A REVIEW AND UPDATE OF EXPERIMENT AND CLINICAL STUDIES OF SPINAL CORD INJURY^{1,2}

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I WOULD like to express my appreciation for the invitation to give this lecture honouring Professor Norman Dott. I first met Professor Dott when I was a resident and later had a chance to get to know him better when I was a young neurosurgical faculty member. He was one of the giants of neurosurgery, and he was one giant that on meeting did not disappoint a neophyte. He was gentlemanly, academically caustic in a conference or discussion, was confident, but not overbearing, and judged people by his own and sometimes unusual standards. He almost overwhelmed me by spending time listening to some work I was doing to support a hypothesis about pain. I might add, his comments were pertinent and helpful even though the subject was not of prime interest to him. Norman Dott did what every young neurosurgeon hopes he or she can do. He became a master surgeon, contributed to the development of his chosen field and trained pupils to continue his influence. Perhaps one of the reasons for his success was his ability to get succinctly to the heart of the matter. Sometimes when I do a transsphenoidal approach to the pituitary, I remember his brief but caustic comment when I told him early in my career that I was not using the approach, because I had been taught it resulted in inadequate resections. He implied I hadn't thought the situation through. I quote him, certainly not word for word but in the sense of his meaning, 'No matter what you were taught, you should know the major reason remains that the patients do better'. Perhaps we, working in the area of spinal cord injury, are missing something that will allow 'the patients to do better'. I am certain, he would like us to find that something.

The title of my talk is A Review and Update of Experimental and Clinical Studies of Spinal Cord Injury. You will have to allow me in condensing such a broad subject to emphasise my interests and not be upset if this prejudice omits some aspects that you feel are important.

I am certain that all of you are aware that a professor of neurosurgery cannot and does not physically nor even conceptually do all the work he presents from his department. Since I will try to present a considerable amount of work in a brief time and cannot give individual credit to my co-workers for what they contributed, I would like to thank them for making this lecture possible and for making my professional life more interesting and satisfying. The National Institute of Neurological Communicative Diseases and Stroke (NINCDS) of the National Institutes of Health in the

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United States has for the past decade supported centres for the study of the acute care of spinal cord injury, and Yale has received one of these centre grants. I wish to thank the Institute, for without their support our experimental group could not have functioned nor even existed in its present form.

It was not until late in the last century that progress was made in the study of spinal cord injury. The early impact models of Schamus (1890), Watson (1891) and Spiller (1899), (Dohrmann, 1972), produced varied histological changes but suggested the possibility that a progressive lesion occurred following the injury. To study this lesion, a reproducible standardised spinal cord lesion was required and, Allen in 1911 and 1914, developed the drop weight model capable of producing graded lesions quantified as gm/cm of impact measured by the product of the weight times the distance it was dropped. With this model, descriptions of partial and complete lesions, the low threshold of the grey matter to contusion, the resulting central haemorrhagic changes and the cavitation that occurs following an impact injury have evolved (McVeigh, 1923; Ferraro, 1927; Ducker *et al.*, 1971). Modifications of the Allen model have been the most commonly used experimental model for the study of spinal cord injury. There have been other models. Cajal (Ramon Y Cajal, 1982) in the second decade of this century studied the changes that occurred at the site of a sharp transverse lesion of the mammalian spinal cord and described the formation of axonal terminal end-bulbs that appear similar but larger than the growth cones of peripheral nerves. He also described the autolysis of 200 to 700 microns of the edge of the spinal cord at both borders of the lesion. Another model that has had considerable study is the compressive injury model as used by Tarlov and his co-workers and Tator and his co-workers. Tarlov (1953, 1954a, 1954b, 1957) used an epidural balloon for rapid and slow compression and Tator and his co-workers (Tator, 1972; Deecke and Tator, 1973; Tator, 1973; Rivlin and Tator, 1977; Rivlin and Tator, 1978) first used a compressing circumferential sleeve and more recently a spring clip. While the compressive models improve the reproducibility of the lesion, a question as to the model's relationship to the clinical situation of an acute impact remains. In all models the same process described by Cajal occurs but over a larger area, contributes to the cavitation that follows cord injury and the process has been proposed as one of the barriers to spinal cord regeneration. The process has been shown to proceed in transverse, caudal and rostral directions, and has been used in support of the concept of a progressive secondary injury.

