4. P. Wolf, *Br. J. Criminol.* **13**, 5 (1962).
5. Recall the preponderance of one-time offenders in the adoptive parents. It was a condition of adoption that the adoptive parents not have a conviction for the 5 years preceding the adoption.
6. Only cases in which neither adoptive parent is convicted were included. In view of the low frequencies of court convictions and recidivism among the adoptive parents and in order to simplify interpretation, analyses include only cases in which adoptive parents have no criminal law convictions.
7. M. E. Wolfgang, R. J. Figlio, T. Sellin, *Delinquency in a Birth Cohort* (Univ. of Chicago Press, Chicago, 1972), p. 88.
8. It should be noted that this is a significantly higher rate of convictions (45.9 percent) than the conviction rate (28.6 percent) for the total population of biological fathers ($\chi^2(1) = 14.6$, $P < 0.01$).
9. For a full report on how these siblings were identified, see T. Teasdale and D. Owen, *Behav. Genet.* **11**, 577 (1981).
10. K. Van Dusen *et al.*, *J. Crim. Law Criminol.* **74**, 249 (1983).
11. Among males, there was a statistically significant association between adoptee criminality and amount of time spent in the orphanage waiting for adoption. This effect, which was not true for females, may be due to institutionalization. Or it may be a function of selection bias ("less desirable" boys adopted later and also being convicted).
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13. Supported by PHS grant 31353 from the Center for Studies of Crime and Delinquency and by a fellowship from the Netherlands Pure Science Foundation to S.A.M.

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Directional Specificity in the Regeneration of Lamprey Spinal Axons

Abstract. *After spinal transection in ammocoetes (lamprey larvae) 4 to 5 years old, functional recovery is accompanied by a limited regeneration in which axons grow as far as 5 millimeters beyond the scar. In axotomized giant interneurons labeled intracellularly with horseradish peroxidase 16 to 120 days after transection, 74 percent of regenerating neurites grew in their normal projection pattern, rostal and contralateral to the cell body. One third of the neurites originated anomalously from posterior dendrites. Despite their initial abnormal orientation, 80 percent of these neurites looped contralaterally and rostrally to assume the normal projection path. The directional specificity persisted when giant interneurons were located in islands formed by double simultaneous cord transection. This limited regeneration seems to be characterized by directional selectivity that cannot be attributed to nonspecific influences, such as a tendency of neurites to grow in an already established direction or a trophic effect of the zone of injury.*

Mammalian central nervous system axons can be induced to grow into peripheral nerve bridges and to regenerate 1 or 2 mm into the nervous system at the distal end (*1*). Such limited axonal regeneration may be useful as an approach to the treatment of spinal cord injury. In contrast to the target-specific regeneration seen in the retinotectal system of lower vertebrates (*2*), however, little is known about the rules governing this growth. In particular it is not known whether such growth is directionally specific.

The transected spinal cords of several lower vertebrates show such a limited form of axonal regeneration accompanied by behavioral recovery (*3, 4*). We have studied the spinal cord of ammocoetes (sea lamprey larvae) 4 to 5 years old because identified cells and axons with known projection patterns can be injected with tracers and their regenerating neurites studied in whole-mounted preparations (*5, 6*).

During the first 2 weeks after spinal transection in lamprey larvae, cut axons die back as far as 2 mm (*6, 7*) or more and then sprout, elongate, or both. Fibers grow no further than a few millimeters beyond the scar, and most fibers do not reach their original targets (*4, 6*). Abnormal directions of neurite growth have also been described in these studies. Thus, it is not yet known whether this limited regeneration is characterized by a specificity in the direction of neurite growth or, alternatively, whether fibers crossing the scar represent only a subpopulation of randomly sprouting neurites. We have now determined the position and orientation of the distal ends of 46 regenerating neurites in 27 axotomized giant interneurons regardless of whether they crossed the scar.

In the first experiments, larval sea lampreys 9 to 11 cm long had single spinal transections at the level of the cloaca (Fig. 1A) and recovered from 16 to 99 days. After this time giant interneurons located within 3.5 mm caudal to the transection scar were injected with horseradish peroxidase (HRP) (Fig. 1C), and whole-mounts of the spinal cords were prepared. Experimental methods and solutions have been described (*4, 6*).

