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Electron microscopic changes of sciatic nerves in rats with experimental peripheral neuropathy caused by paclitaxel.

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This paper presents the experimental work devoted to electron microscopy study of pathomorphological changes in nerve fibers under the influence of Paclitaxel. This antitumor drug was administered to random bred rats intraperitoneally at a dose of 2 mg/kg 4 times every other day. Sciatic nerves sampling of animals was taken on certain days during 120 days of experiment. The following ultrastructural changes of myelinated nerve fibers have been identified: hypertrophy and myelin sheath delamination resulting in formation of interlamellar vacuoles; swelling and atrophy of axial cylinders with diffuse distribution of neurotubules; cristae diffluence; homogenization and vacuolic transformation of mitochondrial matrix; complete nerve conductors degeneration and remyelination.

Keyword: Paclitaxel, electron microscopy, myelinated nerve fiber, peripheral neuropathy.

1. Introduction

Neurotoxicity is a very common side effect of chemotherapy in patients with malignant tumors [1]. Antitumor drug of taxanes group - Paclitaxel (P) is widely used in modern medicine for treatment of the patients suffering from cancer, but its adverse effects on the nervous system limit the required dosage and therefore determine the further course of the disease [2, 3, 4]. In this regard, there appears an increasing amount of research works aimed to optimize the treatment regimens and to study the genesis of neurological disorders caused by P effect on the body [5, 6, 7]. Researchers describe morphological deviation at different levels of the nervous system, as well as their physiological manifestations [8, 9]. However, the onset and distinctions of the pathological changes in the peripheral nervous system haven't been completely figured out yet.

Taking into account the above mentioned facts, the object of this research is to study the changes in the structure of sciatic nerve fibers during P-induced neuropathy development on the electron microscopic level.

2. Materials and Methods

The object of the study was sciatic nerves sampling of 35 white random bred rats weighing 150-200 g, which were administered Paclitaxel (Actavis, Romania) intraperitoneally at a dose of 2 mg/kg body weight 4 times every other day (total dose 8 mg/ kg). 15 animals were administered isotonic solution of NaCl intraperitoneally in equivalent volume to serve as a control set. Collecting material from experimental and control animals was performed on the 1st, 7th, 15th, 27th, 60th, 90th, 120th days after the last injection. Sciatic nerve samples in the volume of not less than 1 mm^3 were immersed into fixing mix - 1% solution of osmium tetraoxide, buffered according to Kolfild, for 2 hours. After washing the material in 0,1 M

phosphate buffer and dehydrating in alcohols of increasing concentrations, the pieces were contrasted in 2% alcoholic solution of uranyl acetate. Then the material was processed in dehydrated alcohol mixed with acetone, acetone, mixture of acetone and epoxy resin and in pure resin. Samples of material were put into gelatin capsules and filled with epoxy resins. A catalyst was addied to it as well. Then they were placed into the thermostat (at t +56 °C) for polymerization for 24 hours. To perform the test, semi-thin sections (1 micron thick) were stained with toluidine blue. Ultrathin sections were obtained by means of ultramicrotome Tesla BS - 490 A. They were mounted on the copper blends with d = 1mm, and were contrasted more with solutions of uranyl acetate and lead citrate. These sections were examined by means of electron microscope PES - 125K, then there followed photographing of the images, enlarged from 1600 to 16000 times.

3. Results of Experiment

During electron microscopy examination of the sciatic nerves samples, on the first day of experiment, we noted polymorphic changes of architectonics in myelinated nerve fibers (MNF). Some of the nerve conductors changed destructively, their axial cylinders atrophied. In other nerve fibers there was determined the myelin sheath delamination and detachment of its fragments, located in axoplasm cylinder in the form of concentric inclusions. Most MNF had the disrupted lamellar structure resulting in forming small intramyelin vacuoles, delaminating the myelin plates. Their axoplasm had a high electron density of hyaloplasm and increased number of microtubules and neurofilaments. Mitochondria were of polygonal shape, had destruction of cristae, sometimes matrix looked flake-like. There were spotted some small enlightened vacuoles in axoplasm, that formed multivacuolar structures (Fig. 1). Some MNF had hypertrophied myelin sheath forming deep wavy invgiations; its plates were mostly homogenized, osmiophilic, but its inner border was slightly delaminated. Axial cylinder was atrophied; the remains of neurofibers and axolemma were located among invaginations in the form of small separate fragments (Fig. 2).

We observed the areas of partial demyelination in some degenerative nerve fibers, despite the distinctive myelin sheath delamination. Contracted and dislocated to the periphery, the axial cylinder was characterized by an increased density of axoplasm and increased number of compactly distributed organelles.

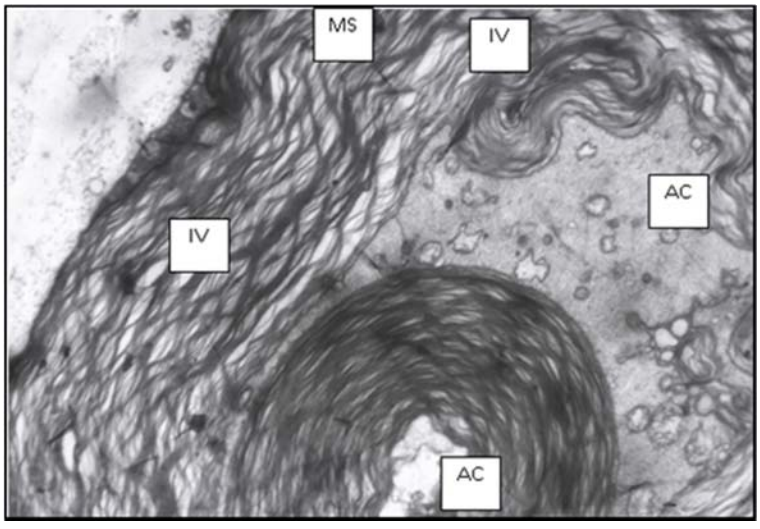

Fig 1: Formation of the small intramyelin vacuoles (IV), disruption of mitochondria architecture and formation of multivacuolar structures in axoplasm on the 1st day of experiment. Electron micrograph. Magnification: x9600. Designation: MS – myelin sheath, AC – axial cylinder.