A major impetus for the experimental study of spinal cord injury has been this concept of secondary injury or the hypothesis that response of the spinal cord to injury causes a portion of the resulting neurological dysfunction. Using a variation of the Allen drop weight model, one of the first to test experimentally that hypothesis, was Freeman and his co-workers in the late 1940s and early 1950s who proposed that loss of vascular perfusion secondary to pial encasement of an oedematous haemorrhagic contused spinal cord was the cause of secondary injury (Freeman and Wright, 1953; Joynes and Freeman, 1963). They reported an improvement in expected neurological dysfunction when myelotomy or hypertonic solution was used as a treatment for graded impact injury. In the 1960s Albin and White and their co-workers (Albin *et al.*, 1968) reported a protected effect

of local hypothermia on primate and canine spinal cord when applied within a few hours of impact injury, proposing that hypometabolism protected the injured spinal cord from secondary injury. This suggested a metabolic cause of the secondary injury. No evidence from the clinical use of myelotomy, solute diuretics or local hypothermia has supported these experimental findings although it must be said that none of the clinical studies to test these therapies was designed to overcome the problems that are inherent in clinical studies of spinal cord injury. Osterholm in the 1970s (Osterholm and Mathews, 1972a) proposed that accumulation of norepinephrine at the site of injury caused localized vasoconstriction and membrane disruption. He supported this hypothesis by showing the protective effect of alpha methyltyrosine an inhibitor of the synthesis of norepinephrine in decreasing the central haemorrhagic changes (Osterholm and Mathews, 1972b). These studies were an impetus to the NINCDS to support more work on experimental spinal cord injury and, therefore, were valuable, but their results failed to stand up to further investigation. We were interested in Osterholm's hypothesis since there are drugs, safer than alpha methyltyrosine, that can inhibit synthesis of biogenic amines. The concentration of norepinephrine in normal cat spinal cord varies from level to level (Rawe *et al.*, 1972a) but no increase of norepinephrine was found at the site of an experimentally produced contusive injury (Naftchi *et al.*, 1974; Rawe *et al.*, 1977b; Rawe *et al.*, 1977c). Alpha methyltyrosine causes hypotension and we could duplicate the decrease in central haemorrhage that he found, with hypotension, which, however, caused increase in the resultant neurological deficit.

Let me take a few minutes to discuss the impact model of spinal cord injury. There are many problems in using it and they should be considered when evaluating experimental studies (Collins and Kauer, 1979). Physiological factors that alter blood flow or metabolism, alter outcome, and the minimal controls in any experimental spinal cord injury model must include, body temperature, blood pressure, PO_2 , PCO_2 and blood pH (de la Torre and Boggan, 1980). Many studies have failed to consider these controls and entered variables that make interpretations of the result difficult or impossible. A major technique in studying possible causes of secondary injury is to determine the effect of various treatment regimes on expected neurological dysfunction following an injury (Ducker and Hamit, 1969; Campbell *et al.*, 1973; de la Torre, 1981). It is thus important that experimental spinal cord injury outcome be predictably consistent. Several studies have assumed that in the Allen model a particular gm/cm force as measured by weight size and distance dropped defines a lesion and its expected neurological deficit. Our laboratory has shown a correlation of resultant neurological deficit and size of spinal cord lesion measured both in volume and maximum cross sectional diameter. Dohrmann, Panjabi and Banks (1978) measuring volume size of the lesion showed no correlation between volume of the lesion and gm/cm measurements of the drop weight model or impounder velocity but rather a correlation with energy and impact transmitted. They demonstrated a five fold difference in lesions produced by a 400 gm/cm impact in the cat when height and weight were changed to keep this product constant. Other variables in the Allen model such as the type of animal, size of the weight, shape of the impact surface, not using or using an impounder resting on the dura and its shape and type of spinal

column fixation all alter the type and extent of the lesion produced (Tator, 1972). It is important that any technique used is carefully evaluated in the laboratory using it, and continually checked as a control during any experimental study, to be certain an unobserved variable has not appeared, or a variable altered, altering the expected outcome. Another concept when evaluating a study of secondary injury is that of the trauma-dose curve (Collins and Kauer, 1979). It is apparent that at the lower end or low impact portion of the curve that almost all therapies as well as time will improve the neurological loss which is usually transient and, therefore, the ability to evaluate a therapy is difficult. At the high impact end of the curve only regeneration might be expected to work since physical interruption of fibers may have occurred. There is a sharp straight slope of the trauma-dose, neurological deficit curve in our laboratories in the cat showing both the narrow range where our model of impact injury can be used to study therapy and the single exponential quality of the curve suggesting that a single factor, impact itself, is the major determinant of the curve.

