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Conference Report

Human spinal cord injury: new and emerging approaches to treatment

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The World Health Organization together with the Iceland Ministry of Health and Social Security sponsored a conference entitled '*Human Spinal Cord Injury: New and Emerging Approaches to Treatment*' held on May 31–June 2, 2001 in Reykjavik, Iceland. To help catalyze the development of new paradigms to address spinal cord injury, the conference's overall goal was to bring in a diversity of perspectives, ranging from state-of-the-art stem cell biology to the ancient wisdom of Eastern Medicine. The purpose of this paper is to summarize the presentations of the conference's 26 speakers.
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Introduction

Workshop held at the Ministry of Foreign Affairs, Reykjavik, Iceland, May 31–June 2, 2001, sponsored by the Icelandic Ministry of Health & Social Security and World Health Organization Laurance Johnston, Ph.D.

The 19th century German philosopher Arthur Schopenhauer stated: '*Every man takes the limits of his own vision for the limits of the world*.' The goal of this workshop reflected this statement by attempting to be inclusive as possible consistent with the diversity inherent in the World Health Organization (WHO). Overall, the workshop strove to provide a different, as Schopenhauer stated, 'vision for the limits of the world,' and, in turn, what may be possible for spinal cord injury (SCI). As a result, diverse SCI approaches were included, ranging, for example, from mainstream to alternative medicine, from the status quo to the controversial, from the large academic medical centre to the small independent clinic, and from Western to Eastern medicine.

Several of Iceland's leaders actively supported the conference. For example, former four-term President and UN Goodwill ambassador, Vigdis Finnbogadottir served on the planning committee and opened the meeting with a discussion of SCI as a human rights issue. She emphasized that medical research is one mechanism by which people with SCI can be meaningfully integrated into society and enjoy mankind's most fundamental freedom of self-determination. Finnbogadottir noted that the overall goal of today's exciting SCI research 'should not be viewed as making one whole again because the spirit is always whole. The goal is empowerment, freedom of self-determination, and the ability to manifest the spirit within.'

In another example, Lara Margaret Ragnarsdottir, a member of Iceland's Althingi or parliament participated in the conference's strategic discussions. Her goal is to develop an SCI focus at the Council of Europe.

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Summaries

Precursor cell transplantation

Paul Reier summarized his recently completed clinical trial in which human embryonic spinal cord tissue was transplanted into humans with post-traumatic progressive syringomyelia. The study showed that the procedure is safe, feasible and obliterates the cyst. Reier now believes that fetal tissue research is essentially stem cell research.

Reier has also evaluated whether cellular grafting can augment spontaneous repair processes by investigating the plasticity of respiratory function following cervical injuries in rats. He has found that a unilateral lesion can induce changes in respiratory function at both segmental and suprasegmental levels, including upstream effects in a brainstem respiratory generator. In animals with C_2 hemisection, fetal grafts favorably influenced several of these compensatory changes.

Reier is exploring alternatives to fetal-derived CNS stem or precursor cells, including the potential of

certain cancer cells to transform themselves into neuronal like cells. Specifically, he has shown that grafts of purified and retinoic acid-treated human Ntera2 neurons into chronic C_{4-5} contusion lesions (i.e., six-month delayed grafts) can differentiate into neuronal subtypes and survive for a year post-transplantation without tumor formation.

Second, Evan Snyder discussed how neural stem-cell biology might play a therapeutic role in SCI. His research, primarily using a rat model of a contused cord focused on motor neurons, shows that stem cells can not only differentiate into neurons that integrate into circuitry, but also give rise to the cells necessary to support them. He believes that there is much communication amongst stem cells and between stem cells and the damaged host. For example, stem-cell differentiation is triggered by repair signals issued by the damaged spinal cord host. His overall goal is to try to understand the various molecular signals and then to try to harness and exploit them to enhance more effective recovery after SCI.

Third, Semion Rochkind discussed the use of low-power laser treatment to enhance the regeneration and repair of a reconstructed injured spinal cord. Specifically, the spinal cords of 31 adult rats were transected. Rat embryonic spinal cord cells were cultured, adhering to microcarriers (MCs) and forming cell-MCs aggregates. After these aggregates reached intensive sprouting, they were implanted into the transected spinal cord of 24 rats. The implants served as regenerative and repair sources for reconstructing neuronal tissue. During 14 post-operative days, 780-nm laser treatment was applied transcutaneously 30 min to the implanted spinal cord area of 15 of the 24 rats. The remaining rats underwent spinal cord transection with no implantation or laser treatment. Somatosensory evoked potential, histological, and immunohistochemical analyses were carried out. The results indicated that the most effective re-establishment of limb function and gait performance, transport of electrophysiological signals and histological parameters (indicating growth of the implanted tissue in the injured area) occurred after nerve cell implantation and laser irradiation, compared to nerve cell implantation without laser treatment.

