MIGRATION OF AUTONOMIC NEURONS INTO REGENERATING TISSUES

A. K. Kolomiitsev

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Besides nerve fibers, autonomic neurons (Dogiel's type I cells) were found among the neural components of the newly formed wall of the esophagus and main air passages after alloplastic repair of circular defects in these structures with Kapron gauze. The migrating nerve cells are innervated by preganglionic fibers, forming pericellular systems on them. Migration of neurons may take place passively or actively. In the latter case the dendrites diminish in number or disappear, the neurofibrillary structure disappears, and the argentophilic properties are weakened.

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Ameboid movement, characteristic of many cells of vertebrates and man, is a feature of certain nerve tissue cells. Migration of lemmoblasts and neuroblasts, for instance, has been described during embryogenesis, in tissue culture, and in the case of metamorphosis of the larvae of lower vertebrates and healing of injuries to their central nervous system [4, 5, 6, 8, 9, 11, 13, 14-16].

There is no reliable experimental evidence of migration of neurons in adult forms of the higher vertebrates in the literature. However, several workers [3, 5-7] have shown that a cambial reserve of nerve tissue exists in many organs of higher vertebrates, composed of cells resembling neuroblasts. The gradual using up of this reserve during postnatal ontogenesis suggests that these cells, after differentiating, may migrate from the places where they were gathered originally into other parts of the organs. More definite results were obtained in Golub's laboratory [1], where it was discovered that after organs had been satured together, nerve cells are often found in the adhesions formed under these circumstances. However, these extremely interesting facts do not prove definitely whether this migration of neurons is an active or a passive process, associated with their drawing into the newly formed tissues.

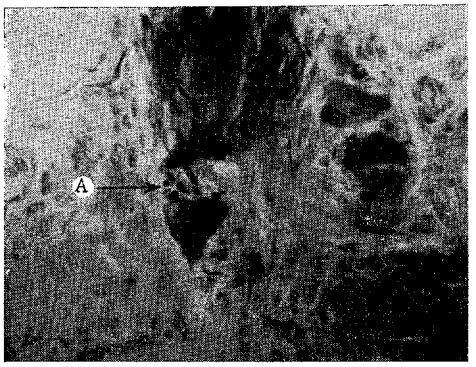

Fig. 1. Autonomic neurons in newly formed connective tissue (esophagus of a dog 3 months after replacement of a circular defect in it by Kapron gauze). A) Regenerating pericellular systems. Thickness of section 40 μ. Bielschowsky's stain, gilding, hemalum–azure II–eosin. 400×.

EXPERIMENTAL METHOD

Alloplastic repair of circular defect of the esophagus and main air passages (trachea and main bronchi) was performed on 18 dogs. The operations were performed at the Kiev Research Institute of Tuberculosis and Thoracic Surgery by Yu. A. Furmanovyi and V. D. Bezverkhii. The size of the defects varied from 2 to 6 cm. A tube of No. 8, 10, or 12 Kapron gauze was used as the prosthesis. The material was investigated between 1 month and 1.5 years after the operation. The newly formed tissues surrounding the alloplastic graft and in contact with it were impregnated and stained by various modifications of Bielschowsky's method, by Spielmeyer's method, with azure II–eosin, hematoxylin–eosin, carmine, etc.

EXPERIMENTAL RESULTS

A study of this material showed that after alloplastic repair of circular defects of the esophagus and air passages

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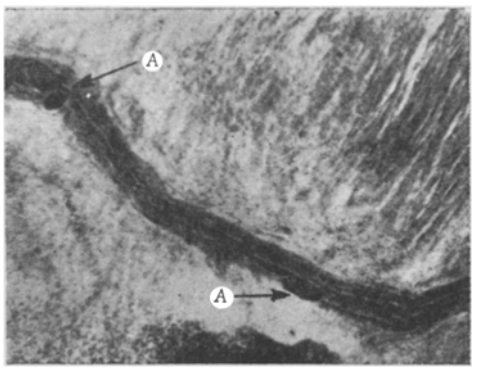

Fig. 2. Nerve cells (A) in a nerve trunk lying in newly formed connective tissue (esophagus of a dog 5 months after replacement of a circular defect in it with Kapron gauze). Thickness of section 40 μ. Bielschowsky's stain, gilding, azure II–eosin. 100×.

a large quantity of connective tissue is formed around the graft and penetrates into its interstices. In some cases partial or complete restoration of their typical epithelium is found on the inner surface of the regenerating wall of these organs. In the case of repair of the air passages the formation of a few masses of cartilage is sometimes observed. Regeneration of the air passages thus exhibits certain organotypical features.