Our studies as well as studies from other laboratories have indicated that changes in spinal blood flow and the production of oedema may alone or in combination be a factor in secondary injury (Griffiths, 1976; Stewart and Wagner, 1979). Post experimental spinal cord blood flow has been measured in our laboratories by the hydrogen clearance method and by carbon-14 antipyrine autoradiography (Senter and Venes, 1978; Senter and Venes, 1979). The studies demonstrate loss of autoregulation 30 to 40 minutes after injury with decrease in local spinal blood flow, with post injury decrease in systemic blood pressure, and increase in local spinal cord blood flow with elevation in blood pressure. Both post injury hypotension and hypertension, the latter probably secondary to increased central haemorrhage, cause increased neurological deficit. More recent work has shown that reactivity of the local blood vessels to changes in pH and PCO₂ remains at a time when autoregulation to pressure has been lost and these complex combinations may explain some of the discrepancies reported in many post experimental spinal cord injury blood flow studies. Although the amount of oedema and its distribution does roughly correlate with the amount of force applied to the cord, in the intermediate zone of the trauma-dose curve which appears to be the most important portion of the curve to study, the amount of oedema formation and its extent does not correlate with neurological loss. The distribution of oedema following an impact injury as seen in fluorescent histological studies with fluorescein tagged albumin as the agent being photographed, is along white matter tracts of the cord (Stewart and Wagner, 1979). It can extend considerable distances cephalad and rostrad and is reminiscent of the white matter spread seen in cerebral hemisphere injuries. Studies attempting to alter the extent and distribution of oedema have not been as fruitful as had been expected. The agents used have included both hypertonic solutions and steroids. Our emphasis in the laboratory has shifted to the study of early changes in the axons, that is, within hours of injury and its relation to oedema and blood flow rather than just the study of oedema following impact injury.

Table I lists drugs and treatments that have been shown to have an effect on the expected outcome of neurological deficit produced by experimental spinal cord injury (Black and Markowitz, 1971; Campbell *et al.*, 1974; Hedeman *et al.*, 1974a; Hedeman *et al.*, 1974b; Lewin *et al.*, 1974;

TABLE I
Treatments that alter expected neurological
outcome in experimental models of spinal
cord injury

Positive	Negative
Carbonic anhydrase inhibitors	Alcohol
Corticosteroids	Hypertension
Dimethylsulfoxide	Hypotension
Hyperbaric oxygen	
Local hypothermia	
Local isotonic perfusion	
Myelotomy	
Naloxone	
Osmotic diuretics	
TSH—Thyroxine	

Flamm *et al.*, 1977; Nemecek, 1978; de la Torre and Boggan, 1980; Dolan *et al.*, 1980; Brodner *et al.*, 1981; Faden *et al.*, 1981a; Faden *et al.*, 1981b; Hall and Braughler, 1981; Means *et al.*, 1981; Young *et al.*, 1981; Braughler and Hall, 1982; Flamm *et al.*, 1982; Hall and Braughler, 1982). The changes in the expected neurological deficits in the above protocols have been confirmed by more than one laboratory but almost all agents have in some study failed to show an effect in one or more other laboratories, which is one of the reasons I mentioned the controls necessary and the trauma dose curve concept in impact models. Taking the entire group together the experimental results indicate that some process or combination of processes produce a secondary injury that may be amenable to therapy. Whether this is caused by altered blood supply, oedema, breakdown of organelles and the release of lysosomal enzymes, by disruption of the adjacent tissues from the pressure of the enlarging end-bulbs, by calcium influx into the cut end of the axons, by prostaglandin cascade effect on the surrounding tissue, by local biogenic amine concentration, or by some unknown factor or a combination of these remain unproven hypotheses. I will not go into the hypotheses of the mechanisms proposed on the basis of results obtained from experimental treatment protocols but rather summarise my interpretation as follows:

1. A secondary injury results from the reaction of the spinal cord to injury.
2. There is more than one mechanism causing the injury.
3. Alterations in spinal cord blood flow including alterations in micro-circulation may be a factor. Agents causing vasoconstriction, vasodilatation, alteration in endothelial cell integrity, and/or changes in platelet aggregation may alone or in combination contribute to the secondary injury.
4. Biochemical and mechanical alteration of cell membranes are another factor. The possible biochemical agents are many.
5. While oedema formation may contribute to the mechanical dis-

ruption of membranes, it appears to be an epiphenomena, well tolerated within wide ranges both of extent and amounts in white matter.

A major limiting factor with experiments concerning secondary injury have been that they consist mainly of recording phenomena related to the effect of different therapy and have not examined in an organised fashion the mechanisms involved. These basic mechanism areas must be studied and since the numbers of possible factors present at the site of injury precludes a treatment shotgun approach, the defining of basic mechanisms involved, and the time sequence of their activity, appears to be the direction to proceed.

While the difficulties involved in the evaluation of the experimental studies of spinal cord injury are a problem, these difficulties are exponentially increased in number and complexity in the evaluation of the clinical aspects of spinal cord injury. An aspect not involved in animal studies is that of the impact of spinal cord injury on society. Not counting the loss of productivity of the victims, the direct medical care costs of new spinal cord injuries in the United States, is over a half billion dollars a year and with the present life expectancy of spinal cord injured patients and medical care necessary for their survival, the resulting medical cost total is well past a billion and a half dollars a year. The majority of these costs in the United States are born by the Federal Government even in our private medical care society. To plan for the effective use of such sums of money, accurate epidemiological studies were required and the National Institutes of Health have supported epidemiological studies as well as experimental and clinical studies of spinal cord injury in order to determine what is needed and what might be done both for the victim and for society.

In the past few decades a number of epidemiological studies have been published that have shown marked variations in incidence, severity and costs of spinal cord injury. Table II is an example of the variations in the reported incidences of spinal cord injury from four countries, with three of the studies coming from the North American continent and two from the United States (Benes, 1968; Gehrig and Michaelis, 1968; Sutton, 1973; Botterell *et al.*, 1975; Kraus *et al.*, 1975; Webb *et al.*, 1978). Despite similar conditions in the North American areas studied, there is almost a four fold difference in incidence and almost a five fold difference among the different countries. Part of the problem is what constitutes a reported case and how

TABLE II
Epidemiological studies of spinal cord injury

Author	Year	Area	Pop/M	Rate/M	Comment
Benes	1952-67	Czechoslovakia	13	12	Hospital discharges
Botterell	1969-70	Canada	7.6	15	Hospital admissions
Kraus	1970-71	California	5.8	53	All cases
Webb	1975-76	Connecticut	3.3	28	Hospital admissions
Gehrig	1968	Switzerland	5.5	13	Hospital questionnaire
Sutton	1963-70	Australia	1.8	14	Spinal cord centres

is it identified. Kraus' study from California with the highest incidence of 55 per million included all injuries, those that died before admission to a hospital, those that were admitted, those that were seen but not admitted, and those identified by any means within a defined population. The same study showed an incidence of hospital admissions of about 33 per million, similar to the 28 per million shown by Webb *et al.* (Webb *et al.*, 1978) of our group at Yale in 1975-76. That survey was of all spinal cord injury hospital admissions in Connecticut. Bracken *et al.* (Bracken *et al.*, 1981) of our faculty, in trying to develop a less costly method used identified hospital discharge codes in the data bank of the National Center for Health Statistics and a subset to correct for multiple admissions, and arrived at a figure of approximately 40 per million spinal cord injury hospital admissions per year. A 1980 study of the National Institute of Health using a selective population survey arrived at a figure of 50 per million population/year. I mention these variations in the studies not to criticise the studies but to point out the problems that have arisen in attempting to define as simple a portion of the clinical problem as the incidence of the event of spinal cord injury in our population. There is, with more sophisticated techniques, a consensus being attained in this quest of an incidence at about 45/mil/pop/yr in the United States. No such consensus is being approached in other aspects of the problems of spinal surgery.