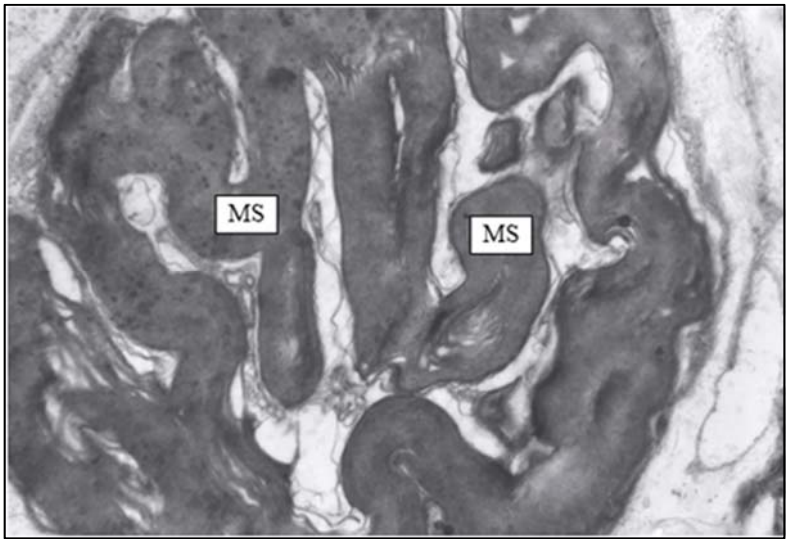

Fig 2: Invegiations of myelin sheath (MS) and fragmentation of axial cylinders in SN of the experimental animals on the 1st day. Electron micrograph. Magnification: x8000.

Mitochondria were dominating among them. They were polymorphic, of small and medium sizes, with diffluent cristae. Matrix was of different density, finely granulated.

Some mitochondria had distinctive areas of enlightenment. Cisternae of smooth endoplasmic reticulum were slightly expanded. A large number of lysosomes were registered.

Occasionally deep inner plates destruction of the myelin sheath was observed due to the formation of large interlamellar vacuoles, filled with moderately dense flake-like contents. These new structures altered concentric layers of lamels resulting in their spotted coalesce into homogeneous masses. Axial cylinder was distructed, the number of neurofilaments and microtubules was increased, and they were smoothly distributed in axoplasm. Mitochondria were of polygonal shape, had destructed cristae. Periaxonal and endoneurium edema were notable. Cytoplasm of the neurolemmocyte was vacuolated (Fig. 3).

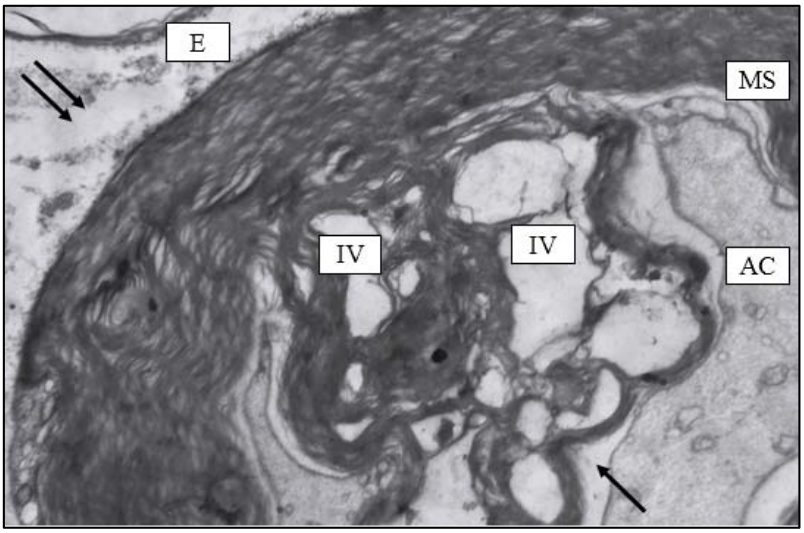

Fig 3: Periaxonal (↑) and endoneurium (↑↑) edema, formation of large interlamellar vacuoles on the 1st day of experiment. Electron micrograph. Magnification: x6400. Designation: MS – myelin sheath, AC – axial cylinder, IV- interlamellar vacuoles, E-endoneurium.

Submicroscopic structure of most unmyelinated nerve fibers (UNF) was preserved. Only in some of them there were observed focal enlightenment of axoplasm because of diffuse neurofibers distribution. Plasmalemma contours were slightly deginerated. Peripheral chromatin condensation was dominating in Schwann cells nuclei. Cisternae expanding of smooth endoplasmic reticulum and mitochondrial cristae destruction were rather distinctive.

The seventh day of the experiment revealed deformation of MNF, which became mostly of polygonal shape because of myelin sheath invaginations and protrusions. Their axial cylinders were slightly contracted, swollen, having flake-like axoplasm. There appeared a distinctive edema of endoneurium connective tissue. Periaxonal myelin lamellae delaminated and detached in some nerve conductors forming concentric inclusions, that were invaginated into the axial cylinder thickness. Axoplasm was heterogeneous, microtubules and neurofilaments were diffusely distributed, either aggregated or enlightened.

