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# **Spinal Cord Injury Treatments: The Challenge of Moving to the Clinic**

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So what I wanted to talk to you about today is practicalities. The practicalities of how, fairly soon, we're actually going to be able to do clinical trials to test the various treatments that are coming along for spinal cord injury treatment, and of course some clinical trials are already ongoing or have been completed. I'm going to go through, roughly, this order of issues that you can see on the board. We start off with the need for expertise (indistinct) is a terrible condition, people are crippled for 50 years. Any society feels strongly that they would like to provide a cure for this condition. But it really hasn't been possible to think about how we would do it until the beginning of the 1990s, which were the publication of the first experiments which really showed convincing repair of spinal cord injury in experimental animals. So at about that time some of us started thinking, "Well, if we are going to have, really, a curative treatment for spinal cord injury, how on earth could we set about proving that they work and doing clinical trials?" That's the process I want to talk about today.

Now, spinal cord injury patients have a variety of priorities and not all of them match up exactly with the sort of research that we do and the sort of things that actually we know how to deliver. But of course patients' priorities depend on their particular condition and the type of lesion they have. This was a study that many of you will have seen from Kim Anderson, published two years ago, showing what patients actually say they would like to have back from treatments that we can deliver. So, of course, if you've got no arm and hand function, what you would like to have best is arm and hand function. But, surprisingly, if you look at the priorities of paraplegics, sexual function comes extremely high on the list of things that they would like to have back, bladder and bowel function, trunk stability, walking movement, then help with chronic pain, and arm and hand function rather lower down the list. So we do need to pay attention, as researchers, to what the patients see as priorities. But, of course, the patients need to pay attention to us when we tell them what we think we can do.

Now, one of the things we thought about when we started this process of how you would do clinical trials is thinking about what would be the threshold for embarking on a clinical trial. In other words, what's your treatment going to have to deliver in order to be worth putting into clinical trials? Now at the time the animal experiments were producing recovery - acts of regeneration, I should say, at the order of 1 or possibly 2 cm. The question we asked is, would that be any use to a patient. Well, 2 cm is about two spinal levels of the cervical region, so the question is, is two spinal levels of recovery actually any use to a patient and is that a reasonable threshold for thinking that we've got a useful treatment.

One way of looking at it is to go to Hans Frankel's book, which many of you will have seen, and look at the abilities of patients at different spinal levels. I can only point, I'm afraid, to this screen here that most of you can't see, so I'll try and do this without doing any pointing. So, first of all, this is what C4 patients can do independently. They can talk, they can swallow and, if they're lucky, they can breathe. Although Chris Reeve was on a ventilator, he was a C3-C4. So these are patients with no shoulder movement, no arm movement and, really, no ability to do very much for themselves and completely dependent on a full-time, 24-hour care team.

So if we were able to do two spinal levels for these people, what would we get? We would get to C6, which, of course, is the commonest level of spinal cord injury. A C6 patient has got shoulder movement, has got upper arm movement, has got elbow movement. They can do, therefore, a lot of things for themselves, including moving themselves around. A C6 patient will be able to live largely independently, but will usually one full-time care person, but is in a position of having a completely

different life to a C4 patient. C6, as I said, is the commonest level of injury and if you could do two spinal levels for them, you would go to C8. C8 patients, of course, have hand movement back, and a C8 patient would be living independently, would not need a full-time care person, will often be able to hold down a job, and therefore is in a very different situation, again, to a patient with a C6 injury. So I think we decided, sometime back, that this was the sort of level of expectation that we should have clinical trials and candidates for treatments, but they should be able to have some ability to produce recovery over two spinal levels.

Now, the truth is that we haven't done it yet. This curve here, the red line, is supposed to represent our progress over the years, and the bottom axis is benefit to the patient. Benefit to the patient, from the sort of research that I do at the moment, is zero. We have not got treatments, regenerative treatments, so far into the patient that it has made much difference to their function. On the other hand of our persecutive, a fantastic advance has been made over the years that I've been involved in spinal research. We now really do have a realistic possibility of getting treatments that will work, into patients. So if you look at the dotted line of 2006, we're actually at a rather historic moment where the trial of the anti NogoA antibody, which is the first really major clinical trial of a regenerative treatment, started about a month ago and we have great hopes that that will lead to real benefit for patients.

