Bulgarian Academy of Sciences

Acta cytobiologica et morphologica, 1

Sofia • 1989

Reactive recombination of myelin nervous fibres in the process of normal myelination

(Hypothesis on the further development of myelination mechanism)

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N. n. tibiales were investigated in 2 to 11-day-old rats, using electron microscopy. All the main types of membrane junctions were found: serial desmosomal, continuous, septate, gap and tight junctions. The junctions were both of glio-glial and axonglial type. These types may be stages of a unified process of membrane interaction. They are located in multiple loci and form intermediate dense myelin line upon merging. Such junctions result from aggregation and retraction of outer paramembrane electron-dense material. The same mechanism of inner surface membrane coupling was observed in lamellopodies of lemmocytes. Thus, "inside-out" local junctions were fomed. Merging of these junctions forms the main dense line of myelin. Consequently, compact myelin, thus formed, should be considered as a gigantic complex membrane junction.

Key words: myelination, ontogenesis, membrane junctions, myelin fibres.

At present there exist two groups of hypotheses trying to elucidate the complex mechanism of myelin sheath formation. The first group supposes myelin to be the product of lemmocyte membrane of the Schwann cell [3, 9]. The second group of hypotheses was based on morpho-biochemical research. According to it, in the process of myelin formation equally important part play both the neuron and the gliocyte. Not only gliocyte but also neuron do participate in the phospholipid and protein provision of the biogenesis of myelin sheath [2, 22]. Both concepts presuppose the existence of certain intermembrane glio-glial or glio-neuron interactions. In this respect, frequently desorbed findings of glio-neuron and glio-glial intermembrane junctions are of special interest. The role of intercellular junctions in ontogenetic development of many organs has been known for a long time [16]. The part these junctions play in the process of myelination seems to be significant. We consider this problem to be of particular interest because our laboratory has shown the reactive nature of some glio-glial

and glio-neural intercellular junctions. They appear in the period of increased activity of the nervous system, during some changes in metabolism and upsetting of homeostasis of intercellular liquid. As one of the main conditions of the commencement of myelination is a certain signal coming from the axon to the glial cell [8, 10,], myelination may be considered a reactive process, a response to the axon signal followed by recombination of the glial membrane. It may well be that this axon signal is not a special factor, but an ordinary primary impulse activity of some developing nonmyelinized axons, connected with the release of potassium ions by the axon and their assimilation by the glial cell [4, 10]. This study considers myelination as a reactive process accompanied by membrane alteration and membrane junction formation.

Materials and methods

Our concepts are based on the study of the myelination process in Wistar breed white rats aged from one to eleven days. The object of research was nervus tibialis. The rats were decapitated, a fragment of the nerve was segregated and fixed in 2,5% glutaraldehyde on phosphate buffer. Postfixation was then carried out in 1% solution of osmium tetraoxide. The substance was enclosed in araldite and examined by means of transmission electron microscopy.

Results and discussion

Rats aged from 24 to 36 hours did not display any myelin nervous fibres (non-myelin period). Around non-myelin axons several flat and broad cytoplasmic processes of lemmocyte (windings) were formed. Forty-eight-hour-old rats showed a few fibres with myelin sheath having sometimes up to 6-8 lamellae (Fig. 1). In this period we succeeded in finding the first structures suggesting the formation of Ranvier nodes and Schmidt-Lantermann clefts. That was the early myelination period. It should be noted that transition from the first to the second stage takes not days but hours.

The period of active myelination was registered in 5 to 11-day-old rats, great variations in the degree of myelination being observed. Some fibres already had a developed structure of nodes and clefts and a thick myelin sheath of up to 30-40 lamellae of myelin. Other fibres were in the incipient stages of myelination or did not have myelin at all. At all stages of nerve fibre myelination there is a great number of membrane junctions. This suggests their sharing in the process of myelin sheath formation.