Other MNF had a destructed configuration of thickened myelin sheath resulting in formation of small and medium interlamellar vacuoles, which were distributed on different levels of myelin plates. The internal contour of myelin sheath was homogenized, osmophilic, closely bordering on axolemma. Hyaloplasm of axial cylinders was heterogenous due to neurofibers diffuse distribution. Mitochondria were scarce, vacuolated, with remains of finely granular matrix dislocated closer to the organelles bordres. Some of the mitochondria were destroyed, and had the destruction of outer and inner membranes. Sometimes the myelin sheath became filamentous, and the lamels disorganization was more distinctive on the periphery. Schwan cells cytoplasm was characterized by vacuolar transformation of endoplasmic reticulum cisternae and of Golgi complex dictyosomes. MNF groups with distinctive Schwan cells edeama were observed. Myelin sheath invaginated toward the axial cylinder, deforming it. Neurofibers density increased significantly in axoplasm per unit area. Some mitochondria were contracted, had homogenized cristae and high electron density of matrix, while others swelled, their cristae were either partially or completely melted (Fig. 4).

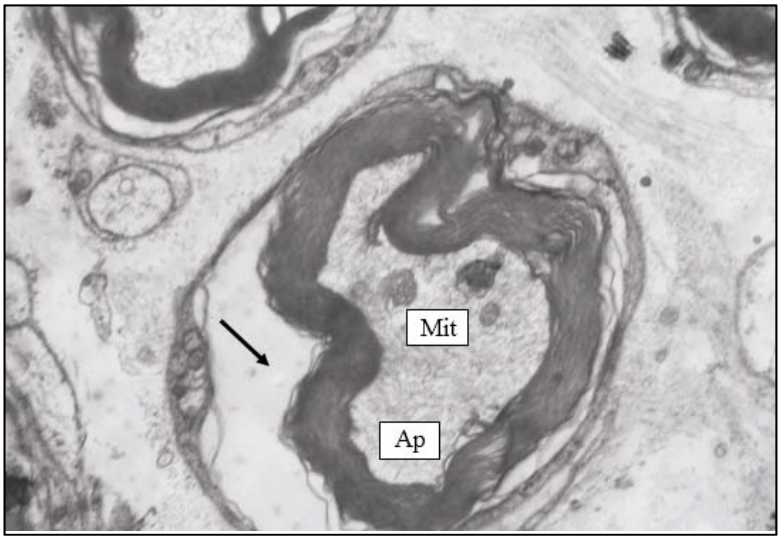

Fig 4: Intraneurolemmal edema (↑), increased density of neurofibers in axoplasm (Ap) per unit area, homogenized mitochondria (Mit) cristae on the 7th day of experiment. Electron micrograph. Magnification: x8000.

Changes in the UNF structure manifested in fibers swelling, sometimes rather distinctive, and in axoplasm diversity which had areas of enlightenment. Mild mitochondria destruction and cylinders expansion of smooth endoplasmic reticulum were registered. Schwan cells cytoplasm, that surrounded them, sometimes revealed the signs of hydropic dystrophy and the increased number of lysosomes.

The fifteenth day of the experiment showed that in SN of the experimental animals there were preserved populations of MNF with the changes equivalent to those described in the previous term of the experiment, but the number of fibers with a large diameter, distinctive signs of axial cylinders and myelin sheath deformations increased progressively. The myelin sheath was hypertrophied and resembled loosely distributed strands on the periphery, and medially it formed the folded figures of densely arranged myelin lamellae. Such nerve conductors had axial cylinders of irregular shape. Neurofibrils were diffusely distributed, some were cut tangentially, others transversely. Mitochondria were scarce, having damaged cristae and coarse flake-like matrix. Myelin sheath of some nerve fibers was detached fragmentarily. Those fragments were loosely arranged in axoplasm as concentric rings with inclusions of axial cylinder inside (Fig. 5).

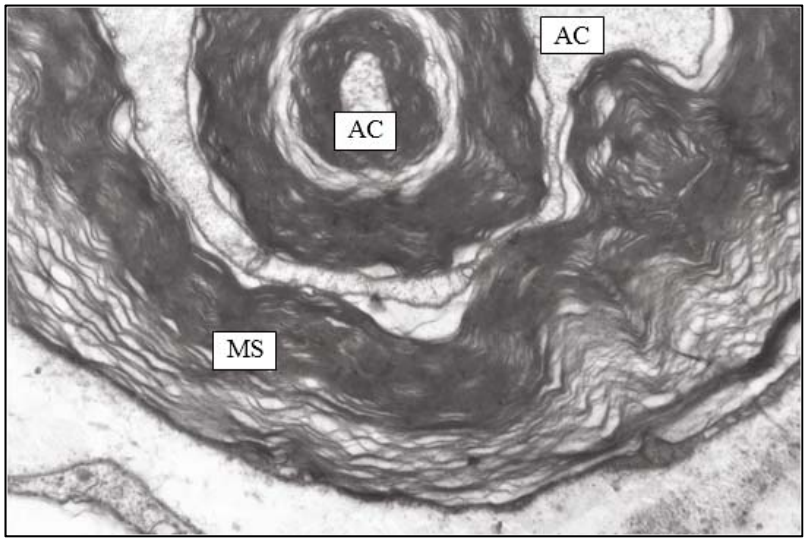

Fig 5: Detached fragments of myelin sheath (MS) are arranged as concentric rings in axial cylinder (AC) on the 15th day of experiment. Electron micrograph. Magnification: x8000.

Ultrastructural disorders of myelin sheath in some MNF were characterized by disruption of myelin plates at the inner contour. There were large vacuoles discovered between lamellae, which delaminated them into separate pieces and broke the orientation. We traced breakes between adjacent myelin plates, progressing towards contracted axial cylinder. Sometimes neurolemma was degenerated, it did not envelop the conductor tightly because of intraneurolemmal edema. There was also a distinctive periaxonal swelling that deformed the axial cylinder. Neurofilaments and microtubules were diffusely distributed in hyaloplasm. We marked the areas of mitochondria aggregation which had membrane degradation and homogenization of content in the form of high electron density spots. Cisternae of the smooth endoplasmic reticulum were expanded (Fig. 6).

