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Transplants of Fetal Neural Tissue and Autologous Peripheral Nerves in an Attempt to Repair Spinal Cord Injuries in the Adult Rat

An overall view

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Summary

Embryonic neurons and autologous peripheral nerve segments constitute selected materials for studying central nervous system plasticity and repair in adult mammals. Transplanted to the brain or the spinal cord, the former are possible substitutes designed to replace lost or deficient host neurons while the latter have useful stimulating and guiding effects upon axonal regrowth from surviving axotomized neurons.

Consequently, these techniques give rise to interesting prospects for short and medium range fundamental research as well as for possible medium and long-term clinical applications.

From a basic viewpoint, utilisation of such transplants is designed to study the survival, the morphological and biochemical differentiation, the reafferentation, the expression of potentialities for plasticity, axonal growth or regeneration, synaptogenesis, of host as well as of transplanted embryonic neurons.

From a clinical viewpoint these studies should attempt at finding solutions to counteract the effects of severe traumatic or neurodegenerative lesions of the brain and of the spinal cord which until now appear quite refractory to therapeutic approaches.
Key words: *Spinal cord injury; Transplantation; Fetal neural tissue; Peripheral nerve autografts; Adult rat; Experimental research.*

A severe local injury to the spinal cord causes, among other effects, a chronic paralysis of the skeletal muscles that are controlled by motoneurons located caudally to the lesion site, as these neurons remain permanently disconnected from the brain. Generally speaking, spontaneous anatomical and functional restoration fol-

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lowing traumatic or neuro-degenerative lesions of the adult mammalian central nervous system (CNS) is not usually observed.

The primary effects of such lesions have to be considered at two different levels of a nerve cell: its soma or its main axon. Direct damage to the cell body leads to immediate cell death. On the other hand, rupture of the axon is not necessarily fatal to the neuron. However, should the neuron survive to axotomy, the part of the axon that is therefore separated from the trophic centre of the cell, namely the neuronal cell body, is bound to degenerate all the way to its target cells (other neurons or muscle cells). Consequently, these are disconnected either from a part of the neuronal circuitry or from the whole CNS and may account for the deficit of function.

In adult mammals, spontaneous recovery from such CNS lesions does not occur because lost neurons are not replaced and because surviving axotomized nerve cells do not usually regenerate the missing part of their cut axon. This can be probably explained, at least partly, in terms of the inhibitory effects from the mature glial cells: reactive astrocytes (35) or distinctive components of the myelin sheath elaborated by differentiated oligodendrocytes.[7,8,38,39] Conversely, lengthy axonal regrowth is known to take place in the mammalian peripheral nervous system (PNS) as well as in the CNS of lower vertebrates.

Yet, recent and extensive experimentation, mainly conducted in rodents, has brought forth new strategies for studying how CNS regeneration can be induced and how neuronal circuitries, either damaged by a mechanical or a chemical lesion, or deficient (congenital or age-related deficiency), can be repaired.

A common approach to these problems is the use of intracerebral and intraspinal grafting techniques: (1) transplantation of fetal neural tissue to replace the lost or the deficient neurons and/or to guide axonal regrowth along short distances[4,12]; and (2) transplantation of autologous peripheral nerve segments as conduits for lengthy axonal growth and elongation.[1]

Transplantation of embryonic neurons

Removed from the embryo at an appropriate stage, transplanted fetal neurons do survive into the adult host CNS, especially when they are placed in close contact with their natural targets. Two main transplantation techniques have been devised using either solid pieces of neural tissue[10,44] or suspensions of dissociated nerve cells.[5]