Just as it has been shown for gliocytes or the central nervous system, the non-participating in myelinogenesis lemmocytes are, firstly, capable of forming all known types of membrane junctions and, secondly, they do it in two different ways. The first one represents a well-known junction between the outer membrane surfaces (Fig. 2) of two adjacent lemmocytes or two adjacent cytoplasmic tongues of one and the same lemmocyte. We observed such junctions at all stages of myelination throughout the fibre. All types of junctions are present: septate (sj), continuous (cj), gap (gj) and tight (tj) junction, as well as others. At later stages, however, the number and size of tj and gj increases. This happens probably as a result of gradual transformation of the various types of junctions into tj and their gradual fusion. As a result of fusion of adjacent junctions formed by their membrane outer surfaces, intermediate dense lines of myelin are formed. Such elongated junctions (lines) may form independently of

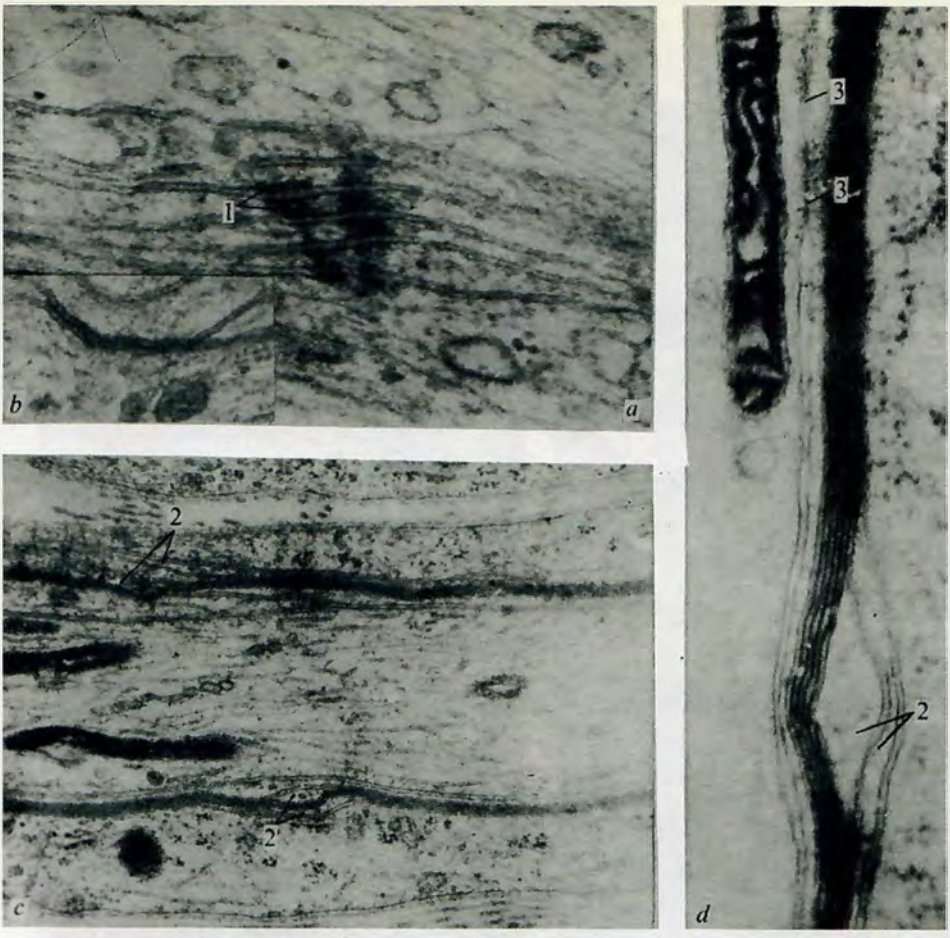
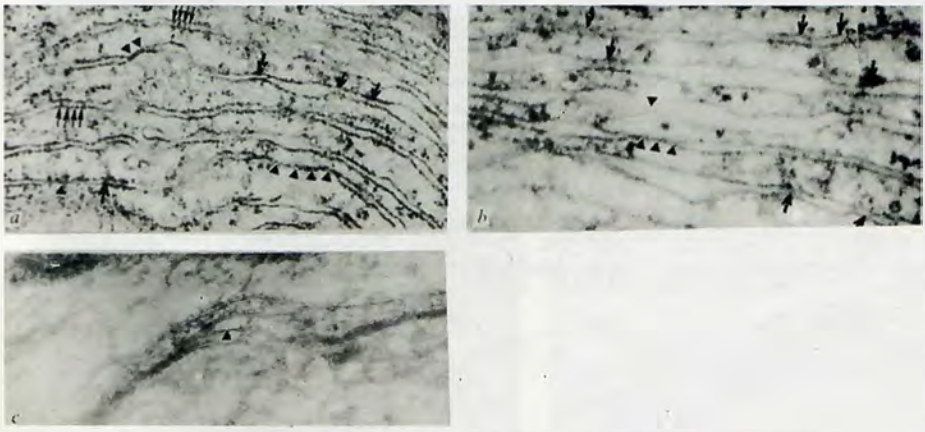