There was present a small number of fibers, which had a 'spotted' myelin sheath due to enlightenment foci formed among homogenised osmiophilic lamellae. There were registered detached particles of the myelin sheath, located deeply in the axial cylinder.

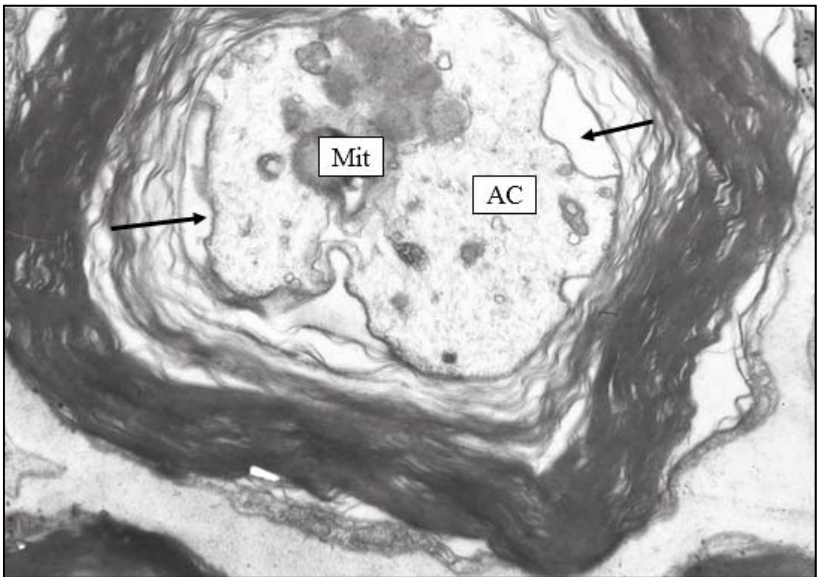

Fig 6: Periaxonal edema (↑), diffusely distributed neurofilaments and microtubules in axial cylinder (AC), areas of mitochondria (Mit) aggregation on the 15th day of experiment. Electron micrograph. Magnification: x8000.

There were observed degenerative MNF having such distinctive disorders as hypertrophy and hyperplasia of the myelin sheath resulting in the axial cylinder atrophy or making it look thin strip and dislocated to the periphery (Fig. 7). Changes in their organelles revealed as destructed mitochondria cristae with coalesced matrix and vacuolated smoth endoplasmic reticulum.

At this stage of the experiment, the number of UNF which had various degrees of morphological changes, increased. We noted the destruction of axsolemma and Schwan cells membrane surrounding the axial cylinder. We sometimes discovered osmiophilic places and the other times, foci of enlightenment in cytoplasm of the neurolemmocytes. Axoplasm was also diffusely distributed in the axial cylinder. Mitochondria were reduced in size, they sometimes formed agglomeration. Cristae were either reduced or completely diffluent, matrix was of high electron density.

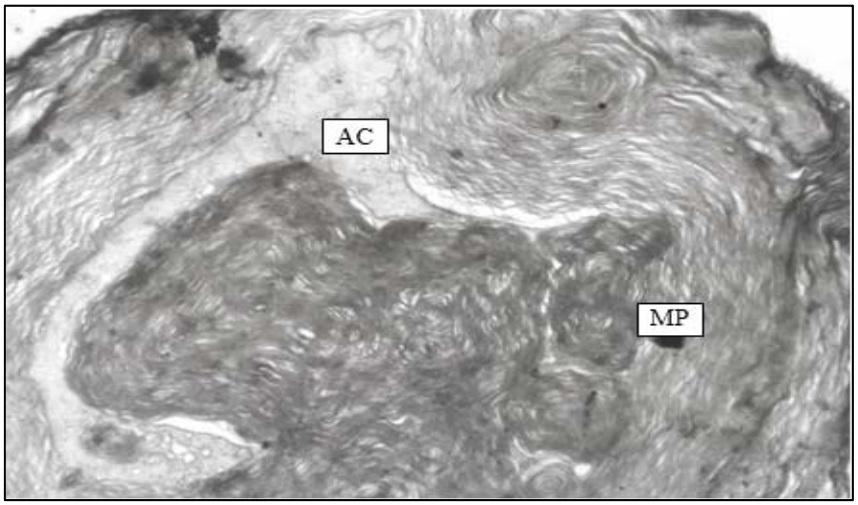

Fig 7: Destruction of MNF in SN on the 15th day of experiment. Electron micrograph. Magnification: x6400. Designation: MP – myelin plates, AC – axial cylinder.