The grafted neurons can, to some extent, functionally replace or compensate lost, deficient or even absent nerve cells by correcting the effects of a lesion,[3] of senescence[14] or of a congenital deficit.[40] Generally, they establish synaptic contacts with at least some target neurons of the host, but seem to be able to extend their action to a much greater number of host nerve cells to which they are not anatomically connected, through diffusion of their neurotransmitter at a distance.[29] Point to point reconstruction of a complex neuronal circuitry is a priori more difficult to carry out as it implies a great specificity of the afferent and the efferent synaptic contacts, this could, however, be achieved by transplanting fetal Purkinje cells into the cerebellum of 'Purkinje cell degeneration' (PCD) mutant mice.[42] In addition, the morphological study could be completed by documenting, electrophysiologically, the functional integrity of the transplanted neurons.[15,16,43]

Transplantation of autologous peripheral nerve segments

Short segments of peripheral nerves or small pieces of peripheral tissues, removed from either adult or new-born mice and transplanted whole into the spinal cord of young inbred animals, were rapidly reinnervated by host spinal nerve fibres. Axonal regrowth into the transplants was clearly related to the presence of living Schwann cells. Optic nerve segments were not reinnervated.[17–19]

More recent and extensive experimentation by Albert Aguayo and collaborators, in Montreal,[1] has definitely demonstrated that different types of neurons of the adult rat CNS have the capacity to regrow injured axons into autologous peripheral nerve (PN) segments one extremity of which had been preferably inserted in the vicinity of their cell bodies, the other being made blind-ended with a tight ligature and attached to peripheral tissues.

This study was made possible by the widespread use of retrograde axonal tracing methods which allow precise location of the neuronal somata from which the new axons originate. These axons do regenerate all the way through the transplanted nerves (several centimeters). It must be recalled that the intrinsic regenerative capacity, if any, of these CNS neurons, is not spontaneously expressed in their normal 'central' environment.[33] On the other hand, the elegant experiments of the Canadian group clearly show that this capability for axogenesis can be expressed again in the new environment afforded by the non neuronal components of the denervated PN grafts, namely Schwann cells, basal laminae and extracellular matrix. In addition, a primary effect of these transplants is to increase the number of neurons that survive axotomy.[46]

Under these more favourable conditions, the probability for a cut axon to regenerate into the PN graft is, however, a function of the distance that separates the neuronal soma from the site of injury and grafting.[2,11,20,36,37,41] In addition, this regrowth is more likely to orginate from axotomized neurons, by a process of terminal regeneration, rather than from intact nerve cells, by a process of collateral sprouting.[13,20] Moreover, this axonal regeneration into PN grafts can be directed towards CNS[45] or PNS[22–24] targets and thus lead to the establishment of new functional synaptic contacts, as will be further developed.

Attempts at repairing the damaged spinal cord with the help of transplantation techniques

Several types of transplants are commonly used in animal experimentation aimed at spinal cord repair or reconstruction. They differ mainly by their nature and origin: fetal extraspinal (heterotopic) or spinal (homotopic) CNS tissue, autologous peripheral nerve; but also by their mode of action: protective and/or trophic effect on the host neural tissue, inhibitory influence on glial reaction, guiding effect on axonal regrowth, role of substitution.

Different kinds of transplants appear to have a protective effect against the secondary degeneration of spinal nerve fibres that were not damaged by the initial traumatism.[9,27,28] All transplants have a trophic influence whose clearest expression is an increase in the number or neurons surviving intraspinal axotomy,[6] whatever the location of their cell bodies, inside or outside the spinal cord. Yet, the number of these rescued neurons is higher and the effect is more lasting with homotopic (spinal cord) transplants.

All transplants do have the capability to alleviate the astrocytic reaction at the interface host/graft but looser scarring is obtained with homotopic and homotypic (spinal cord) tissues.[26,34]

All transplants can stimulate and guide axonal regrowth from host nerve fibres but this action is far more important and conspicuous with PN grafts.[1]

Whatever it may be, it is clear that fetal neural transplants are mainly used as substitution material, aimed at replacing inefficient, deficient or lost neurons in traumatic or neurodegenerative lesions of the spinal cord.