The British Isles are famous in our medical meetings, and our mal-practice courts for non-interventional care of spinal cord injury with the results from the Stoke Mandeville group being the basis to indicate that the non-surgical postural reduction approach is more effective than the relatively common concept in the States of rapid reduction and frequently early surgical intervention (Frankel *et al.*, 1967). I would like to review a few of these clinical studies. Table III is to briefly remind you of the Frankel Functional Classification of spinal cord injury that can be used for

TABLE III
Summary of Frankel's functional classification of
spinal cord injury

A—No sensory or motor function
B—Incomplete sensory—No motor function
C—Incomplete sensory—No useful motor function
D—Incomplete sensory—Useful motor function
E—Normal function—May have spasticity

comparing different series. The A group is a total lesion and the E group is normal function with or without abnormal reflexes. In order to decrease variables, I have picked cervical spinal cord injuries. There are enough variables in any clinical series to please the most dedicated biostatistician and using one anatomical area helps limit if not overcome some of these variables. Table IV is a review of three modern series—one the Stoke Mandeville series and the other two from the States and one not so modern series (Hartwell, 1917; Frankel *et al.*, 1967; Young and Dexter 1978; Maynard *et al.*, 1979). The vertical axis of each box is the functional grading on admission to and the horizontal axis on discharge from the hospital. Thus,

TABLE IV
Four clinical series of spinal cord injury. Vertical axis is Frankel's classification on admission; horizontal axis on discharge

Stoke Mandeville						Southwest Region					
	A	B	C	D	E		A	B	C	D	E
A	81	21	10	11	0	A	41	6	1	1	0
B	3	9	2	14	5	B	0	4	2	10	0
C	0	1	4	11	5	C	0	0	2	3	0
D	0	0	0	30	11	D	1	0	0	14	6
E	0	0	0	0	0	E	1	0	0	3	0
N = 218						N = 95					
California Region						MGH Boston 1917					
	A	B	C	D	E		A	B	C	D	E
A	50	4	3	4	1	A	25	0	0	0	0
B	0	3	2	13	0	B	2	0	0	2	0
C	0	0	2	17	4	C	3	0	0	1	1
D	0	0	0	4	7	D	0	0	0	0	0
E	0	0	0	0	0	E	0	0	0	0	0
N = 114						N = 34					
						A = Mortality =					
						88 per cent					

as in the Southwest Region series a patient with a 'C' on admission and an 'A' on discharge deteriorated while one with a 'B' on admission and a 'D' on discharge improved. Unchanged patients form an oblique line from the upper left hand corner, that is, the 'AA', 'BB' to the lower right hand corner of each block. In case you are discouraged with the present treatment of spinal cord injury, the fourth box was made by extrapolation of data presented by James Hartwell in an article published in 1917 in the Boston Medical and Surgical Journal (Hartwell, 1917). It consisted of a series of 133 cases of spinal cord injury admitted to the Massachusetts General Hospital between 1900 and 1914, 34 patients had cervical spinal cord injuries. The only change in that box is that the 'A' discharge line is mortality because with one exception no one with a complete lesion on admission survived, and that exception died 11 months after admission. The causes of spinal cord injury in the Boston series had a different distribution than modern series with 62 per cent caused by falls, 19 per cent from forces that cause acute flexion, such as, sports or falling objects, 5 per cent from altercations, with no mention of gunshot wounds and 8 per cent from vehicle accidents. The majority of the vehicles accidents involved trains but one was an automobile accident. Twenty-three of the cervical spinal cord injury patients were X-rayed and twelve fractures were diagnosed. The use of X-ray for diagnosis was just starting and a comment was made of the difficulty in diagnosing fractures of the cervical spinal column with an anterior/posterior X-ray and the difficulty in obtaining lateral X-rays of

the lower cervical spine. Eleven of the 34 patients underwent laminectomies, 7 within the first 24 hours and 9 within the first week, evidence for some historical continuity of opinion in the States. There were 10 postoperative deaths including one patient each in 'B' and 'C' category on admission to the Massachusetts General Hospital. The eleventh patient who improved after a laminectomy from an 'A' on admission to a 'C', developed complications and remained at the hospital until he died 8 months later from renal failure. While listed as a complete lesion on admission, at post-mortem examination he showed a significant portion of the spinal cord intact and Mixter and Chase reported this case in 1904 as evidence of the value of laminectomy in protecting the injured spinal cord (Mixter and Chase, 1904). Dr Hartwell, however, concluded from this series that laminectomy was not of value and postulated that at least two patient might have had functional return if they had not been operated upon and that the remainder benefited only by having their agony shortened by the surgery.

