in CNS injury. Ca$^{2+}$ channel antagonists have a variety of physiological effects. These include enhancement of cerebral blood flow (Gelmers, 1982), selective dialatation of CNS vessels (Haws, 1983) and inhibition of vascular contraction due to substances such as thromboxanes and serotonin (Brandt, 1981). The deleterious effects are interference with cellular energy metabolism, increased susceptibility of tissue to ischaemic damage, or reduction of mean arterial pressure (Harris, 1982).

Gelbfish et al., (1985) showed that the Ca$^{2+}$ antagonist verapamil protected neurological function in dogs subjected to ischemia of the spinal cord by aortic clamping. Hall and Wolf (1986), tested the effects of three Ca$^{2+}$ antagonists, diltiazem, nifedipine and verapamil in spinal cord blood flow in a cat injury model. Both nifedipine and diltiazem prevented a significant post-ischemic decrease in SCBF. Faden et al., (1984) could not find any improvement in functional deficit that followed temporary aortic occlusion (Faden, 1984). There are inconsistent reports from various laboratories regarding
the efficacy of Ca$^{2+}$ channel antagonists in spinal injury.

Calcium antagonists are promising agents in the treatment of vasospasm. Interacting at the cellular membrane level, these compounds block the entry of Ca$^{2+}$ into the cells. Nifedipine, first member of the dihydropyridine class, of Ca$^{2+}$ antagonists show preferential cerebrovascular reactivity. In vivo experiments with nifedipine demonstrated that it prevented cerebral vessel contraction induced by serotonin, phenylephrine and prostaglandin E2 (Allen et al., 1975). Calcium channel blockers have a protective action against calcium mediated cell death (Balentine, 1977; Young, 1982; Stokes, 1983). A recent study has shown that prophylactic treatment with calcium channel blockers may limit secondary ischemia following experimental spinal trauma (Hall, 1985). Faden et al., found that nimodipine at doses that had proved effective in the treatment of experimental cerebral ischemia failed to improve ischemic spinal cord injury in rabbits (Faden, 1984). Verapamil was found to be ineffective in improving the neurological outcome in spinal injury (Cheng, 1984). These inconsistent results with calcium antagonists may be due to incorrect dose of drug used and the time of administration. Verapamil is bound closely to serum proteins and may not cross the blood brain barrier. There are no studies in the literature suggesting whether higher dosages get access to the neural tissues. Verapamil concentrations in
sera, cerebrospinal fluid (CSF) and spinal cord tissues were determined after one week drug treatment in both sham and experimental group.

**Opiate receptor antagonists:** Laboratory studies by various investigators have demonstrated a beneficial effect of naloxone in promoting motor recovery after experimental spinal cord injury. Naloxone at high doses in the mg/kg range when administered either before or after injury, has been found to improve spinal cord blood flow, somatosensory-evoked responses and neurological outcome in cats subjected to spinal cord injury (Faden, 1981, 1981a; Young, 1981; Flamm, 1982). Beneficial effects of naloxone depends on the dose and time of its delivery with respect to the onset of spinal cord trauma. The effect of naloxone is mediated by kappa-receptor, as very large doses (10 mg/kg) produces beneficial effect. The kappa-receptor is the most prevalent opiate receptor in the spinal cords of a variety of species including man and this receptor appears to be unregulated following traumatic injury (Krumins, 1986).

Naloxone is shown to stabilize lysosomal membranes and thereby reduce the release of proteolytic enzymes and myocardial depressant factors (Curtis, 1980). Naloxone inhibits lipid peroxidation in a dose dependent manner (Koreh, 1981), has potential activity as an antioxidant (Marzullo,
1981), a calcium ion modulator (Guerrero-Munoz, 1979) and a potentiator of cyclic adenosine monophosphate (cAMP) activation of prostaglandins (Collier, 1974).

Wallace and Tator reported that naloxone failed to improve spinal cord blood flow after clip induced compression injury in rats (Wallace, 1986). Black et al., (1986) found no benefit in motor recovery after spinal cord injury. As naloxone has a short half life, adequate drug levels should be maintained for beneficial effect. The beneficial effect of naloxone may be related to peak level rather than to the total amount of drug given.