Fig. 1. Initial period of myelination (2 to 4-day-old animals)

a — serial desmosome-like structures (1) in 6-layer glial non-myelin sheath; *b* — local "inside-out" junction glio-glial junction; *c* — beginning of myelination, cleft formation (2); *d* — axonal-glial junctions (3) and a developing cleft; *a b d* — × 40 000; *c* — × 16 000

Fig. 2. Formation of junctions between lemmocyte membrane outer surfaces

a — adhesion aggregates and developing continuous junctions (thick arrows); *b* — septate junctions (fine arrows) and tight junctions (trangles); *c* — tight junction in the zone of a developing cleft; *a, b* — x 40 000; *c* — × 18 000



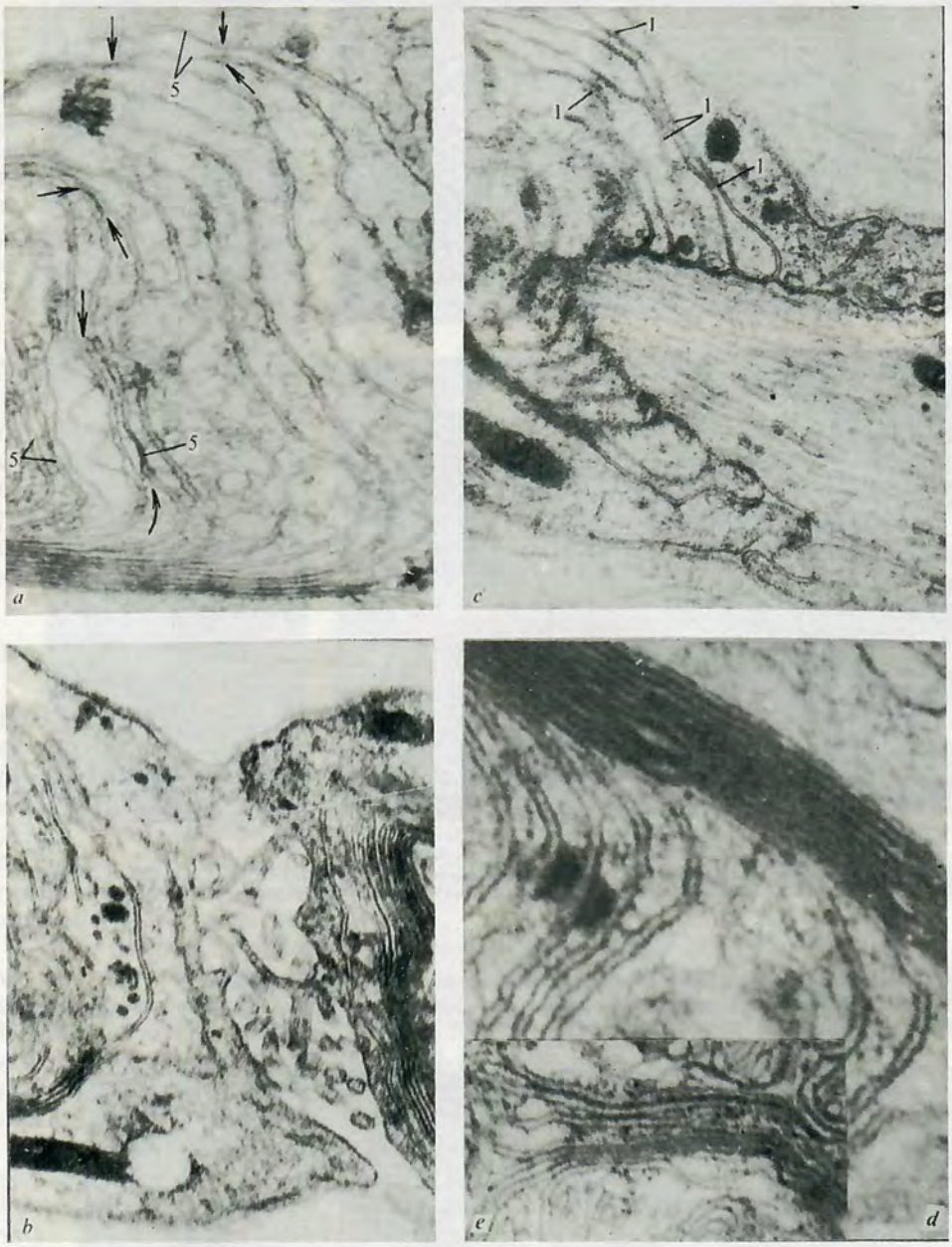


Fig. 3. Junctions of outer and inner glial membrane surfaces ("inside-out" junctions) in the zone of Ranvier nodes

a, b "inside-out" junctions (long arrows); *c* continuous junctions (1); *d* septate junction passing into "inside-out" desmosomal-like junctions; *e* serial "inside-out" tight junctions (5); 6 lemmocyte plasma; *a, e* × 40 000; *b, c* × 20 000; *d* × 60 000

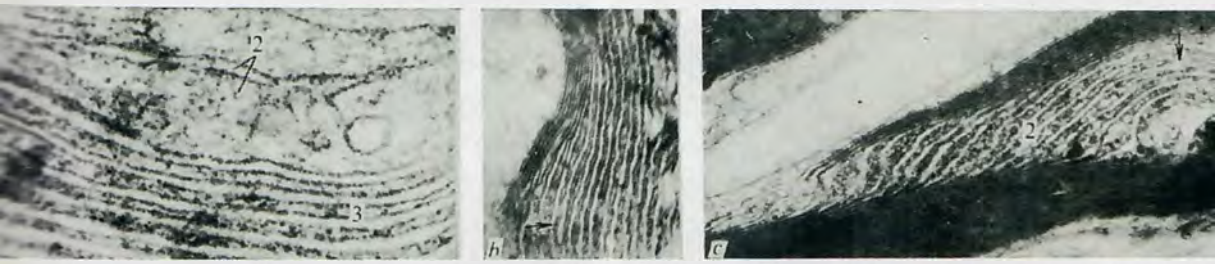
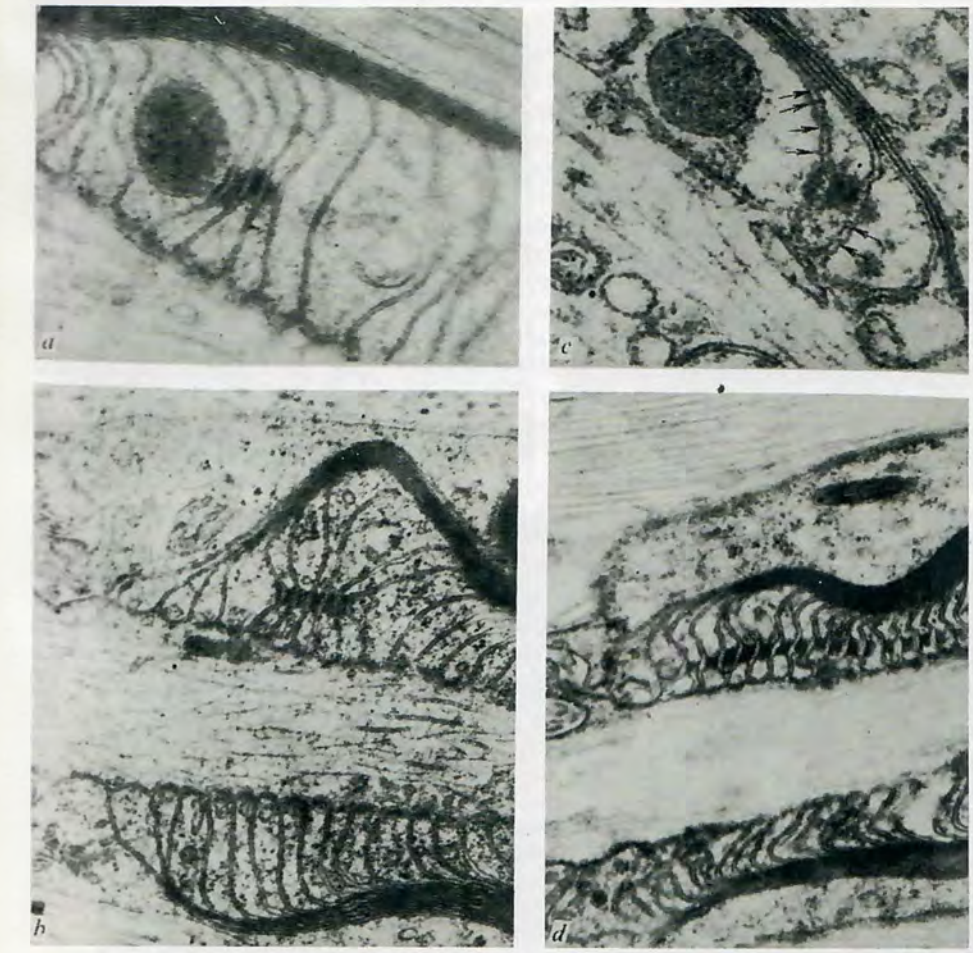