Fourth, Fernando Ramirez discussed his use of xenotransplants to treat 47 patients with SCI over the past decade. The program targets those who have sustained a compression injury in which some neurons remain structurally intact across the injury site. Initially, his surgical team removes bone fragments and scarring tissue from the injury site. Any cysts that have developed are drained, and a shunt is inserted to keep fluid from accumulating. The spinal column is then reconstructed and strengthened. Following this surgery, blue shark embryonic neuronal cell cultures are injected within the dura mater. This procedure is based on xenotransplantation therapies developed by Swiss physician Dr Paul Niehans beginning in the 1930's and, in turn, by German scientist Dr Wolfram Kuhnau. Ramirez stated that the transplanted cells would eventually form an infrastructure matrix that will accommodate neural transmissions, and, in turn, restore some function over time.

Peripheral nerves

Tarcisio Barros has grafted peripheral nerve tissue into the spinal cord gap caused by gunshot wounds in seven male adults with thoracic level injuries. The gap is repaired using a peripheral nerve bridge obtained from the sural nerve plus fibroblast growth factor and fibrin glue. The patients were evaluated according to ASIA/IMSOP standards, and with magnetic resonance imaging and somatosensory evoked potential. After 30 months, the grafts remain viable. Although no change has been observed in motor or sensory recovery, less spasticity was observed in the operated group.

Second, Giorgio Brunelli has rerouted the ulnar nerve to leg muscles. The nerve is cut at the Guyon canal and elevated through a zigzag approach. Motor branches for adductor pollicis and first interosseous, for interossei, and for flexor carpi ulnaris and flexor digitorum profundis of the little and ring finger are respectively sutured to the motor branches for gluteus medius and maximus and for quadriceps (the latter by means of an intercalated sural nerve graft). Temporarily, the patient has to think to move the hand to obtain hip movement. Rudimentary walking is regained with the help of a light walker. EMG shows interference of the muscle is under volitional contraction. Proprioceptive sensation is also regained over time.

Third, Zhang Shaocheng has rerouted the intercostal nerve to spinal cord nerve roots below the injury. Specifically, after microsurgically releasing and decompressing the cord, intercostal nerves were transferred and bridged to the root that controlled the function to be restored (e.g., muscle function, bladder control, or sensation). Over 30 patients followed for an average of 2.5 years regained lower extremity muscular control and could stand up and walk a short distance with crutches and braces. Many had improved bowel and bladder control and proprioception recovery.

Avulsed nerve roots

Thomas Carlstedt has replanted avulsed ventral roots, frequently caused from motor vehicle accidents, into the cord. These implanted roots serve as a conduit for outgrowing motor axons. The procedure restores some useful function about 30% of the time and also reduces the pain associated with this type of injury. The first signs of recovery are often not observed until 9–12 months after surgery.

New supporting circulatory and physiological connections

Harry Goldsmith (Conference Chairman) discussed the transposition to the injured cord of omentum, a highly physiologically active, stem-cell-containing tissue that hangs like an apron over the intestines and lower abdomen area. The omentum is surgically tailored to create a pedicle of sufficient length with intact blood and lymphatic circulation to reach the injury site. The omental pedicle is tunneled underneath the skin, placed over the exposed cord, and sutured to the dural membrane edges. The procedure was used to treat a woman with a nearly totally transected cord. In this case, the scar tissue that filled the 1.6-inch gap in her cord was replaced with an omental-collagen bridge. Prior research with animal models, discussed by another speaker, Jack de la Torre, has shown that this procedure promotes regeneration and adrenoreceptor contact distal to the transection. The patient has gradually gained strength and control of muscles below the injury, including leg movement. Her MRI now shows the continued development of structure connecting the spinal cord segments.

Second, Hernando Rafael reviewed his experience with grafting an unattached piece of omental tissue over the injured cord and connecting it to a surrounding vascular source. Over 13 years, he has treated 232 patients with traumatic SCI with the procedure. About 43 per cent have neurologically improved, including 43 who are walking with or without the use of orthopedic devices.

Third, Georgie Stepanov has used reconstructive microsurgical vascular operations to revascularize the injured cord by displacing the intercostal neurovascular fascicle into the cerebrospinal channel and also by microsurgical omentomyelopexy. The method of suture of the vessels with small diameter allowed them to perform microsurgical anastomosis of the Adamkevich's artery. The procedure has been applied to several patients with encouraging results.