Now, there are a number of treatments that are either in trials or are coming soon, and this is one of the reasons for the urgency of what I'm talking about. Currently undergoing trials: As I say, there is a very large trial of the NogoA antibody, the Rho inhibitor, Cethrin, is under trial in Canada, and there is a (indistinct) trial, which I think has just currently gone on hold from the (indistinct). But there are various compounds being developed actively by companies, which should be coming to trials in the next few years, and that's the list of them you can read on the screen in front of you. When you think about how you should do this, we all decided sometime ago, those of us who were involved in running spinal injury charities, that there should be an international effort to put together protocols for spinal cord injuries. The ICCP, of which David Prast is the chairman, and to which these are the member organisations, decided to become active in this area. The first thing that they did was to run a meeting. I'm not quite sure how well you can read that, but this actually was a historic occasion. It was the first trial, the first meeting that had ever been held on the design of clinical trials on an international basis. People from all round the world came and a discussion, a useful discussion, was started on how we were all, internationally, going to agree on running spinal cord injury trials. The introductory address, I should say, was given by David Prast.

So one of the outcomes of that meeting was that they told some of us to go away and do better and to come back with some detailed protocols on the design of spinal cord injury treatments. So a panel was set up, of which this is most of the members, which was run primarily by myself, who you can see lurking in the background there, John Steeves, who is the bloke in the middle there, in the blue jacket and the beard, and Mark Tuszynski, who is the chap with the brown hair and the long nose at the back of the group. But you can see that this - and this group involved many of the people who had been involved in clinical trials over the past years.

We are producing four papers, which are available in first draft form, on the ICORD website. I'll show you the address in a moment. Those four papers are on the following subject: The natural history of spinal cord injury, spontaneous recovery, and that's mostly what I wanted to talk about today, outcome measures for measuring outcome in clinical trials, selection criteria, ethics and the fourth one on

trial design statistical analysis.

Now, there have been some fairly heroic trials over the past decade or so, for treatments of spinal cord injury. Those have been crucial to us in working out some of the protocols and some of the figures that I'm going to talk about. The biggest trial that's been done is the Sygen trial which was finally published in 2001, which was 760 patients and also 760 patients in a preliminary study group. This was a trial of a magnitude, really, that took up all the spinal injury centres in the United States. It's really, I think, not something that we're ever going to be able to do again. But it did provide a fantastic amount of data on spontaneous recovery and on trial design in general. Naomi Kleitman and Alain Privat, who was part of the group that I've just shown you the picture of, was one of the key figures in that. Unfortunately, what it showed was that this treatment didn't actually help spinal cord injury. What you can see on the bottom is the ASIA motor scores from this particular trial. The black bars on the left are the ASIA motor scores on admission to trial, and the white ones on the right are the score of one year, and the four sets of data are placebo and three dosage groups. You can see that they, basically, all turned out with the same motor outcome, which was sad.

Another trial that's been published recently, which was also fairly heroic, was a trial of treadmill motor training which was done in Los Angeles. This was compared with conventional walking training. Unfortunately, the patients got so motivated by the conventional walking training that the non-treatment group did fantastically well, and so the effects of treadmill training were not obvious in this trial. But, as I say, there are three trials currently ongoing, the biggest of which, funded by Nevartus, is the one with anti NogoA treatment, which I'll talk more about later.

So let me move on now to which type of injury you might want to put into clinical trials. I'm going to be talking a lot about ASIA motor classic occasions and motor scores, so for those of you who are not familiar with these, let me just quickly tell you what I'm talking about. This is the standard chart that gets filled in when you're admitted to hospital with a spinal injury, which classifies you according to your motor abilities and your sensory abilities. Just to look at the motor scores, which is the one on the left, you'll see that there are boxes you fill in for C5, C6, C7, C8 and T1, for instance motor function, and you can get a score between 1 and 5 on each side at each of those final levels. So that means, for instance, that if you make a complete motor recovery over one spinal level, you would have five on either side. In other words, 10 motor points increase. So if we're talking about complete recovery over two spinal levels, as I've been talking about earlier, that will be a 20-point increase in ASIA motor score.