For instance, serotonergic neurons of the raphe (brain stem), which project to the spinal cord, participate in the control of some of the sexual functions. When they are axotomized through a complete transection of the cord, they permanently lose their anatomical and functional connections with the target neurons located below the lesion site. Yet, it has been possible, in paraplegic rats, to re-establish, at least in part, the reflex of ejaculation by transplanting embryonic raphe neurons into the caudal part of the host spinal cord, below the transection lesion.[32] The grafted serotonergic nerve cells do re-establish specific and accurate synaptic contacts with their natural targets in the host that may account for the return of lost functions.

Intrinsic spinal neurons, whose somata lie in the grey matter of the spinal cord, can also be replaced by substitution homotopic (or heterotopic?) transplants in an attempt to counteract the effects of traumatic or neuro-degenerative injuries. This aspect of spinal cord repair is being developed in our laboratory and will be now considered along with our other experimental studies in the field.

As for any CNS neuron of the adult mammal, a given motoneuron of the spinal grey matter can be either totally or partially (axotomized in the spinal cord) destroyed through an experimental traumatic lesion. Considering that there is no spontaneous repair following such trauma, the brain will have lost, in both cases, at leat one of its connections with a peripheral muscular effector. An identical situation is created when the damage is inflicated on the afferent projections of an uninjured motoneuron.

With this in mind, our research group in Paris V University is studying, in the adult rat, the possibilities of an anatomical and functional reconstruction of the severed spinal cord and peripheral motor connections by means of the above-mentioned transplantation techniques.

Several experimental models are being studied which correspond to different types of spinal severance (focal and mild lesion, without substantial neuronal loss; mechanical or chemical depletive lesions, involving important neuronal loss) and, consequently, to different ways of repairing the injured spinal cord (without or with fetal neural tissue). On the other hand, an operation which is common to our different experimental models consists in bridging the severed spinal cord and a nearby denervated skeletal muscle with the help of a PNG.

In a first model, studied in collaboration with Monique Pécot-Dechavassine and Jean-Claude Mira,[22–24] one end of an autologous PNG (a 30 mm segment of the common peroneal nerve), was introduced into the cervical spinal cord, thus producing a small and localised lesion which did not cause any apparent functional deficit. The other end of the PNG was inserted into an aneural area of a nearby skeletal muscle of the dorsal musculature (m. longissimus atlantis (LA), that was carefully denervated prior to grafting (Fig. 1). From 2 to 21 months after surgery, we

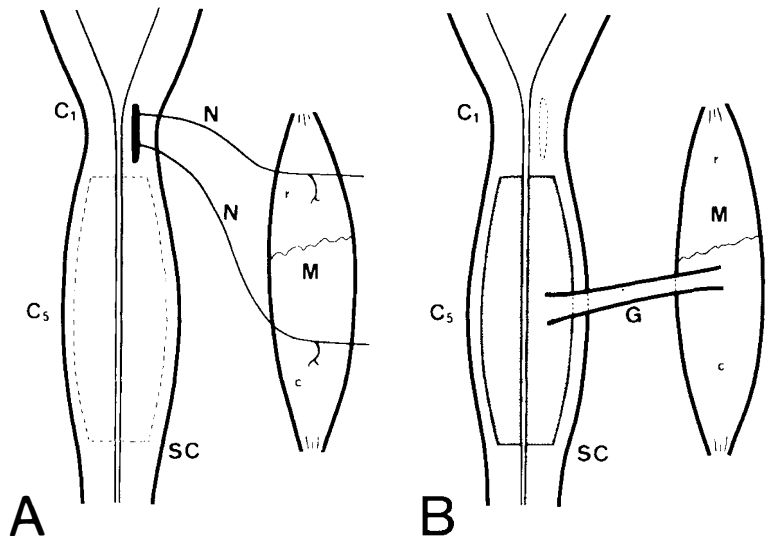

Figure 1 Schematic representation of the cervical spinal cord (SC) before (**A**) and after denervation and peripheral nerve grafting. **A:** Intrinsic innervation (N) to the rostral (r) and caudal (c) parts of the LA muscle (**M**). **B:** A PNG (G) joins the SC to the caudal part of the LA muscle. Retrograde labelling from the transected intrinsic nerves (in **A**) or from the PNG (in **B**) led to neuronal labelling within the black or grey areas, respectively. C1, C2: cervical segments of the spinal cord (Horvat, Pécot-Dechavassine & Mira, 1989).