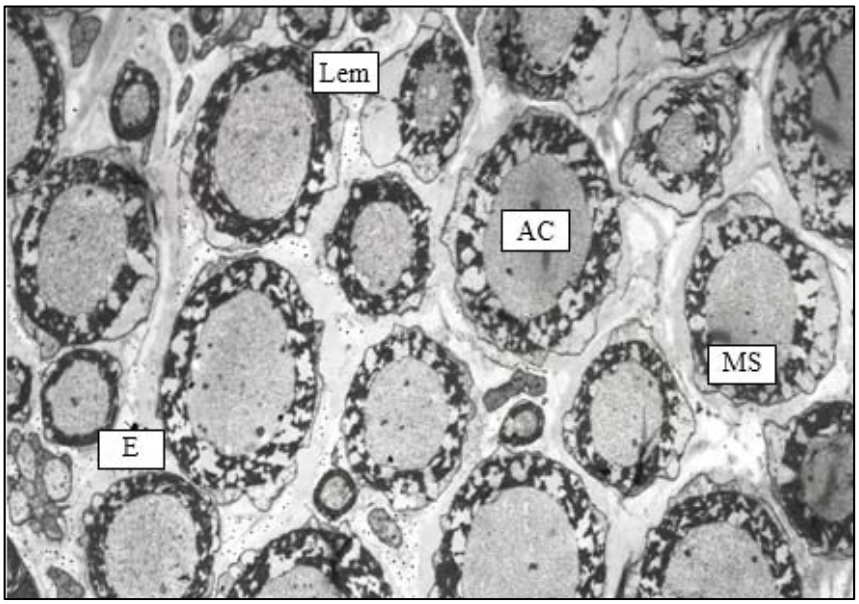

Fig 8: Deep degeneration of MNF in SN on the 27th day of experiment. Formation of large polymorphic vacuoles with low electron density among homogenised osmiophilic plates of myelin. Electron micrograph. Magnification: x1600. Designation: E – endoneurium, AC – axial cylinder, MS - myelin sheath, Lem – neurolemmocyte.

On the twenty-seventh day of experiment we marked the increase of deep MNF degeneration (Fig. 8). Rounded fibers with thick spotted myelin sheath dominated. Their chimeric look resulted from large polymorphic vacuoles formation which had low electron density among homogenised osmiophilic plates of myelin.

Axial cylinders were swollen, they had a dense axoplasm. Neurofilaments and microtubules architectonic was disrupted. Their number was significantly reduced in some areas. Neurolemmocytes had a distinctive hidropic degeneration. Organelles of the most nervous conductors were poorly visualized. Only MNF, myelin sheath of which was slightly changed, had large areas of mitochondria aggregation. They were mainly of large and medium size, rounded, vacuolated. Some of them revealed partially or completely melted mitochondrial cristae, their matrix was enlightened. While others had homogenized cristae and matrix of high electron density. We noted sometimes the mitochondrial membranes fragmentations.

The axial cylinders of nerve fibers appeared to be distracted and reduced in size, because of a significant periaxonal swelling. Their hyaloplasm looked finely granular, neurofibers were diffusely distributed. Sometimes fragments of axoplasm detached, locating separately in the periaxonal area (Fig. 9). There were scarce MNF, which had almost no myelin sheath. Focally, myelin fragments covered destructed residue of axial cylinder. Neurolemma appeared to be degenerated and fragmented occasionally. Glyocyte cytoplasm was totally enlightened (Fig. 10).

Many parts of nerve fibers preserved the changes characteristic to the previous term of the experiments. The fibers were polymorphic, their hypertrophied myelin sheath was delaminated by interlamellar vacuoles. Delamination was sometimes concentrated either on the periphery or at the inner contour. Axial cylinders were of irregular shape, with high electron density of axoplasm. There was a very distinct axoplasm

swelling on its border, that hadn't been observed previously.

UNF had changes of various degree. There was a large number of microtubules and neurofilaments in some of them. Mitochondria had a natural structure and individual profiles of smooth endoplasmic reticulum. Along with the above mentioned, orientation of the neurofibers in other fibers was broken. Axoplasm enlightenment was defined, sometimes almost on the entire cross sectional cut of the axial cylinder.

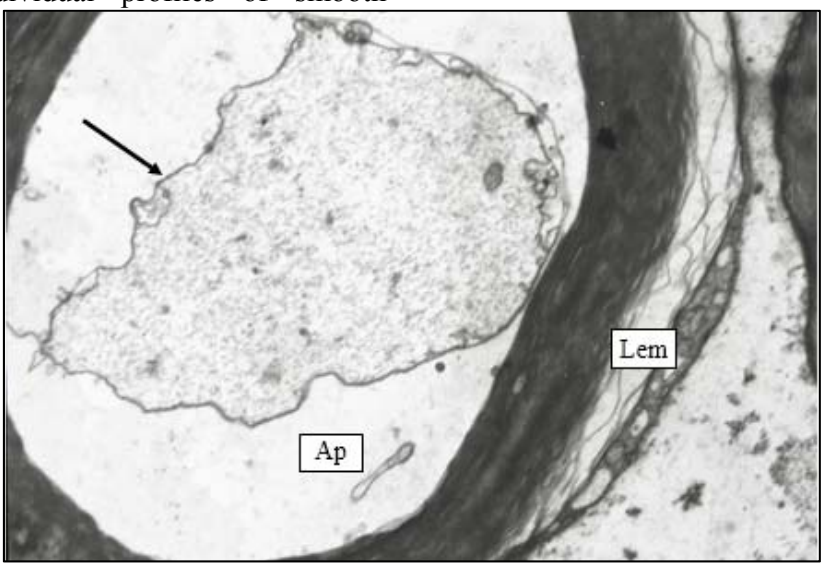

Fig 9: Distruction and reduction in size of axial cylinder, periaxonal swelling (↑), hydropic dystrophy of neurolemmocyte (Lem), detached fragments of axoplasm (Ap) on the 27th day of experiment. Electron micrograph. Magnification: x6400.