SCI in the developing world

Based on his Red Cross experience treating the Afghan war wounded in Pakistan and the Romanian poor, Anba Soopramanien discussed SCI rehabilitation in the developing world. Most of the world's SCI patients do not have access to the sophisticated, costly, rehabilitative technology that those in developed nations take for granted. For example, Somalia's $11 per capita health-care expenditure (compared to about $1,800 in Iceland and $4,700 in the US) can do little to promote SCI rehabilitation. Given such economics, Soopramanien felt, among other things, that Western-trained SCI professionals should supplement their expertise with the wisdom offered by more affordable and accessible traditional or indigenous medicine. Overall, there is little appreciation of the concept of integrated SCI health care in developing countries. To truly alleviate the world's SCI-related suffering and mortality, we must work with the third world as a partner to develop new SCI-care approaches, strategies, and paradigms suitable to unique cultural conditions.

Alternative and Eastern medicine

Laurance Johnston provided an overview of various alternative, complementary, energy-based, or non-mainstream therapies that have the potential to benefit individuals with SCI. He believes that these therapies can not only help a variety of secondary conditions but have the ability in some people, for certain injuries to restore function. Alternative therapies highlighted included Traditional Chinese Medicine approaches (e.g., acupuncture and qigong), Ayurvedic medicine, surgical interventions, craniosacral therapy, chronologically controlled developmental therapy, homeopathy, and electromagnetic approaches.

Johnston summarized the results of a self-report, pilot study he carried out in 13 paralyzed veterans using a commercially available Ayurvedic multi-herbal product (ReGen^{TM} Maharishi Ayurveda Products). The anecdotal results suggested that the product exerted a variety of subtle effects in many subjects, e.g., reduced spasticity. Others have shown that extract of mimosa pudica, a key herbal component of the product, can promote regeneration in rat peripheral nerve injuries.

Second, Margaret Naeser summarized several Chinese studies that she had reviewed for a 1997 NIH Consensus Conference on acupuncture. Although none had a control group, 94% of the 360 treated patients regained some function, including reduction in muscle spasms, increased sensation, and improved bowel and bladder function. The authors recommended electroacupuncture along the bladder meridian (paravertabral) area and beginning acupuncture as soon as possible after injury. Additional studies published since 1997 supported these findings.

From her own work, Naeser noted that stimulating acupuncture points with low-level lasers (5 – 500 mW, red beam or near infrared, 600 – 1000 nm wavelength) reduces muscle spasticity in the hand and foot and promotes decubitous ulcer healing. Evidence indicates that the effects may be mediated through the increased production of cellular adenosine tri-phosphate (ATP).

Third, Albert Bohbot discussed laserpuncture, a therapy based on Traditional Chinese Medicine and a quantic explanation of the energetic physiology of the acupunctural network. Laserpuncture focuses on a new matrix of 300 acupuncture points located on the abdomen and back. With the treatment, an infrared laser triggers a dialog with the body under the lesion in the form of tingling, hot, cold sensations. The propagated sensation along the meridians is qi expression. The choice of acupuncture points is patient specific. Laserpuncture has promoted motor, sensation, and visceral recovery. Bohbot believes that with laser therapy, the brain is able to convert the electrochemical nervous impulse conduction into an

electromagnetic post-lesion conduction, through the conversion of wavelength of the potential of normal depolarization, allowing it to cross the lesion.

Acute injury

Jack de la Torre discussed the use of fructose 1,6-diphosphate combined with dimethyl sulfoxide to treat acute spinal cord trauma. Extensive research shows the benefit of dimethyl sulfoxide in stabilizing spinal cord trauma and fructose diphosphate as a high-energy substrate to the injured tissue. This cocktail therapy addresses some of the immediate physiological, biochemical, and metabolic problems associated with acute SCI, such as reduced spinal cord blood flow, free radical formation, sodium channel activation, inflammatory reaction and energy substrate depletion.

Second, Anders Holtz reviewed various neurosurgical considerations following acute SCI. For example, before surgery, there is a need to be aware of the secondary injury damage stemming from residual compression; to establish the extent of neurological damage using ASIA/IMSOP criteria; and to radiologically characterize the injury. Initially, it is also important to focus on the respiratory system, to help the cardiovascular system, and to initiate methylprednisolone treatment within the drug's therapeutic window. Overall, the aim of surgery is to minimize neurological deterioration, to restore alignment and stabilization, to facilitate early mobilization, to reduce pain, to minimize hospital stay, and to prevent secondary complications. Holtz summarized some of the factors that are often used to choose surgical over conservative treatment. Specifically, surgery is often preferred if there is concern with secondary injury, the fractures are unstable, there is a contusion to the cord, there is canal compromise, there is ongoing neurological deterioration, the lesion is incomplete, it is a lower injury, and the patient is younger.