The projection patterns for regenerating neurites is summarized in Table 1. Overall, 74 percent of the neurites projected rostralward in their normal position in the contralateral axon tracts (Fig. 2A). These findings might simply indicate that axons tend to grow in an already established direction. This simple explanation does not, however, account for our observations on 4 of 14 injected cells in animals with single transections and an additional four of nine cells in animals with double transections in which the axons died back completely and had not regenerated. In intact animals the axons of giant interneurons invariably originate anteromedially. Thus, the absence of an axon originating from the anterior side of some cells in animals with spinal transections indicated total retrograde degeneration. In these cells, one or more neurites grew out of posterior dendrites and were therefore initially oriented posteriorly. In spite of this initial incorrect orientation, eight of ten such neurites looped anteriorly and crossed the midline so that their growth was now oriented in the normal direction (Fig. 2B). Thus these

Table 1. Projection patterns of 46 neurites in 27 axotomized giant interneurons. The neurite projection is determined by the orientation of the distal end of the fiber. The normal projection of axons of giant interneurons is crossed and rostral. For neurons below a single transection and for those located in islands of spinal cord formed by double transections, the majority of neurites were oriented normally, even for neurites with posterior origins.

Neurite origin	Neurite projection	Transection		Total
		Single	Double	
Anterior (normal	Rostral (normal)			
	Crossed (normal)	20	6	26
	Uncrossed (abnormal)	0	1	1
	Caudal (abnormal)			
	Crossed	9	0	9
	Uncrossed	0	0	0
Posterior or medial (anomalous)	Rostral			
	Crossed	5	3	8
	Uncrossed	0	1	1
	Caudal			
	Crossed	1	0	1
	Uncrossed	0	0	0

regenerating neurites did not grow randomly but selectively favored their normal projection path. A similar tendency to assume a normal projection path after initial misorientation has been noted in the developing Mauthner axon of amphibian larvae after grafting and reversal procedures on the presumptive hindbrain region of the neural tube or plate (*8*).

Most regenerating neurites terminate within 3 mm of the scar even if they successfully grow past it (*4, 6*). Therefore, it seemed possible that neurite growth was not selective for the direction of the original targets but that the glial-ependymal scar exerted a trophic influence that attracted growing axon tips toward it. The tips of fibers that had successfully regenerated beyond the scar would then experience a negative gradient for the effect and stop growing. To rule out this possibility, we performed double simultaneous transections approximately 4 to 9 mm apart and studied giant interneurons located within the resulting islands 60 to 120 days after transection (Fig. 1). If the injury zone attracts regenerating axon tips, the direction of growth of neurites within the islands should be random. However, all the neurites of nine giant interneurons successfully injected within these islands projected rostrally (Table 1), even though the perikarya of six of these cells were located closer to the more caudal cut. The cell shown in Fig. 2C was located 6.5 mm below the rostral transection and only 1.5 mm above the caudal transection and had an axon-like neurite that grew anomalously from the caudal side of the cell. Despite its initial caudal projection, this neurite crossed the midline and turned rostralward to ascend the spinal cord in the normal position for axons of giant interneurons.

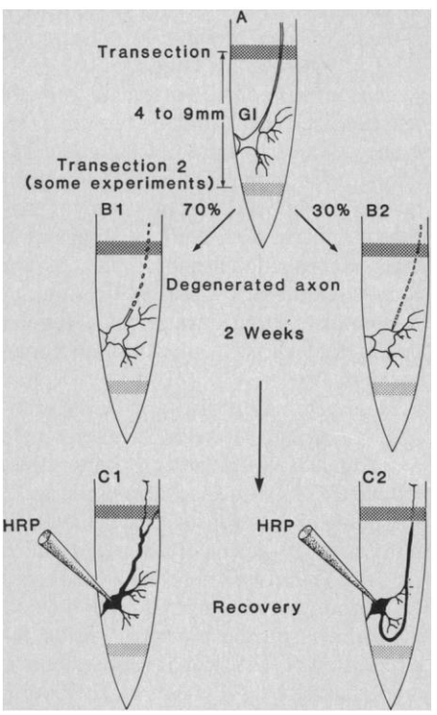

Fig. 1. (A) Spinal transection produces close axotomy of giant interneurons (*GI*). (B) During the first 2 weeks after transection Wallerian degeneration takes place above the cut and partial dieback below. In 30 percent of cases retrograde degeneration was complete (*B2*). (C) After recovery, injection of HRP into giant interneurons showed most regenerating neurites oriented in their normal projection path, whether they arose from the original axon (*C1*) or from posterior dendrites (*C2*). The directional selectivity of regeneration was still seen if a second simultaneous cut was made below the giant interneuron.