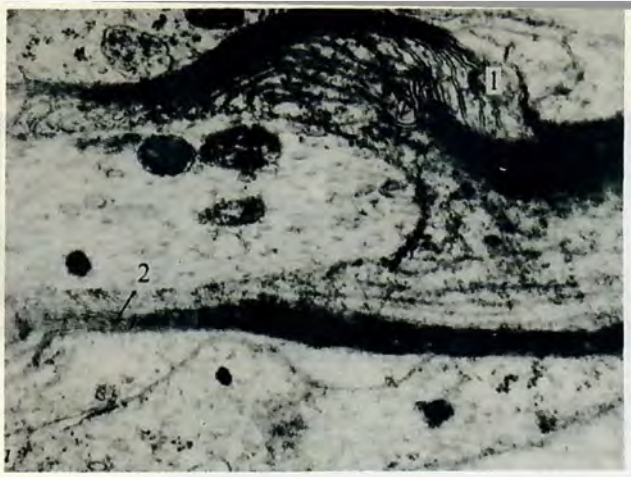
Fig. 5. Sites of membrane premyelin organization (arrows)

a — second (2) and third (3) types of glial layer organization; *b* — premyelin formation in paranodal zone; *c* — formation of premyelin (serial "inside-out" continuos junctions) in the zone of clefts; *a* — × 48 000, *b*, *c* — × 36 000

Fig. 6. Serial desmosomal junctions

a, *b* — retractive activity of serial junction submembrane aggregates; *c* — stick-like junction structures participating in membrane "zip-fastening" (arrows); *d* — serial junction as indication of long-ran — local membrane interactions; *a* — 48 000; *b*, *d* — × 18 000; *c* — × 60 000





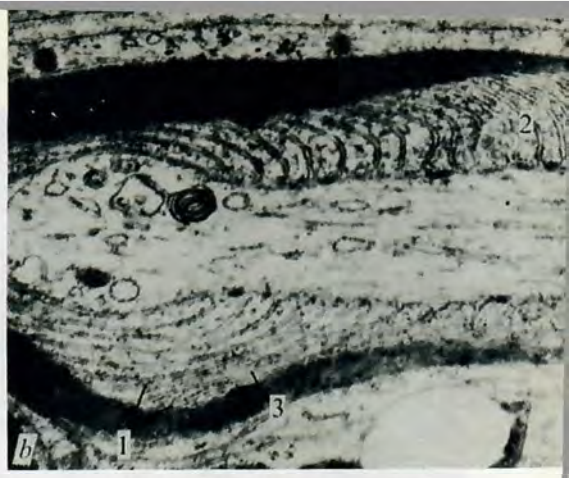
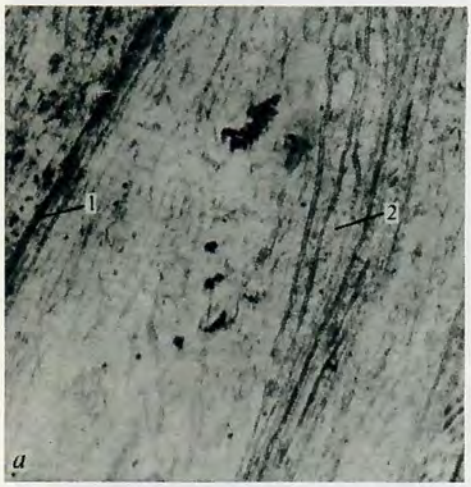
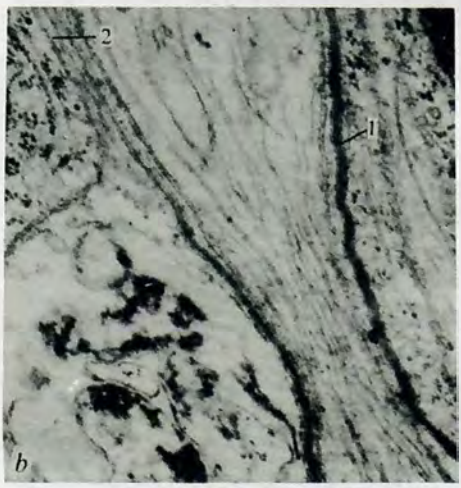