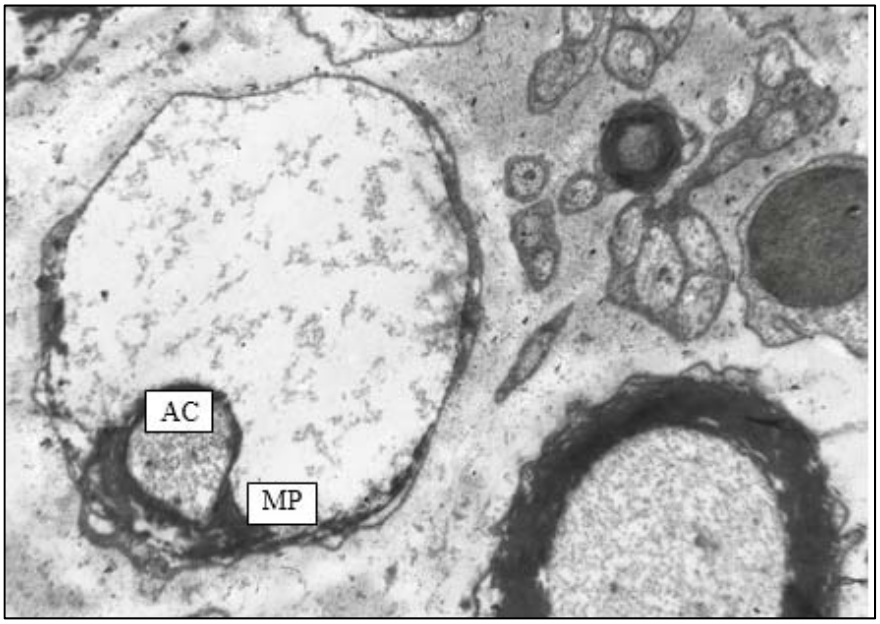

Fig 10: Demyelination of MNF in SN on the 27th day of P- induced peripheral neuropathy. Electron micrograph. Magnification: x4800. Designation: AC – axial cylinder, MP – myelin plates.

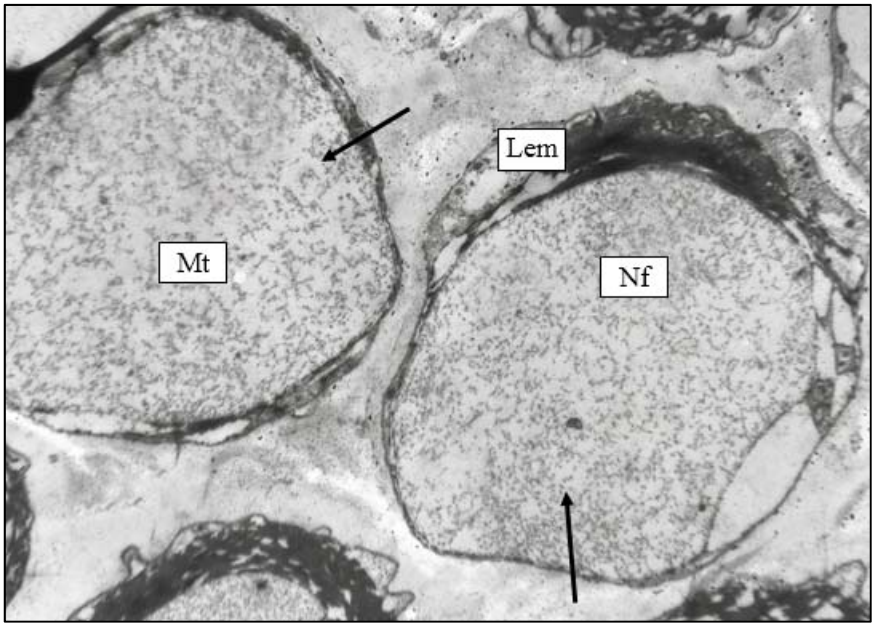

Fig 11: Total demyelination of axons (↑), diffuse distribution of microtubules (Mt) and neurofilaments (Nf), vacuolization of the Schwann cells (Lem) cytoplasm on the 60th day of experiment.
Electron micrograph. Magnification: x4000.

Axolemma contours in certain areas disappeared. Mitochondria were swollen, their cristae and membranes were destructed. Schwann cells had lysosomes, nuclei of mostly oval shape in the cytoplasm. Euchromatin was finely granular and dense. Basal laminae were preserved and surrounded the cells along the entire perimeter.

On the sixtieth day of the experiment, demyelinated nerve conductors appeared to be the most common changes of moderately altered MNF. Their myelin sheath was completely degenerated or located under neurolemma as small homogenized myelin particles. Axial cylinders were swollen, sometimes deformed due to the periaxonal edema. Axoplasm was mostly of moderate electron density and had diffuse distribution of microtubules and neurofilaments. Schwann cells looked like a thin strip with focally vacuolated cytoplasm (Fig. 11). The remains of altered myelin plates covered the contracted axial cylinders either from one side or concentrically in some nerve fibers. Mitochondria were closely arranged and had disrupted cristae architectonics and matrix granulation. We revealed an increase of agranular endoplasmic reticulum cisternae, as well as compact distribution of microtubules and neurofilaments. Intraneurolemmal swelling was often rather distinctive.

Sometimes the destruction of MNF reached its peak and revealed not only the destruction of the myelin sheath, but of the axial cylinder as well. Axolemma patches and preserved axoplasm remains were distributed loosely in a swollen hyaloplasm. Neurolemma was extremely degenerated, it had sometimes distructed bordres (Fig. 12). There was discovered subpopulation of nerve fibers with myelin sheath hypertrophy. It revealed a variety of invaginations in some fibers, while in others it delaminated into separate plates. We could observe rarely inclusions of neurolemmocyte cytoplasm among myelin patches. It contained a great deal of vesicles of various diameter, as well as loose ribosomes and polysomes.

There were also MNF groups, which had a slightly altered myelin sheath, but orientation of their non-membrane axoplasm organelles was broken. Neurofibers were diffusely distributed, forming areas of dark, dense aggregations separated by light, loose interlayers of hyaloplasm. Myelin sheath distruction was

another type of MNF pathological changes. It was characterized by enlightenment foci among osmiophilic compact lamels. Mitochondria of the axial cylinder were reduced in size, homogenized, but cisternae of agranular endoplasmic reticulum were expanded. We noted a hydropic dystrophy of Schwan cells, in which organelles were not visualized.