noticed that the reconnected muscle contracted under an adequate electric stimulation of the nerve bridge (Fig. 2). From then on, it was imperative to search for the precise origin and destination of the nerve fibres, necessarily regenerated, that were responsible of the observed muscular contraction.

Answers to these questions could be provided by different morphological techniques and by electrophysiology.

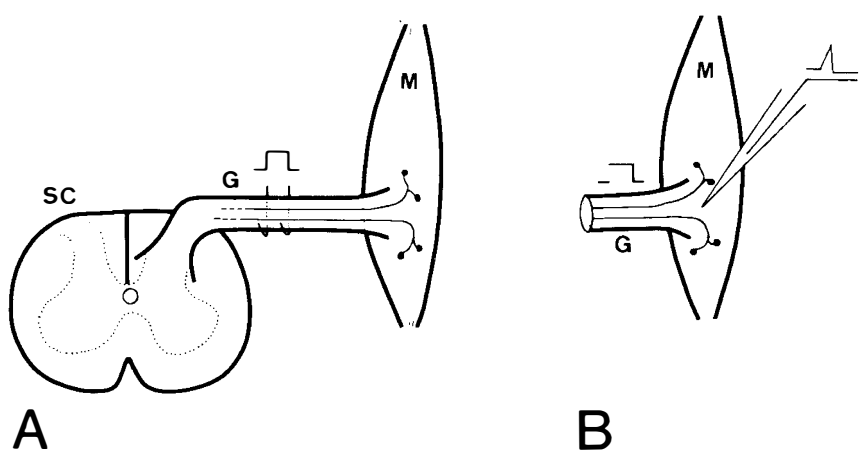

Figure 2 **A:** Schematic illustration of a PNG (G) connecting the spinal cord (SC) to the LA muscle (**M**). From 2 to 21 months postgrafting, electrical stimulation of any point of the PNG bridge could produce partial or full contraction of the muscle. **B:** Schematic representation of in vitro electrophysiological recordings from the nerve-muscle preparation, removed straight from the animal (Horvat, Pécot-Dechavassine & Mira, 1989).

Application of different axonal tracers (horse radish peroxidase (HRP) fluorescent dyes) to the nerve bridge led to an extensive neuronal labelling in the whole spinal grey matter, between C3 and C7. Yet, when the tracers were injected directly into the muscle, the neuronal labelling was mainly restricted, in the same segments, to typical motoneurons of the ventral horn, different from those that normally innervate the LA muscle (as they are located unilaterally in C1 and C2) (Fig. 3).

In the reconnected muscle, morphological studies revealed that motor end-plates had been reformed not only at the sites of original innervation but also and mainly in ectopic locations all around the grafted nerve (Fig. 4). These neuromuscular junctions were quite functional and necessarily formed by regenerated axons in the PNG, as electrical stimulation of this graft triggered the contraction of the muscle