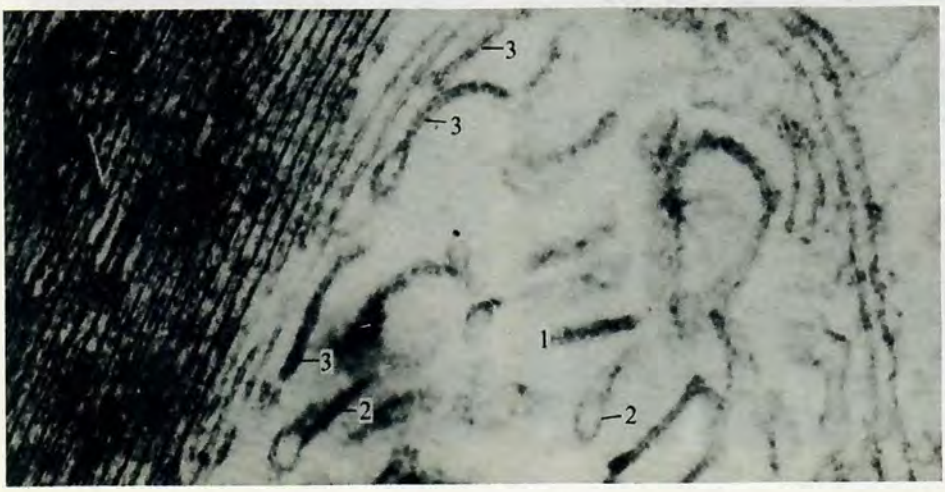
Fig. 7. Different types (*a*, *b*) of unusual structures (cleft-nodes) in developing myelin
1 — developing cleft; 2 — developing node; 3 — developing membrane junctions. × 16000

Fig. 8. Asymmetry in main dense line formation (*a*, *b*)
1 — main dense lines of developing myelin; 2 — non-myelin areas

Fig. 9. Building in of stick-like (1) and racket-like (2) structures into compact myelin; 3 — main dense lines







the main dense lines. Thus, the intermediate dense line may be considered to be the result of fusion of the local membrane junctions, with the formation of one gigantic intercellular junction.

The other way of junction formation is fusion of membrane inner surfaces of one and the same glial tongue. We call these "inside-out" junctions (Fig. 1*b*, 3). The latter also include all types of junctions. "Inside-out" junctions of membranes appear early, when the axon is covered with only a few gliocyte cytoplasmic layers. Such layers are of varying thickness. At the sites of their narrowing, accumulations of aggregated electron dense material could be noticed. The higher the electron density of the material, the thinner is the layer and the closer the inner surfaces of two membranes of the same cytoplasmic layer. In this case, when the distance between gliolemma sheets drawn together reaches that of the intercellular gap, single submembrane aggregates unite, join the inner membrane surfaces together and form the sj pattern. In case the thickness of electron-dense cytoplasmic layer is less than the intercellular gap, we get a pattern not differing from gj. Finally, along the cytoplasmic processes of lemmocyte there are areas where complete membrane fusion takes place with the formation of tj-like structures. The only morphologic feature of these membrane junctions, as compared to ordinary intercellular ones, is that they are not formed by the outer but by the inner surfaces of the same cell. Many intermediate junction forms could be observed. The fusion of these junctions is actually equivalent to formation of the main dense line. Thus, the main dense line formation could be pictured as a mosaic process of appearing and fusing together of a great number of "inside-out" junctions finally forming a single gigantic membrane junction.