The other thing you get is an ASIA impairment scale, which can be A to E, and A are patients who have no motor or sensory function below the level of the injury. B have sensory and then motor, C are incomplete, etcetera, etcetera, until you get on to E, which is normal function. So when we think about what type of injury is best for clinical trials, there are various considerations. One consideration, of course, is which level of injury. Really, you're choosing between thoracic injuries and cervical injuries. Now, what are the advantages and disadvantages? The great advantage of thoracic injuries is that, frankly, if your treatment makes a patient worse, it's not catastrophic, because what you're losing is a few ribs, you're not losing function that's critically important at keeping you alive. Whereas if your treatment does some extra damage in cervical injuries, you're losing arm function, hand function, and this is a real catastrophe. So there are real reasons for starting your clinical trials, for doing the safety trials in thoracic injuries. The problem with thoracic injuries is it's very difficult to evaluate whether your patient has got better or worse, and I'll talk a little bit more about that later, because some protocols have

been developed now which allow you to determine the level in thoracic injuries. So I think the general conclusion that people have come to is that you start your clinical trial looking at thoracic injuries, you do some safety studies in thoracic, then you hope to move up to cervical injuries where you can evaluate success or failure of your treatment much more precisely.

The second question is what density of injury should you go for? Should you go for patients who have no motor or sensory function, in other words ASIA A, or should you go for patients with some function, Bs or Cs. Well, the issue here is the issue of spontaneous recovery. Now, what you've got here, on the left graph, is the ASIA motor recovery in patients in four different studies. What you can see is that the ASIA A patients recover about 12 ASIA motor points from the time of injury until one year later. This is substantial recovery, but if you think your treatment might improve them by, say, 20 ASIA points, then this is something that you could probably use as a battleground. On the other hand, if you're looking at ASIA B or ASIA C patients, their spontaneous recovery is nearer to 40 ASIA points, and you're seeing a 28 ASIA point improvement against that background. So the completeness of the injury is clearly an issue. But on the other hand, of course, if you've got a complete spinal cord transection, none of the treatments that we know about are really going to help you very much. It's probable that, actually, many of the treatments would be more effective in ASIA B, ASIA C patients, than they would in ASIA A. So this is a difficult issue.

Now, as well as motor recovery, patients have grade recovery. In other words, ASIA A patients become ASIA B, ASIA C, and there are substantial ASIA grade conversions during the year after injury. So what we've got here is ASIA grade conversions over the first year from ASIA A, ASIA B, ASIA C and ASIA D patients. What you can see is that at the end of the first year most ASIA A patients are still ASIA A. 80 something per cent of them are still ASIA A, but a small number of them have converted to B, C and D. But if you take ASIA B patients, who are motor complete, sensory incomplete, almost all of them have moved to a better ASIA grade over the first year. So there is really substantial recovery also seen on the ASIA impairment scale. Also, C and D and patients show very substantial improvement. So clearly you've got to think carefully about what your treatment can deliver relative to the type of patient you're going to put into the trial.

The next issue is when to do it. When to do it, of course, depends on the sort of treatment that you're delivering. You can think of treatments that would act at the acute phase, and those, really, are neuroprotective treatments that are designed to prevent the increase in the size of the injury that will occur after the first hours of injury. Subacute treatments, one to four weeks, is probably appropriate for treatments that will promote nerve fibre regeneration. But if you get to chronic patients, and chronic patients are going to be very much easier to do trials with. Some of the treatments that promote plasticity may well be active in that group of patients.

There are some issues: Basically, you can't really do a very reliable examination that will predict outcome until 72 hours. There are issues such as spinal shock, the fact that your patients are often unconscious and have various other problems. So it's difficult to start before 72 hours, although some of the trials, for instance the NASCIS trial, did start at 24 hours and before. Your patients go on getting better for nine months at least, as I'll show you. There is a high level of spontaneous improvement, which is least in ASIA A patients, greatest in ASIA C and D patients. As I'll tell you in a moment, the earlier the trial starts, the more patients you're going to have to recruit.