Observations on a second cell type, the primary sensory dorsal cells, showed similar specificity. In 17 of 18 cells located between double transections, the orientation of the regenerating axon followed the normal projection pattern rostral and ipsilateral to the cell body. Thus the directional specificity of regeneration was not determined by the location of the scar.

Electron microscopic observations on developing and regenerating fibers in spinal cords of newt and trout (*9*) have suggested that growing axons are guided through preformed channels bounded by proliferated glial cells. Such channels could be formed by degenerating axons after spinal cord transection and could help guide regenerating fibers. In the lamprey spinal cord, the majority of potential spaces would be formed by Wallerian degeneration of long unbranched axons of relatively uniform caliber, such as the giant Müller and Mauthner axons. The volume of spaces opened by the degeneration caudal to any individual cell should be approximately the same as that rostral to the cell at least within the 5-mm range of regeneration of lamprey spinal axons. Although such factors as preformed channels, or the chemical effects of the degenerating debris, may play a role in facilitating and guiding the elongation of regenerating fibers, it seems unlikely that they would cause the regenerating neurites to prefer an anterior rather than a posterior path or to change paths if they have started to grow posteriorly. It is possible, however, that the regenerating axon shows an affinity only for the debris or immediate environment of its own degenerated distal stump.

The directional specificity in axonal regeneration might result from a selective retraction of incorrectly oriented fibers after an initially random neurite outgrowth. A profusion of axon-like neurite outgrowths originating in portions of the neuron distinct from the original axon hillock have been described in the large reticulospinal neurons of lampreys when axotomy was performed within several hundred micrometers of the cell body (*10*). These neurites were similar to the looping neurites with anomalous origin we have found, but they were more numerous and did not grow selectively in their normal caudal path. They developed only at late stages after transection. Early after transection giant interneurons simplify their dendritic tree rather than develop profuse long neurites (*11*). However, we have noted multiple randomly oriented sprouts at the ends of a few axons 2 to 3 weeks after transection. If these short sprouts are not counted, the proportion of correctly regenerating

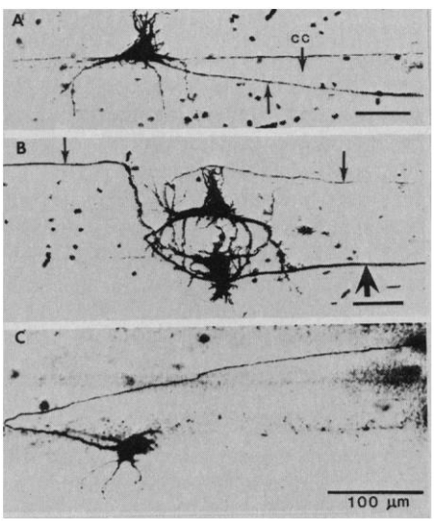

Fig. 2. Projection patterns of axotomized giant interneurons. (A) Normal axon origin from the anterior end of the cell body. The axon (arrow) projects rostrally and contralaterally. Abbreviation: *CC*, central canal. (B) Two giant interneurons located approximately 1.2 mm caudal to a transection performed 20 days earlier. Their original axons have undergone complete retrograde degeneration. Two neurites (small arrows) grow from a caudal dendrite of the cell on the bottom. One neurite (large arrow) extends from a caudal dendrite of the top cell. Two of the three long neurites that initially project caudally reverse direction and grow rostrally and contralaterally in their normal projection path. (C) A giant interneuron in an island formed by double transection 60 days earlier. This cell was located 6.5 mm below the rostral cut and 1.5 mm above the caudal cut. Despite the proximity to the more caudal scar, a long neurite that initially grew posteriorly loops to project rostrally on the contralateral side. A second neurite (not in plane of focus) originating medially also projects rostrally. Scale, 100 µm.

neurites is not 74 percent, but 89 percent, of 35 neurites. Thus directional specificity of regenerating axons of giant interneurons may result partly from secondary retraction of an initially random short neurite outgrowth with continued growth of correctly oriented sprouts.