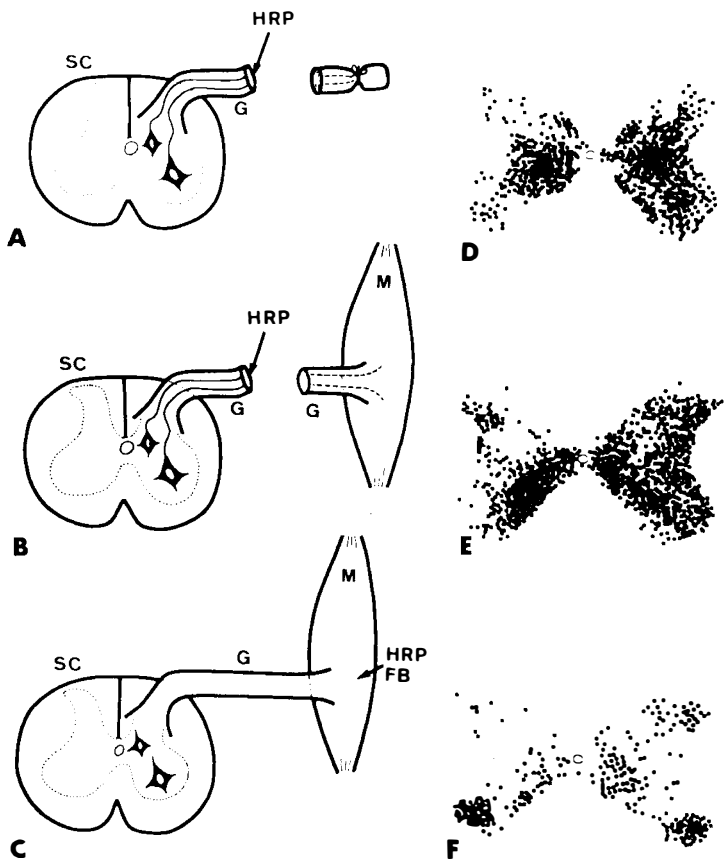

Figure 3 Diagrammatic representation of retrograde labelling studies in three experimental groups **A (D), B(E)** and **C (F)**. The site of tracer application is indicated by an arrow. Each labelled neuron is represented by a black dot the approximate position of which is defined with respect to the central canal. In each group, all labelled cells encountered in serial cross sections of the spinal cord of all animals are collected on the same diagram (**D, E** or **F**). Each dot corresponds to a neuron that has grown an axon into the PNG, at least to the site of tracer application. When the tracer was directly injected into the LA muscle, the higher density in neuronal labelling was seen in the ventral horn of the grey matter. HRP: horse radish peroxidase; FB: fast blue; G: peripheral nerve graft; SC: spinal cord; M: LA muscle (Horvat, Pécot-Dechavassine & Mira, 1989).

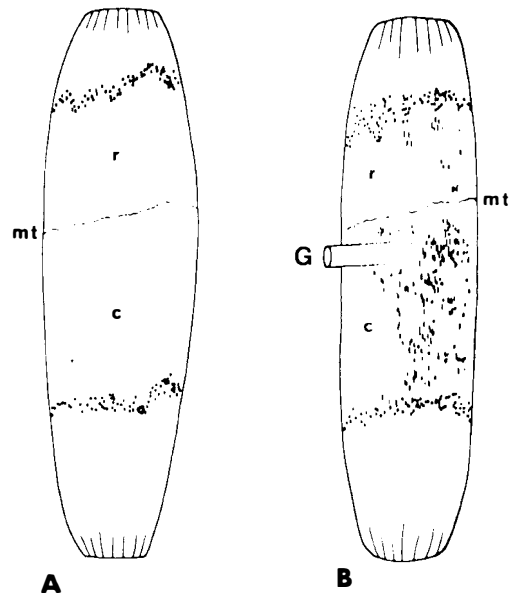

Figure 4 Semi-schematic representation of the distribution of the endplates in the LA muscle, visualized by cholinesterase activity. a: control muscle; b: grafted muscle: the reformed endplates are located not only at the sites of original innervation but also in ectopic locations, around the tip of the PNG (Horvat, Pécot-Dechavassine & Mira, 1989).

to which it was attached. In addition, the reformed endplates were cholinergic insofar as the endplate potentials, evoked by the stimulation of the PNG, could be suppressed by the action of curare, added to in vitro preparations.