Now, just looking at grade conversions, which is what this graph is, relative to the time at which you start your trial. This is a further analysis we've done of the Sygen trial, the Sygen database, which was published in 2001. Bill Coleman, who was the statistician on that study, has looked further at these for us. So on the left-hand side you've got ASIA grade conversions for patients who were ASIA A or ASIA B at the beginning of the study; in other words, at 72 hours. On the right-hand side we've reselected the patient for being ASIA A on the top, ASIA B on the bottom, at eight weeks. You can see that the amount of spontaneous recovery after eight weeks is very, very much less, particularly in the ASIA C patients. So if you start at eight weeks, your level of spontaneous ASIA grade conversion is very much less than it would be at 72 hours. If you look at motor recovery, again Bill has done a re-analysis of the Sygen data here. We've selected patients who are ASIA A, that's the top two graphs, or ASIA B, which is the bottom two graphs, and we've selected patients who are ASIA A at the beginning of the trial, which is the hard line you can see on the top, who are ASIA A or B at the four weeks, eight weeks and 16 weeks and half a year. Those are the other curves. You can see that ASIA motor scores go on improving for certainly six months and, basically, almost up to the end of the year, but that the majority of improvement is within the first two or three months. Also you can see that if you select patients who are ASIA A or ASIA B at half a year, or at 16 weeks, the degree of spontaneous recovery is very, very much less. But as I said, you probably can't really read what it says on the vertical axis, the ASIA B patients are recovered by about 40 ASIA points, the ASIA A patients are recovering by 12.

Sensory recovery shows a similar pattern, again with recovery occurring mostly in the first six months over a similar time (indistinct) to motor recovery. So here is a plot, simply, of recovery rates, showing that recovery rates are highest shortly after the injury, and come down almost to zero by nine months. So those issues are going to, obviously, influence when you want to start your trial.

The next issue I wanted to talk about is how to assess your patients during the course of the trial. Now, one of the big advances that's happened in recent years is the establishment of EMSCI. This is an organisation that's been established primarily to conduct the trial of the NogoA antibodies, and these are the centres that are currently involved in doing this study—these six countries in Europe. But I think their protocol is, sort of, becoming the de facto standard now for the conduction of clinical trials. So their assessment protocol looks like this: They're doing standard ASIA examinations, so ASIA Impairment Scale, light touch, pin prick and ASIA motor skills. That's the scores on the top left. They're doing some electro physiological tests for (indistinct) sensory and motor nerve conductions (indistinct) velocity. They're also doing functional studies, which I'll talk about in a moment. WISCI, which is a walking test, up and go, another walking test, a 10-metre walking test, and SCIM, which is the Spinal Cord Independence Measure. So that is, basically, the EMSCI protocol, and they're developing some new protocols particularly to do with hand function. But still the baseline of assessment remains the ASIA motor classification, based on this chart that I've shown you.

So the other tests that have been done, as I said, are somatosensory evoked potentials, in which you stimulate peripherally and you look for a response in the cortex. What you will see is that there is an initial stimulus artefact, and then a long, delayed response in the cortex, which represents the sensory information being responded to in the brain. That somatosensory evoked potential, of course, disappears if you stimulate below the injury in a complete patient. Motor evoked potential is a way you stimulate the brain using a magnetic stimulator and you then look for the responses in muscle recordings. This is a set of motor evoked potentials from an incomplete patient and what it shows is that the sudden increase

in the latency of the response in the muscles, at about thoracic 11 to 12, is at roughly the level of the injury. So this is an incomplete patient and it's showing, basically, that the main change is the latency, the time it takes for stimuli to get from brain down to the spinal cord. But, of course, if this was a complete patient, you would see a cut off of the motor evoked potential at that point.