On the basis of these data compact myelin could be supposed to be formed not only as a result of continuous Schwann wound membrane fusion as it is usually considered, but also by discontinuous mosaic-like formation and fusion of local membrane junctions. In this case the myelin sheath could be visualized as a model of a gigantic complex autojunction of the gliocyte membrane (Fig. 4).

Extended "inside-out" junctions (main dense lines) may form, topographically and in time, independently of the junctions formed by the membrane outer surfaces (intermediate dense lines). Frequently enough, however, one can notice bounded areas with distinct topical interrelations between several gliocyte membranes and the formation of local serial junctions of both kinds, the number of which increases not longitudinally but radially, transverse to the fibre axis. The formation of serial (multi-storey) junctions was found to be due to a certain type of gliocyte layer organization.

Four types of lemmocyte layer (tongue) organization, following one another in sequence, can be singled out. The first type is chartacterized by loose irregular winding of gliocyte layers around a neurite (Fig. 2*b*). The layers vary in thickness and spacing. The outer layers display it more vividly. Thus, it can be supposed that in many cases true intercellular gaps have not yet formed. Single short glio-glial junctions appear. This primary type of gliocyte tongue organization was encountered by us at all stages of myelination investigated.

The second type of glial layers organization is characterized by the formation of a stereotyped intercellular gap (Fig. 1 *a*), i. e. stabilization of distances between the outer surfaces of gliocyte outer cellular membranes occurs. At the same time, some thinning out of cytoplasmic layers of the sheath was noticed, though their thickness may remain relatively irregular. This type of layer organization is accompanied by the formation of numerous outer and inner junctions.

The third type (Fig. 5) is characterized by unification of glial layer thickness. Crystal-like membranes are formed, which are not yet myelin. The important

feature of this type of organization is that the thickness of these cytoplasmic layers becomes equal to the width of intercellular gap. The intermembrane distance is equalled and stabilized not only between gliolemma outer surfaces, which was characteristic for the previous type, but the intermembrane distance between the inner surfaces of gliocyte membranes equalizes and reaches its critical level. This strictly geometrical type of gliocyte layers could by termed premyelin. Actually, premyelin sites are serial membrane junctions looking like single continuous or septate junctions (Fig. 2 *b*).

Two other general regularities have attracted our attention. First, the types of gliocyte layer organization mentioned are in no way developing simultaneously in different fibres. Second, they do not appear simultaneously along one fibre either. So the area occupied by each type of organization is usually limited, while different patterns of glial layer organitzation could be seen along one fibre (Fig. 5). Sites of true myelin formation in single fibres are also characterized by considerable time-straggling and restricted area.

The restriction of original premyelin site areas, as well as strict geometrical regularity in relative position of inner and outer surfaces of the membranes make it possible to suppose that among the myelination mechanisms an important place belongs not only to general cellular processes but also to local physico-chemical mechanisms of molecular interactions of membranes drawn together. It is well known that at the basis of intercellular junction formation there is an increase in adhesive property of conformly changed membrane protein macromolecules of increased hydrophoby [24]. Formation of serial membrane junctions shows the long-range and cooperative nature of the reaction of submembrane cytoplasmic, transmembrane and extracellular proteins of the intercellular gap.