This attitude of despair concerning spinal cord injured patients prevailed up to and through most of World War II, even though Riddoch and Head in England during World War I had shown that paraplegic patients could survive when given the correct care. With these surviving patients, Riddoch in 1917, (Riddoch, 1917) settled the long standing argument as to whether the isolated human spinal cord functioned and, therefore, laid the groundwork for possible treatment by techniques of regeneration. He demonstrated spinal reflexes in the human and their loss with sepsis and joint contraction. The spinal cord injury patients however who survived often became nonfunctional chronic nursing patients, addicted to opiates and usually succumbed within a year or two to urinary tract dysfunction, sepsis from decubiti and/or pulmonary disease. It was the concepts and the enthusiasm of Sir Ludwig Guttmann in England who almost single handedly changed this. He believed and demonstrated that with appropriate care the associated complications of spinal cord injury could be controlled indefinitely and that with rehabilitation the spinal cord injury victim could be returned to an independent productive life. This led to the Stoke Mandeville Centre concept and the results led to changes throughout the entire western world as to how spinal cord injury should be handled. His success was so great that his concepts of the treatment of spinal cord injury became almost revered and in much of the western world questioning and investigation of the early care of the injured spinal cord patient ceased. Although the rehabilitation results were spectacular compared to what had preceeded, the return of spinal cord function has remained almost unchanged from the time of Riddoch to the present. No scientifically valid effort to study clinically the hypothesis arising from experimental studies, was made until a few years ago. A patient with a spinal cord injury, although now often capable of self care and productive work, has no more significant possibility of return of spinal cord function with treatment in 1982 than he did in 1917 nor have his physicians attained any scientifically valid new information to use to increase those chances. But to return to the other series to illustrate two points. They are what happened among these series to patients with complete lesions on admission and what percent of patients deteriorated with treatment. At first glance the fact that 8 per cent of the Stoke Mandeville total functional loss or 'A' admission patients improved to a functional level would document the superiority of their

treatment. However, the California series also had an 8 per cent improvement even though 29 per cent received early operations and almost all had rapid reduction of their fracture. Maynard in the California group reviewed the five charts that constitute that 8 per cent and found all had some impairment of consciousness at the time of the first examination. Other reasons for improvement in total lesions in other series are very early admission with improvement in the first few hours after injury, or inadequate admission neurological evaluations for any reason. In my opinion with any of the presently used treatment regimes, a series of spinal cord injury patients that has more than an occasional complete lesion patient showing functional return, indicates the authors of that series have either discovered the Holy Grail of spinal cord injury, have a large number of admissions within minutes of injury, or have an error in admission examinations. I intellectually cannot believe that slow reduction, and non concern for compression of the spinal cord for days is that sought for Grail.

Does the lack of deterioration in the Stoke Mandeville series demonstrate the superiority of the method? The California series also had no deterioration. The common denominator of both series is they are spinal cord injury centres not acute trauma hospitals. One bias may be that the referred patients have rehabilitation potential and the patients with other injuries, cardiovascular disease or other medical conditions are either not referred or referred when these conditions are stable. The Southwest Region series contains admission exams to acute hospitals and has the highest deterioration rate of these three series. Finally and perhaps most importantly, it should be noted that in reporting the Stoke Mandeville patients, the series is defined as follow, and I quote 'All patients who had had operations on the spine before admission—all patients who died in the first three months or who were discharged from Stoke Mandeville Hospital prematurely for any reason—are excluded from analysis'. The number and condition of these patients are not discussed further. From a statistical point of view, a major bias could exist with their exclusion.