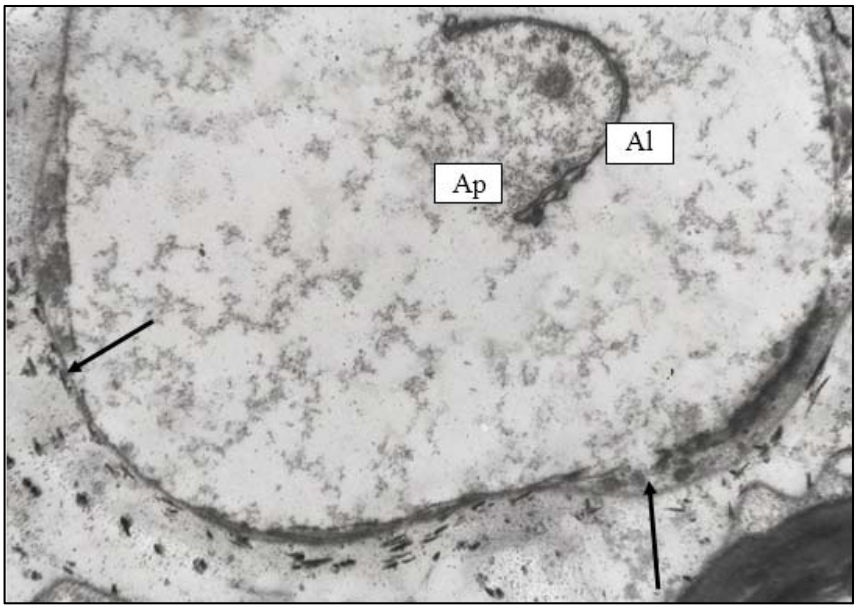

Fig 12: Destruction of the axial cylinder, axolemma (Al) patches and preserved axoplasm (Ap) remains, distructed bordres of neurolemma (↑) on the 60th day of experiment. Electron micrograph. Magnification: x6400.

The ninetieth day of the experiment is characterized by uniformity of MNF changes, among which the most typical were the axial cylinders edema and myelin sheath degeneration. Axolemma usually bordered on the inner layer of myelin sheath, but there were nerve conductors with distinctive periaxonal swelling. Also we marked occasionally the formation of intra-axonal vacuoles, filled with diffluent hyaloplasm and diffusely distributed neurofilaments and microtubules. The number of organelles, especially lysosomes significantly increased in some nerve fibers. Mitochondria were mostly large and rounded. Their cristae were preserved, but reduced and distructed, with foci of matrix enlightenment. Occasionally complete cristae destruction with homogenization of contents was found. Most MNF axoplasm was of high electron density, due to increasing number of cytoskeleton elements, which were diffusely distributed. Myelin sheath of several nerve fibers became filamentous. There were large interlamellar clear vacuoles observed in the outer layers. Axial cylinders of such MNF, were of irregular shape, sometimes with axoplasm enlightenments, swelling and destruction of mitochondria.

Nerve conductors with distinctive degenerative processes were occasionally found. Configuration of their hypertrophic myelin membrane resulted from the vacuoles formation of various sizes, which delaminated myelin plates and broke their concentric orientation. Axial cylinders were atrophied. At the same time there were registered fibers subpopulations with distinctive remyelination signs. Some MNF revealed areas, where the myelin sheath failed to cover the axial cylinder completely, and axoplasm was surrounded by neurolemma. Cisternae of smooth endoplasmic reticulum were frequently expanded and proliferated, some of them were vacuolated. Mitochondria were fine, had cristae destruction and homogenization, as well as matrix enlightenment.

At this stage of the experiment most UNF did not reveal any changes. Only some of them had edema of surrounding them neurolemmocytes'

axoplasm and cytoplasm. Mitochondria were sometimes increased in size with thin or completely destroyed cristae. Mitochondria matrix was flake-like and had low electron density (Fig. 13).

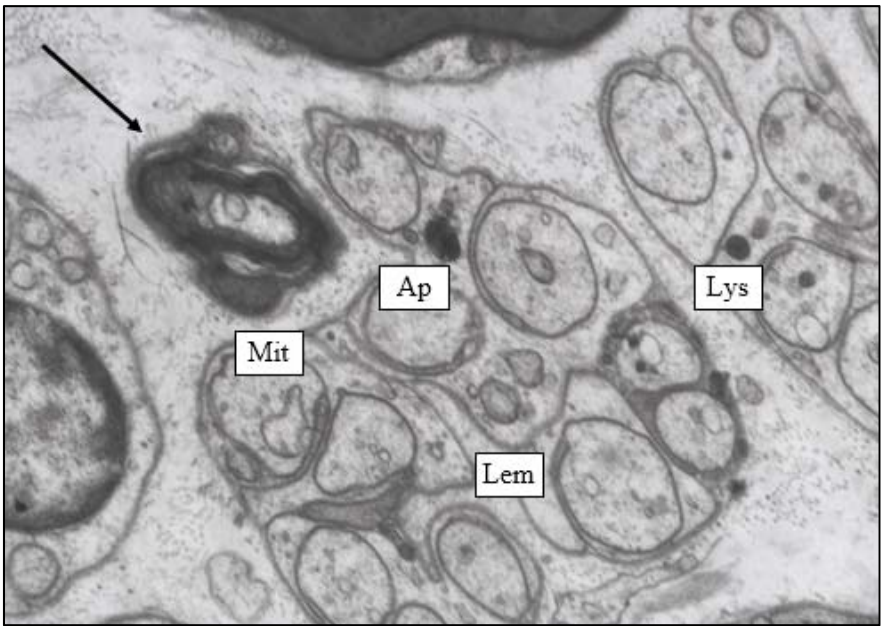

Fig 13: Edema of UNF axoplasm and surrounding them neurolemmocytes cytoplasm, distinctive remyelination signs (↑) on the 90th day of experiment. Electron micrograph. Magnification: x8000/
Designation: Lem - neurolemmocyte, Mit - mitochondria, Lys - lysosomes, Ap – axoplasm.