Functional electrical stimulation (FES) and orthotic devices

Jack Edwards reviewed his upright mobility programs, which have cumulatively treated 470 people with SCI. With training, most users of reciprocal gait orthoses (RGO) can walk distances of over 300 meters at speeds from 0.2 to 0.5 m/s. Furthermore, after standing rest, they can continue up to distances of 0.6 Km without sitting down. The most common complaint was upper limb pain and discomfort, especially the hands. To reduce these effects, Edwards used a number of advanced orthotic designs, including hybrid RGO–FES systems and microprocessor controlled orthotic knee joints, which allow the RGO knee to bend during the swing phase of walking. The devices reduced the force on the hands by 15% and energy expenditure by up to 30%. Overall, the incidence of urinary tract and lower respiratory tract infections, spasms, and pain were less in individuals that were part of their upright mobility program compared to general wheelchair users.

Second, Maurizio Ferrarin discussed how biomechanics allows the optimal design of mechanical orthoses for restored walking in paraplegics and provides information for the development of musculoskeletal system models useful for the design and test of strategies for the control of FES systems. Multi-factorial movement analysis techniques allows the quantification of the functional advantages of a single treatment, the comparison of different solutions, and the adaptation of a device to the characteristics of a specific individual. The following examples were presented: the development of a new hip joint for the RGO that provides a more physiologic pelvic rotation; the analysis of the improvements provided to patient hemodynamics by the combination of FES to the RGO; and the development of a control strategy for FES-induced standing up, based on the EMG signal of supralesional muscles.

Third, Anatoly Vitenson has used FES muscle stimulation to artificially correct movements in 900 patients with SCI. In his study, which focused on lumbar-sacral injuries, the hip and knee joints muscle extensors were stimulated in 20 sessions. The program resulted in improved anthropomorphous walking properties; enhanced walking velocity, cadence, and step length; decreased fatigue; growth in muscle force and electrical activity during maximal effort; and partial normalization of innervative gait structure. Also, the therapy has restored some pelvic organ function. Vitenson believes that excellent, good, and satisfactory results have been obtained in 6, 83, and 11% of his patients, respectively.

Fourth, Michael Keith summarized the results of implanting the Freehand^{TM} neuroprosthesis to recreate gripping hand motion in quadriplegics. To date, over 200 neuroprostheses have been implanted using 50 surgical and 55 rehabilitation centers. Typically, the implanted muscles are those that represent key movements, such as the thumb abductors, flexors, extensors, and finger flexors and extensors. The chosen muscles are strong and have good innervation. The muscles after having been instrumented by the implantable device are then programmed by an external computer. The patient carries a portable device, which has information regarding the quality of muscles and the patterns of motion that the patient is to have. Up to eight muscles can be controlled by a variety of control sources. Patient independence was improved by average of 85% over their pre-operative state. Adverse effect incidence has been low.

Fifth, Nick Donaldson discussed possible locations for and issues surrounding the placement of implanted stimulators. Overall, he believes that implanted stimulators are more convenient to use, give more repeatable responses, and more muscles may be stimulated. However, there is no consensus about where the electrodes should be sited. Possible sites include nerve twigs, nerve branches, nerve trunks,

nerve roots, or the spinal cord. The most promising methods seem to be stimulation of the nerve roots in the cauda equina and spinal cord microstimulation.

Finally, Antony Tromans summarized a variety of potential FES applications beyond limb movement, including respiration; bladder, bowel, and sexual function; and skin problems.

Aggressive physical rehabilitation

As the likelihood of real-world SCI therapies increases over time, Arnie Fonesca emphasized that it will be important to have follow-up aggressive physical rehabilitation to maximize function in long dormant muscles. Professional athletes rehabilitate more efficiently because they have access to the best care and equipment and are surrounded by highly motivated people to complement their own skill and motivation. Fonesca believes that if we similarly treated SCI, functional recovery would be much greater. At minimum, the individual would be in better physical shape, better able to endure SCI secondary conditions, and have a self-confidence boost. As an example, Fonesca discussed how aggressive physical rehabilitation enhanced function following omental transposition therapy.

Speakers

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David Gunnarson, Secretary General, Ministry of Health

Vigdis Finnbogadottir, ex-President & UN Goodwill Ambassador

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