Thus was reformed a functional motor system of substitution that, however, appears anatomically to be far from the original model as its motoneuronal pool, the course of its motor axons and the sites of terminal innervation are different. In this sense, this experimental model constitutes an additional example of the remarkable plasticity of the adult mammalian central and peripheral nervous systems.

The studies concerning our second experimental model have been developed more recently, in collaboration with Claude Baillet-Derbin, Jian Hui Ye, Fatiha Rhrich and Fatima Affane.[21,25,47] Their main objective is an attempt at repairing larger spinal lesions, implicating important neuronal loss.

The last stage of this experimentation will consist in joining, by means of a PNG, a fetal neural transplant of substitution, designed to fill a cavity made by unilateral aspiration of the host grey matter and dorsal funiculi in C5, and the LA muscle used in our first set of experiments.

The studies carried out so far concern a preliminary stage where the distal end of the PNG, unconnected to the muscle, is made blind by crushing and stitching it to extraspinal tissues (Fig. 5). Should the aspiration procedure be gentle enough, the resulting motor deficit is apparently restricted to paralysis of the right upper limb. The cavity is filled with solid pieces of neural tissue (cortex, spinal cord or dorsal root ganglia), removed from E13 to E18 inbred embryos.

From 1 to 6 months following the double transplantation, the animals had a car-

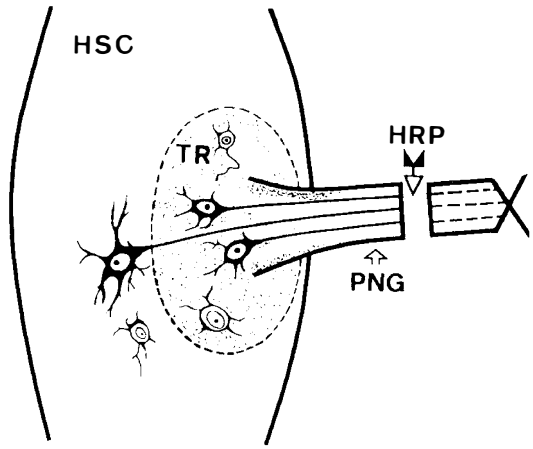

Figure 5 Schematic illustration of the experimental set up and results obtained in double-grafted animals. Some neurons (black), located in the transplant (TR) or in the host spinal cord (HSC), have grown axons into a co-grafted PNG segment, which has one end inserted into the fetal graft tissue (Horvat, Baillet-Derbin, Ye, Rhrich & Affane, 1991).

diac perfusion with different fixative solutions. Then, adequate sections of the injured host spinal cord, incuding the grafts, were processed according to various histochemical and immunocytochemical techniques as well as to HRP histochemistry following retrograde axonal transport from the PNG.

Healthy appearance of the three types of transplants and integration with the host tissues were consistently observed. Surviving neurons in the grafted tissues developed processes, some of which became myelinated. Yet, the ability of the grafted neurons to extend axons into the PNG differed strikingly from one type of graft to another, being apparently non-existent for cortical grafts, moderate for spinal cord grafts and quite extensive for dorsal root ganglia transplants. Interestingly, these differences reflected what was observed for the corresponding, fully differentiated neurons in adult animals when their cut axons were also put in contact with non-neuronal components of peripheral nerves. In addition, some host spinal neurons, mainly located around the transplants, appeared HRP-labelled, indicating that they had also grown axons into the PNG (Fig. 5).

Other models are being developed in exterior collaborations. For instance, kaïnic acid-induced cavitation lesions of the lumbar spinal cord have been filled with dissociated fetal spinal cord tissue.[30,31] A great number of grafted neurons did survive and some of them were shown to grow axons into blind-ended PNG.

Studies of the possibilities are in progress for all of these neurons of substitution to form whatever connections with denervated skeletal muscles, as well as that of their eventual reafferentation by regenerating central nerve fibres of the host.

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