I know I have been critical of the Stoke Mandeville series, not because I do not appreciate what has been accomplished there, but with critical review even their series does not disprove the hypothesis that is based on evaluation of many series and my personal experience. The hypothesis is that no treatment of spinal cord injury that is within the bounds of good medical care can be shown to be superior to any other. I conclude that none of these present series or any other series demonstrate a statistically significant better or worse result from one form of therapy rather than from another.

It is suggested from the experimental studies of spinal cord injury that there is some loss of function of the spinal cord that relates to the response of the nervous system to injury that may be controlled by therapy. In the clinical situation this may apply to only a portion of the cases and have limited effect but even that limited effect can have significance to the social problem and may mean the difference of nervous system functional life rather than a mechanical functional life for the individuals helped. Patients with rapid onset of complete loss of spinal cord function following injury are not likely to be the group where the effectiveness of any treatment can be demonstrated and I conclude, that since there is no evidence to support that any specific treatment of spinal cord injury is better we morally can

and medically should develop prospective randomised studies in order to study and improve the acute treatment of spinal cord injury. These almost certainly will have to be multicentre studies since experimental data indicates that at the most the first 48 hours is the window for treatment and probably only the first 4–12 hours, the promising portion of the trauma-dose curve is the one containing partial lesions and there are multiple variables requiring large numbers of cases for statistical significance to be obtained. There is a paucity of cases in any one centre or even one area of the country that can fulfill the requirements for a satisfactorily rated study.

We have made a start with a randomised collaborative study but it is only just a start. In 1977 we submitted to the NINCDS following a two-year feasibility study, a project to evaluate low-dose, high-dose steroids in the treatment of spinal cord injury to be organised at Yale. The steroid used was methylprednisolone with high-dose protocol of a 1000 mgm loading dose and 1000 mgm per day for 10 days and the low dose of 100 mgm loading and 100 mgm per day. I personally would have preferred a study that included a placebo arm but even though there is no clinical evidence that steroids are of value in spinal cord injury we could not get agreement of the various centres proposed for the study to use a placebo. The reasons were both moral in that they believe the experiential studies showed that it had value, and medicolegal, feeling that any physician not using steroids might be open to a malpractice suit. The first patient to enter the study was on 17 February 1979 and the last on 6 November 1981. Three hundred and thirty patients that were randomised into the two steroid treatments. The types and frequency of injuries are shown in Table V. Of the randomised patients, 24 were excluded for various reasons. The ex-

TABLE V
Distribution (in per cent) of types of injury in the National
Spinal Cord Injury Collaborative Study

Characteristic per cent	Treatment group		Significance test
	High (n = 152)	Low (n = 154)	
<i>Cause of injury</i>			
Automobile accident	32.2	27.3	p = 0.23
Fall	21.7	21.4	
Missile	15.8	22.1	
Water related	12.5	14.9	
Motorcycle accident	7.2	7.8	
Crush	5.3	0.7	
Other	5.3	5.2	
Unknown	0.0	0.6	

cluded patients were evenly distributed between the two steroid protocols and have been analysed to show that there is no bias caused by their exclusion. The UpJohn Corporation provided the two doses of methylprednisolone in uniquely numbered look alike packages and organised random codes. They otherwise did not participate in any aspect of the trial. An advisory committee was established by the NINCDS to monitor the

conduct of the trial and data collection and an analysis was conducted to monitor intermediate results with only two investigators, myself and an epidemiologist, Dr Bracken, being aware of the assignment of patients in the randomisation during the study. Standard forms for reporting the history, neurological examination, treatment and complications were developed during the previous two-year feasibility study. The only significant difference between the two treatments modes was a higher rate of wound infection in the high steroid group. The results of the study will be published this coming year. Only 6 weeks and 6 months follow-up are available at this time since the complete evaluation for the one year follow-up cannot be done until mid-1983. Five groups of patients were looked at and a multivariate analysis was done of the results, Quadriplegia with total sensory loss or Frankel Grade A and paraplegia with total sensory loss also a Frankel Grade A were combined as were quadriplegic with partial sensory loss and paraplegic with partial sensory loss or a Frankel Grade B, while those with some motor function and variable sensory loss or Frankel Grades C and D were combined as a group (Table VI). At 6 weeks there was a trend that suggested that the high-dose steroids may be having some effect in the C and D group but it was not statistically significant and at 6 months there does not appear to be a statistical difference between the patients in high-dose vs the patients in low-dose groups.