The newly formed parts of the organs receive their innervation by ingrowth of large numbers of nerve fibers. These penetrate into the regenerating tissues from the residual parts of the organs and also from the cellular tissue surrounding them. Subsequently most axons combine to form nerve bundles or trunks. Along their course, in the connective tissue of the regenerating organs, autonomic neurons (Dogiel's type I cells) can be detected (Fig. 1). Their study showed that the migration of neurons may take place by one of two mechanisms. Some (the minority) enter the newly formed tissue passively as a result of displacement of the regenerating material and contraction of the collagen fibers during scar formation. The passively migrating neurons lie immediately next to the part of the organs damaged by the operation. A very characteristic feature was that such neurons usually kept their processes, and in their outward appearance they were almost indistinguishable from nerve cells located in parts of the esophagus or air passages far removed from the site of operation.

However, even during the passive migration of neurons an active response of certain elements of the nervous system is seen. The axons of bundles along whose course or near to which these nerve cells are situated frequently formed collaterals terminating in loops or boutons. These nerve fibers sometimes reached to the nerve cells and formed typical pericellular systems on them. This fact demonstrates that preganglionic nerve fibers exhibit well-marked neurotropism relative to neurons which have migrated.

Meanwhile, other neurons (the majority) migrate into newly formed tissues. This is confirmed by the following facts. 1) Characteristic changes are observed in the shape of the nerve cells associated with some degree of morphological simplification. They are manifested as disappearance of or a reduction in the number of the dendrites, masking of the neurofibrillary structure, and weakening of the argentophilic properties of the neuroplasm. Weakening of differentiation often accompanies the migration of cells. 2) Migration of neurons occurs only along the course of preliminarily regenerating nerve fibers or bundles of fibers, resembling the migration of neuroblasts. 3) Migration of neurons takes place only when a short time has elapsed after the onset of regeneration. This fact demonstrates that migration of neurons requires certain preliminary conditions, among them a definite degree of maturity of the connective tissue and the penetration of nerve fibers into it. 4) The direction of migration of the neurons cannot be related entirely to the orientation of the fibrous structures of the regenerating tissue. In some cases nerve cells could be seen in trunks lying obliquely or perpendicularly to the collagen bundles (Fig. 2). 5) The nerve cells may be far from the cut surfaces of the organs, 1.0-1.5 cm from the pre-existing tissues.

Synapses also were formed on neurons migrating by virtue of their own mobility. In the beginning migration of nerve cells is accompanied by proliferation of nearby axons, the terminal structures (bulbs of growth) of which are situated in the immediate proximity of the cell bodies. Later the bulbs of growth come into contact with the neurons and are converted into pericellular apparatuses. This fact not only confirms the possibility of innervation of mobile structures, but also provides evidence that regardless of the mechanism of migration of the neurons, they are provided with connections with the appropriate nerve centers.

Neurons migrating into newly formed tissues may occur singly or may form microganglia. The accumulation of nerve cells into ganglia is apparently an expression of one primitive form of their integration, for similar processes have been observed under explantation conditions when combined cultivation of nerve and other tissues is carried out [2, 12].

Neurons occurring in regenerating tissues usually exhibit considerable resistance. No essential changes in their structure were detected even very long after the operation.

The number of neurons migrating into a regenerating organ may vary; in some cases, on the other hand, no migration was observed. The factors preventing or delaying migration of nerve cells into newly formed tissues are still unknown.

As regards the actual migration of neurons, it can be concluded from data in the literature that this is largely explicable in terms of the specialized processes of tissue regeneration associated with alloplasty. The indrawing of nervous structures is brought about principally through a biologically active material [10]. The alloplastic graft, as the framework on which large masses of new tissue are formed, with enormous numbers of actively proliferating cells, stimulates the development of a tissue complex characterized by a particularly high intensity of metabolism. Substances passing from it into parts of organs not injured at operation may stimulate both the regeneration of nerve fibers and the migration of neurons supplying the regenerating tissues with their innervation.

It must be concluded from this analysis of the migration of neurons that it reflects a compensatory reaction of the nervous system. Whereas hitherto these reactions have been linked on the morphological plane chiefly with the formation of new nerve fibers and endings, in the case now being discussed a redistribution of nerve tissue elements, so highly differentiated that they cannot reproduce or can do so only to a very limited degree, evidently took place.

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