On the 120th day, sampling material of the experimental animals demonstrated prevalence of MNF with preserved tinctorial properties. At the same time there were observed bundles of polymorphic MNF with axial cylinders swelling, decreased number of microtubules and neurofilaments which were oriented diffusely. Vacuoles were transformed in some mitochondria. They contained destroyed cristae and flake-like matrix. We also noted nerve conductors of small and medium size, deformed, with myelin sheath invaginations and contracted axons.

There were occasionally found MNF with broken myelin sheath configuration. The fibers looked stellar- like due to numerous invaginations of thickened myelin sheath. Axial cylinder was destructed and axoplasm was of high electron density. These nerve conductors appeared to have vacuolization of the neurolemmocyte cytoplasm.

None of the animals had MNF of very large diameter with distinctive symptoms of degeneration during the last material sampling, which were present in the previous terms of the experiment. At the same time the number of remyelinated nerve fibers significantly increased.

Bundles of UNF rarely revealed axoplasm swelling, but they had a decreased number of neurofibers. Smooth endoplasmic reticulum cisternae were mainly grouped within limited areas of axoplasm. Some of them were expanded, filled with high electron density content.

4. Results and Discussion

The results obtained during the experiments coincide partially with the results of researches made by Flatters S.J.L. and Bennett G.J. [10], who simulated P-induced neuropathy on the rats, administering the drug intraperitoneally at a dose of 2 mg/kg on 0, 2nd, 4th, 6th days of experiment. They consider the affected mitochondrial axons of nerve fibers in subcutaneous nerves are the basic factor that contributes to peripheral

neuropathy on the 7th and 27th days of experiment and due to it there are no structural changes on the 160th day, when the signs of painful stimuli disappear.

We observed mitochondrial restructuring of various degrees in all stages of the experiment. The above mentioned authors also point to the absence of axonal degeneration of nerve conductors in subcutaneous nerve and to the general structure integrity and orientation of their microtubules. However, these data do not coincide with ours, because swelling, deformity and axial cylinders atrophy with diffuse distribution of neurofilaments and microtubules was common within our experiment.

Our data concerning architectonics abnormality of fibrillar and tubular axoplasm components coincide with the results of Shemesh O.A. and Spira M.E. [11], who indicate that a massive polar neurotubules reconfiguration, accompanied by the broken organelles transporting plays the leading role in the peripheral neuropathy development. Recent studies made by Gilardini A. *et al* [12] as for chemotherapy influence on the sciatic nerve of rats, including P drug, administered intravenously at a dose 10mg/kg, once a week during 4 weeks, proved the absence of any myelin sheath affecting. We can not agree with such conclusions, since we found significant changes in the myelin sheath structure under the influence of P (for example, the 1st day - the intramyelinic vacuoles formation that split myelin plate; 15th day-hypertrophy, invaginations with separate detached fragments; 27th day - formation of large polymorphic vacuoles of the moderate electron density among the homogenised osmiophilic myelin plates, making myelin sheath look spotty; 60th day - the complete degeneration of the myelin sheath, nerve conductors demyelinated). At the same time, our results are consistent with data of Mimura Y. *et al* [13], who describe the myelin plates fragmentation and phagocytosis in nerve fibers of the sciatic and tibia nerves after administration of P at a dose of 30 mg/kg every other day 3 times.

5. Conclusion: This ultramicroscopic study demonstrates various changes of nerve fibers in SN during the dynamics of P- induced peripheral neuropathy. The disease begins as a primary myelinopathy but worsens with the myelin sheath disruption, resulting in forming small intramyelin vacuoles, delaminating the myelin plates (the 1st day after the last P injection), causing also hypertrophy, hyperplasia with the formation of demyelinated fragments. There appear deep destructive disorders resulting in transverse lamella ruptures that progress to the 60th day of the experiment. These changes are accompanied by the increased degenerative disorders in nerolemocytes: edema, mitochondria destruction, vacuolar transformation in endoplasmic reticulum, increased number of lysosomes, gradual development of hydropic degeneration. Destructing process is completed by axial cylinders demyelination, and occasionally by nerolemocytes cytolysis. Regenerating processes in MNF structure begin on the 90th and continue until the 120th day in the form of developing, weakly myelinated single axons. However, full recovery of nerve conductors isn't observed.

Along with degenerative disorders in nerolemocytes, there is observed progressing disorders of axial cylinders ultrastructure varying from slightly manifested disorders of axon transporting, of electron microscopic mitochondria and smooth endoplasmic reticulum cisternae restructuring to axons deformation and degeneration. Within the 90th and 120th day there is determined a gradual decrease in axial cylinders alteration, however, axons with extensive degenerative changes are frequently defined.

Changes in UNF are less distinctive. They reveal the signs of lemocytes cytoplasm and axoplasm swelling, dissociation of the basement membrane and of the cytomembrane, slight changes in organelles.

Thus P- induced neuropathy is the primary myelinopathy (Schwann cells pathology) followed by delayed axial cylinders disorders, with the period of maximum degenerative processes manifestations on the 60th day and a gradual decrease in their intensity and developing regeneration on the 120th day. An important

feature is the diversity of changes in particular bundles that make up the sciatic nerve structure.

6. Research Prospect

We plan to study pseudounipolar neurons of the spinal ganglion and motor neurons of the spinal cord under the influence of P, to detect pathological changes and compare the degree of their affecting to the nerve conductors of peripheral nerves during P- induced neuropathy development on the electron microscopic level.

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