TABLE VI
Distribution (in per cent) of functional deficits on admission
to the National Spinal Cord Injury Collaborative Study

Neurological status	Frankel grade	Steroid protocol	
		High (n = 152)	Low (n = 154)
Quadriplegic; Total sensory loss	A	27.0	33.1
Paraplegic; Total sensory loss	A	24.3	27.9
Quadriplegic; Partial sensory loss	B	4.0	5.8
Paraplegic; Partial sensory loss	B	11.8	9.1
Paretics; Variable sensory loss	C + D	32.9	24.0

I know of the cost and the amount of work that was done attempting to evaluate a single drug two dose treatment and it produced a negative result. We as physicians must realise that any treatment which has been considered to alter the acute care of the spinal cord injured patient must be evaluated in a similar fashion. Anything less than this is not acceptable but no evaluation is even less acceptable.

In the few remaining minutes I would like to discuss the directions we are taking at Yale in our continuing work with spinal cord injury. One is a continuation of animal models in spinal cord injury in the hopes of defining mechanisms of secondary injury more accurately. Another is the continuation of the clinical series of prospective treatment protocols, and the third is the study of central nervous system regeneration. We have decided to study regeneration in the central nervous system because we

believe it is the only hope for the majority of spinal cord injury victims. Some 20 odd years ago, I worked on central nervous system regeneration and after a few years came to the conclusion that none of the models we were using nor the methods available were able to answer even the simple question as to the ability of central nervous system neurons to regenerate. I swore, at that time, I would not get involved with central nervous system regeneration experimentation again, but now the question of central nervous system neuronal regeneration can be answered in the affirmative but whether central nervous system neurons can functionally regenerate, and what starts, stops and controls the process cannot be answered. Working with Professor Cohen in the Department of Biology, Professor Shepard in Anatomy and Dr Van den Pol in my department, we have two models of spinal cord regeneration and a model of neuronal regeneration that can be asked these questions. The first is in the Lamprey eel that does functionally regenerate a transected spinal cord and whose giant reticulo-spinal neurons make it possible to follow the course of individual identifiable fibers during regeneration (Wood and Cohen, 1979). Preliminary observations suggest anatomical junctions, including gap junctions, their numbers and positions on the regenerating axon and not glial or fibrous scar limit the amount of spinal cord regeneration in the Lamprey. They also suggest that electrical fields may alter both initial fibre die back and nondirectional branching. The second model is in the rat and is a study of a hypothalamic spinal tract that contains neurophysin. Its fibres can be identified by immunohistochemical techniques proximally and distally to a spinal cord lesion. This allows identification of regenerating fibers coming from the proximal end of a tract in a lesioned spinal cord. This model will allow studies in a mammal to check the findings of the Lamprey model. The third model of regeneration can be asked more basic questions of neuronal reorganisation during regeneration by studying olfactory neurons in the mouse and salamander (Greer and Shepherd, 1982). These have been demonstrated to regenerate. All three models are under active investigation. While the work is a long way from any application to the clinical theatre, the models allow questions to be asked and data that can be evaluated to be obtained.

In summary, although considerable advances have been made in the care of the total patient with spinal cord injury, little has been accomplished in improving the spinal cord functional result. No clinical therapy for spinal cord injury has shown superiority in accomplishing the goal of protecting the spinal cord from further loss of function after injury or reversing the initial injury and no clinical studies have given support for the hypothesis that secondary injury is important in determining resulting neurological deficits. The need to clarify the problems of secondary injury is apparent but prevention of injury and techniques to re-establish spinal cord function after an injury are the most likely way of altering the problems faced by victims of spinal cord injury. Neurosurgeons probably have to be optimistic in order to continue in neurosurgery but even so the present models for regeneration are so interesting that I hope my career can extend as long as it will be necessary to study these and other models that are certain to be developed. I am too old to believe that we can prevent our population from killing or maiming themselves and, therefore, I hope that sometime in the future a Dott lecturer can announce that techniques for

functional regeneration of the central nervous system are available or at least close to hand, I certainly cannot, but I believe a future lecturer will.

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