An attractive hypothesis that remains consistent with our observations is that directional selectivity of growth is imposed by an attraction between the regenerating axons and their original target neurons. A chemoaffinity between optic nerve and optic tectum has long been suggested to explain specificity in regeneration of fish and amphibian optic nerve (*2*). Thus far there is no direct evidence for such a mechanism. In the case of the giant interneurons and dorsal cells of lamprey, such a mechanism need not act over long distances, since the axons of these neurons normally make incidental synaptic contacts with other neurons along their length.

Our previous studies on the giant reticulospinal axons suggested that their regenerating neurites tended to grow in the direction of their normal projection (*4, 6*). The present findings suggest that the tendency for regenerating neurites of giant interneurons and dorsal cells to grow rostralward reflects a specific preference for their normal pattern of projection that cannot be accounted for by nonspecific effects, such as a tendency for neurites to continue to grow in an established direction or a trophic action of the scar. We conclude that, since the spinal axons of large larval lampreys maintain directional specificity in their growth, the limited distance of axonal regeneration seen in the transected spinal cord is probably not due to a maturational loss of target-seeking ability in these axons.

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Prenatal Alcohol Exposure Alters Adult Expression of Sexually Dimorphic Behavior in the Rat

Abstract. *Saccharin preference and performance in a Lashley III maze were found to be altered in adult male and female rats that had been exposed to alcohol during gestation. Specifically, the sexual dimorphism normally observed in both behaviors was absent in fetal alcohol-exposed animals. The lack of sexual dimorphism appeared to result from a masculinization of the exposed females and a feminization of the exposed males.*

Perinatal androgen status is critical to the neurobehavioral differentiation of the male brain (*1*). Interference with the metabolism or utilization of androgens during this period produces both demasculinization and feminization of reproductive behavior patterns (*2*). In addition, an influence of perinatal androgen status on nonreproductive behavior has been established (*3*). Central nervous system organizational influences of androgens appear to be principally responsible for the expression of several nonreproductive behavioral sex differences in the adult rat, including maze learning performance, active avoidance acquisition, and saccharin preference (*4, 5*).

Alcohol is known to suppress testicular hormone production (*6*). Although exposure of fetal rats to alcohol has been reported to have no influence on their subsequent reproductive behavior (*7*), the possibility that it might influence the expression of nonreproductive, sexually dimorphic behaviors has not been examined. We now report that the normal sex differences observed in saccharin preference and maze learning are absent in fetal alcohol-exposed (FAE) animals.

Table 1. Results of adult behavioral tests of animals exposed to alcohol during the third week of gestation.

	Pair-fed		Alcohol-exposed	
	Male	Female	Male	Female
	*Saccharin preference**			
$\bar{x}$	11.63	25.43	16.38	20.49
S.E.M.	1.65	3.36	2.04	2.52
N	12	11	12	12
	Maze learning†			
$\bar{x}$	33.50	50.00	45.54	35.00
S.E.M.	3.19	5.49	4.31	1.56
N	14	12	13	12

*Milliliters of 0.25 percent saccharin solution consumed per 100 g of body weight. †Number of trials until achievement of criterion.

Saccharin preference is a pronounced sexually dimorphic behavior that is dependent on androgen titers during the perinatal period for its adult expression. Normal adult female rats exhibit a marked preference for this nonnutritive substance when compared with males (*8*). Early postnatal administration of testosterone propionate to female animals masculinizes their adult saccharin preference, whereas estradiol benzoate administration to male animals in this period has no effect (*5*). Conversely, feminine saccharin preference is observed in male rat pseudohermaphrodites of the Stanley-Gumbreck strain, which are androgen-insensitive because of a genetic defect that causes a lack of androgen receptor (*9*).

Maze learning is also a strongly sexually dimorphic behavior, wherein male performance is statistically better than female (*3*). As with saccharin preference, the adult expression of this behavior is influenced by perinatal androgen status (*3, 10*). Therefore, if prenatal exposure to alcohol disrupts an androgen-mediated pathway during a critical period for expression of these behaviors, we postulated that adult FAE males would exhibit feminized behavior patterns relative to control males.

In the first experiment, pregnant Sprague-Dawley dams from Charles River breeders were pair-fed a liquid diet containing 35 percent ethanol-derived calories ($N = 7$) or an isocaloric liquid diet containing no ethanol (Bio-Serv) ($N = 6$). The diets were administered on day 7 of pregnancy and were continued until parturition; at this point, all dams were given free access to Purina Lab