There are some other tests that have been developed, I think, which will come into clinical trials protocols. This is one that was developed by Nick Davey in England. It's called the Cutaneous Electrical Perceptual Threshold. It's rather simple to do, you just put an electrical stimulation on the skin and you just turn up the knob until the patient says that they can feel it, and then you plot that on a graph. What these graphs show you, the black line and the dotted line, are the normal mean stimulus intensity that a patient would need to feel that sensation at that level. The outer dotted line is two standard deviations away from that. It gives you, basically, a numerical estimate of the patient's sensory abilities. There is also something which was developed which is known colloquially the Proddagram, which is crucial to the assessment of motor (indistinct) in a thoracic injury. What you do, basically, is just prod the paraspinal muscles, or their attendants, while recording from the muscles as an EMG. What you get is an immediate sort of stimulus where you prod the muscle, and then a longer term EMG response, which is the reflex coming back through the spinal cord. That disappears below the level of the injury. So this gives you a reasonable estimate of spinal level of thoracic injuries.

So there is a long list of tests that are going to be incorporated into spinal injury trials. Some of them I have talked about, but let me just say something general about the two categories I've got here. There are the tests that test neurological function, which is what I've really been talking about, which are objective tests of which bit of the nervous system is connected to the (indistinct). It describes, if you like, the nervous system anatomy. But there is another set of tests which are also going to be just as important and are more important to the patient, which is really what the patient can do with the neurology they've got. These are functional tests. So the WISCI is a walking test. There is various other walking tests. There is the spinal cord independence measure and the quality of life measure. When we go into clinical trials we're not going to be able to get treatments into patients, approved by the FDA and other organisations, without showing some benefit on these functional ability tests. These are difficult because patients will have different abilities in the functional tests depending on their degree of fitness, their age, how long after the injury, their degree of determination. All sorts of issues will alter the functional tests independently of their neurological state.

There is, though, some reasonable correlation between neurological state and functional tests. This is just one example from John Ditunno, showing the correlation between WISCI, which is a walking test, and the ASIA motor score, which is on the bottom line. You can see that the correlation is not exactly one, but on the other hand it clearly is a correlation between the neurological state and walking ability, as you might expect.

So let me now say something about how many patients to recruit. This is a key issue and a very difficult one. Now, of course, how many patients you need to recruit depends on which phase of the trial you're in. Phase 1 of the trial is basically designed to find out if your treatment is safe or not, and you don't need to recruit a very large number of patients. Phase 2 is preliminary evidence of efficacy, and you need to recruit a large enough group that you could see, in some appropriate test, which could be electro physiology or it could be ASIA motor score, whether your patient has been improved or not. Phase 3 is going to be the most difficult phase of all, because there you have to prove that the patient has got

better, but it has to be in a fairly wide variety of patients, rather than your carefully selected subgroup, and it has to involve a test that involves the patient's ability to cope with their life; in other words, one of the functional measures.

Now, the number of patients you have to recruit depends very much on the spontaneous recovery that your patients are going to show after the time when they've been admitted to the trial. As I've said and as is shown on this chart, spontaneous recovery rates depend on which type of injury and on when you start the trial. So this is, again, a re-plotting of the Sygen data, showing that ASIA A patients, at the time of injury, will recover 12 ASIA points and ASIA B will recover 40, but if you start your trial at six months, then your ASIA A patients will recover about four (indistinct) points (indistinct) than the points, and the ASIA B, roughly similar.

Now we've recently completed some power calculations based on, again, the Sygen data. Bill Coleman did these for us. They're actually slightly scary. These are power calculations based on the assumption that your only outcome measure is the ASIA motor score. Now, of course, we're going to use multiple measures for our trials, but if the ASIA motor score was your only outcome measure, these are the number of patients you would have to recruit into a trial. So ASIA A patients, the assumptions that we've made here are that your treatment will either improve your patient by five ASIA motor points, or by 10 ASIA motor points. Some of us might hope that the treatments will be more effective than this. But let's say that your treatment is going to help by 10 ASIA motor points. That means, if you're recruiting ASIA A patients, your experiment groups would have to lead to around 50 patients, if they're recruited at time of injury. But that number comes down to really quite small numbers if you start after 12 weeks, six months. If you're looking at ASIA B patients, the numbers are scarier because you're going to have to recruit around 200 patients for trials that begin at time of injury, although that, again, comes down to in 10s as you get further away from time of injury. These really are numbers that are not going to be easy or perhaps feasible. The Sygen trial, as I told you, had 760 patients, but this was an absolute killer and I don't think anyone is going to be able to do a trial of this size again. So I think we are going to need to develop, perhaps, composite outcome measures, or measures that are going to reduce the number of patients that have to be recruited from the numbers that are shown on this graph.