**Dimethyl sulfoxide:** Dimethyl sulfoxide (DMSO) is an organic solvent that freely permeates biological tissue and membranes and is rapidly absorbed after intraperitoneal injection (Denko et al., 1967; De la Torre, 1975). It crosses the blood brain barrier readily. DMSO was found to be effective in experimental brain injuries or spinal cord contusions (De la Torre, 1975). The exact mechanism of action for DMSO in CNS trauma remains speculative. DMSO was found to increase brain and spinal cord blood flow during ischemia (De la Torre, 1975). It also increases cAMP, a potent platelet-aggregating inhibitor by blocking phosphodiesterase, its degrading enzyme (Wieser, 1977). DMSO increases the synthesis of prostaglandin E1, a strong vasodilator (Le Hann, 1975), reduces platelet
ADP, a stimulator of platelet aggregation and protects cell membranes from disruption following physical injury (Lim and Mullar, 1975). De la Torre (1975) proposed that the mechanisms of action include protection against mechanical cell damage, stabilization of lysosomal membranes, action as a free radical scavenger and reduction of tissue edema.

**Thyrotropin Releasing Hormone:** TRH acts as a physiologic antagonist of endogenous antagonists, unlike opiate-receptor antagonists such as naloxone, it does not interfere with the analgesic effects of endogenous opioids (Holaday et al., 1978) thyrotropin releasing hormone antagonizes β-endorphin hypothermia and catalepsy. TRH appears to act in vivo as a partial physiological antagonist that spare analgesic systems. This activity may be useful in spinal cord injury.

Endogenous opioids (endorphins) are released after spinal injury and they exacerbate post-traumatic ischaemia to the spinal cord by causing a reduction in SCBF associated with systemic hypotension (Faden, 1981). Opiate receptor antagonists like naloxone also block the analgesic action of endogenous opioids or exogenous opiates. They may have the adverse effect of exacerbating post-traumatic pain. Thyrotropin releasing hormone is a tripeptide that has many physiologic effects in addition to its function regulating pituitary thyrotropin secretion. Thyrotropin releasing hormone
significantly improved functional neurological recovery after experimentally induced spinal injury (Faden, 1981). The purpose of pharmacologic treatment in spinal injury is usually to limit post-traumatic spinal ischaemia which occurs within the first six hours (Sandler, 1976; Ducker, 1978).

Decreases in TRH and muscarinic receptor binding were not found at 24 hours after traumatic spinal cord injury in the rat or even at 48 hours after ischaemic spinal injury in the rabbit. There is substantial decrease in TRH immunoreactivity in the spinal cord below the injury site (lumbar region) at 1 and 3 weeks after injury. TRH has a very short plasma half life so it should be administered as a bolus injection or continuous intravenous infusion. TRH immunoreactive material is markedly reduced below the injury level and mildly increased above the injury level (Faden et al., 1986). The beneficial effects of pharmacologically administered TRH in experimental spinal injury have been observed up to 24 hours after trauma but not at later time periods (Faden, 1984). The beneficial effects of TRH on motor recovery after experimental spinal injury temporarily associated with preservation of spinal concentration of TRH and TRH receptors (Faden, 1986). Changes in concentration of TRH combined with damage to corticospinal tracts and or motor neurones would contribute to the neurological dysfunction observed after trauma. The neurologic dysfunction caused by traumatic spinal injury only
in part from direct disruption of spinal nerve cells or fibers.

Dipyridamole: Platelet aggregation, barrier breakdown and edema formation are frequently seen following spinal cord trauma (Green, 1973; Goodman, 1979; Balentine, 1978). The platelet borne prostacyclins may be involved in edema formation by affecting endothelial cells, neurotransmitter uptake and Na⁺, K⁺, ATP-ase activity (Chan, 1984). Dipyridamole is thought to modify platelet behavior by inhibiting the platelet's ability to adhere to a damaged but unlacerated endothelium (Weiss, 1982). Dipyridamole is a phosphodiesterase inhibitor.

Osmotic Diuretics: In SCI, it has been shown that although rapid tissue dehydration can occur as a result of the osmotic effect exerted by mannitol. It is thought that this dehydrating action is specific only in the capillary endothelium and astrocytes. Low molecular weight dextran showed some protection in spinal injured dogs (Hedeman, 1974). Urea is also found to be a useful drug in spinal injury.

Antioxidants and Free radical Scavengers: Free radicals may contribute to the pathophysiology of secondary spinal cord injury in several ways, though lipid peroxidation of membrane phospholipids with subsequent effects on lipid dependent
enzymes such as Na\(^+\), K\(^+\), ATP-ase (Demopoulos, 1980; Anderson, 1984) or Coenzyme Q10 (Sugigama et al., 1980).

**Enzyme Therapy:** There are reports on the positive effects of enzyme therapy in SCI. The rationale for the use of these enzymes was to create a favorable tissue environment for the regeneration. The enzymes are trypsin, elastase and hyaluronidase.
Fig. 3. Injury apparatus—primate weight drop model.