So let me just finish off by bringing up a couple of issues that I think are important. First of all, there is the extremely vexed issue of controls and placebos. Now, any clinic, in a trial that is going to be successful, has, at the very minimum, to have a control group with blinded observers. Blinding observers is relatively easy, but what's going to be really hard is producing what you would call a firm trial in which we have also blinded patients. Because if we're going to do treatments that have to be actually inserted physically into the spinal cord involving fusions in the spinal cord, as in the NogoA trial, or transplantations into the spinal cord, a true placebo group would have to include sham surgery. Clinicians vary greatly in their views on this. On the one hand you're subjecting your patients to a treatment that isn't going to do them any good and may even put them at some hazard. On the other hand, there is a huge importance in producing a trial, in doing a trial that produces an outcome that actually people can believe in. If you do a trial which doesn't have a proper control group, then all the danger that you put all the patients in the trial to is wasted. It is important to have a control group and it's important to be robust about having a control group that really works. So placebo surgery is something that I don't think is something that should be dismissed lightly. The control group has to be a good control group and that may have to involve some form of placebo surgery. To give you an example, there were was trial done recently of embryonic

tissue transplants (indistinct) these implants go to the brain. The placebo group, there, went to surgery, had a general anaesthetic, had incisions over the skull, and had burr holes that didn't go right through the skull as their placebo surgery.

It is possible to think of other sorts of controls and number 3 is baseline controls. Now, this is a controversial area. People who design trials don't like them terribly, but if you're thinking of patients like spinal cord injury patients who are completely stable in their condition and who haven't changed for a long time, then you may be able to use patients, to some extent, as their own controls.

Finally there is the issue of recruitment. Now, this is a graph of (indistinct) talking about recruiting to the EMSCI study and showing the difficulty of actually recruiting the number of patients you'd need to conduct a spinal cord injury trial. So here he started off with 477 spinal cord injury patients. These are the various selections that he's done along the way to get the patients that actually go into the trial. First of all, patients who have traumatic injuries. That gets you down to 430, tetras rather than paras, who are down to 197. Then, if you select by ASIA impairment level, you select ASIA As you've got 83, ASIA Cs you've got 41, then you've want patients (indistinct) for 24 hours and you're down to 40 to 20 patients. So recruitment is going to be a big issue. That's really why we have to do multicentre trials, while national networks, such as the sort that you're talking about setting up, are going to be the key to successful trials in spinal cord injury.

So finally let me just say something about treatment of patients. Any patient who is injured today is almost certainly going to have some form of reparative treatment during their life. It's not going to be next week, but it is going to happen during their life. Therefore, you need to think, those of you who are looking after patients, of optimising the chances of patients of having a successful treatment in the future. Now, you're not going to have a successful treatment in the future if the spinal cord below the injury is completely atrophied and non-functional. A lot of the care that patients have received in the past has taken the assumption that the spinal cord below the level of the injury is useless and it's never going to be needed again. I think you need to be thinking in terms of keeping that spinal cord below the level of the injury as vital and as non-atrophied and as ready to accept a treatment as you possibly can. This certainly does require the sorts of things that David was talking about; exercise regimes and general attention to the condition of the disconnected spinal cord.

So I'm going to stop there. Spinal cord injury trials are going to be difficult, but they're far from impossible. We have done some already. We now, I think, have some pretty fair ideas of how to conduct one successfully. The documents I've been talking about are, as I say, available in the first draft form on the ICORD website in Vancouver. They're about to go off to Spinal Cord, the journal, for being roughed up by referees there, but we hope to get them into publication fairly soon. These are the names of the group: John Steeves, Mark Tuszynski and I were the, sort of, bossy people who got this started, and the other people on the list, including Perry as the Australian representative, have taken part in the discussions and the writing of these documents. Thank you very much for your attention.