It is in the loci of glial winding having a crystal-like premyelin type of organization that mass cooperative formation of gap and dense membrane junctions begins, accompanied by membrane convergence and fusion of the membrane inner and outer surfaces. However, it should be noted that serial junctions can be formed not only on the basis of premyelin organization but also when the 2nd and 1st types of glial layer organization are present. In the latter cese, more frequently junctions of serial desmosome type are formed (Fig. 1, 3 *d*). They are usually seen at later stages in the zone of nodes and clefts (Fig. 6). Three features characterize the serial desmosome junctions. First, the inner layers of plasmolemma sites are usually connected by large aggregates of electron-dense material (membrane "inside-out" junctions). Second, the width of gliocyte tongue is narrowed here as a result of aggregated material retraction. Third, the intercellular gaps are locally broadened, adjacent membranes are stretched out in different directions by retracting aggregates of glioplasm. Local discrete formation of dense myelin lines is substantiated by the presence of specific structures, cleft-nodes, characteristic only of the developing myelin sheath (Fig. 7). These are complex non-differentiated structures consisting of broad lemmocyte tongues, some of which are narrowed and form membrane junctions (dense lines) on some area limited in length. A pack of serial membrane junctions is formed out of these single long junctions, which partially divides the primary complex structure into a node and a cleft. The other part of the lemmocyte tongues, however, remains broad and connects the zone of paranode and cleft (Fig. 4 *e*). The only way to completely divide the myelin sheath structures is formation of new local membrane junctions between them. Gradual narrowing of the lemmocyte tongue causes the inner gliocyte surfaces to draw together and form a local "inside-out" junction. Then, this junction elongates and "zips in" the

tongue space occupied by glioplasma like a zip-fastener, turning into the main dense line and separating cleft structure from node. The junctions thus formed supplement the pack of serial junctions in the zone of maximum thickness of the latter. Such processes contradict the existing notion of a gradual nondiscrete process of squeezing the glioplasma out of the spiral glial tongues during mesaxon rotation.

Heterogeneity and time straggling in the formation of local sites (main dense lines) are responsible for some unusual patterns of myelin fibres. Thus, at the beginning of myelination some asymmetry in the arrangement of myelin main dense lines on longitudinal sections is often observed, when there is a well-formed compact myelin of one side of the axon, and on the other side the axon is still covered with a few layers of gliocyte cytoplasm which have no formed dense lines (Fig. 8), or contain only single local "inside-out" junctions. Even the fibres with distinct myelination reveal this asymmetry by one-sided arrangement of clefts (there is compact myelin on one side of the axon, while on the other side there are islands of glioplasma deprived of any dense lines).

Common membrane and "inside-out" junctions are constantly found in relatively well-formed nervous fibres with developed myelin in the region of Ranvier nodes, i. e. in the zone of continuing myelination (Fig. 3, 4 *e*). It is known that in the process of development nodes appear early and simultaneously with the commencement of myelin maturing [2, 17]. In our studies Ranvier nodes were registered in two-day-old animals. Paranodal loops of developing nodes are of considerable length and are like the cytoplasmic layers of a premyelin fibre glia cell. At this point, besides fusion of single membrane junctions, the main dense line formation takes place also by "sewing" the membranes together, just like "zip-fastening", at the edge of compact myelin (Fig. 6 *c*). This leads to gradual elongation of the compact myelin zone and simultaneous shortening of paranodal loops (Fig. 4 *c-e*). As a result, they acquire a rounder form and more uniform thickness, which is characteristic of mature nodes. This process is in synchronization with the formation of glio-neural junctions of paranodal loops and axial cylinder (Fig. 3 *c*, 4 *d*), which are likely to be those highly permeable sites through which low-molecular premyelin substances penetrate from the axon into the glial cell.

Along with the appearance of Ranvier nodes, Schmidt-Lantermann clefts are formed. First, several very long gliocyte cytoplasmic islands of irregular thickness appear at the site of the future cleft (Fig. 1 *c, d*; 4 *f*; 5*c*). Their matrix contains ribosomes, assembled microtubules, transparent and granular vesicles and vacuoles of different size. Later, glio-glial intercellular junctions are found in the zone of developing clefts. Between the membranes of adjacent cytoplasmic islands desmosome-like substances can be found. Glio-glial junctions of gj and tj type are of great importance in the formation of a mature cleft junction. These junctions are formed at the periphery of cytoplasmic islands of the cleft, where glial processes are thinning out or intercellular gaps are narrowed. Subsequently, these junctions fuse with one another, the extent of compact myelin being increased and the length of cytoplasmic islands diminishing respectively. The analysis of such patterns allowed us to suppose that the Schmidt-Lantermann clefts are formed as a result of intermembrane junction fusion and irregular "sewing together" ("zip-fastening") of the membranes along the main dense lines (Fig. 4 *f*).

Thus, different sections of the myelin sheath develop on the same principle — formation of an intermembrane junction system. In our opinion, the data obtained make it possible to render concrete the existing notion of myelination at the expense of gliolemma resources.

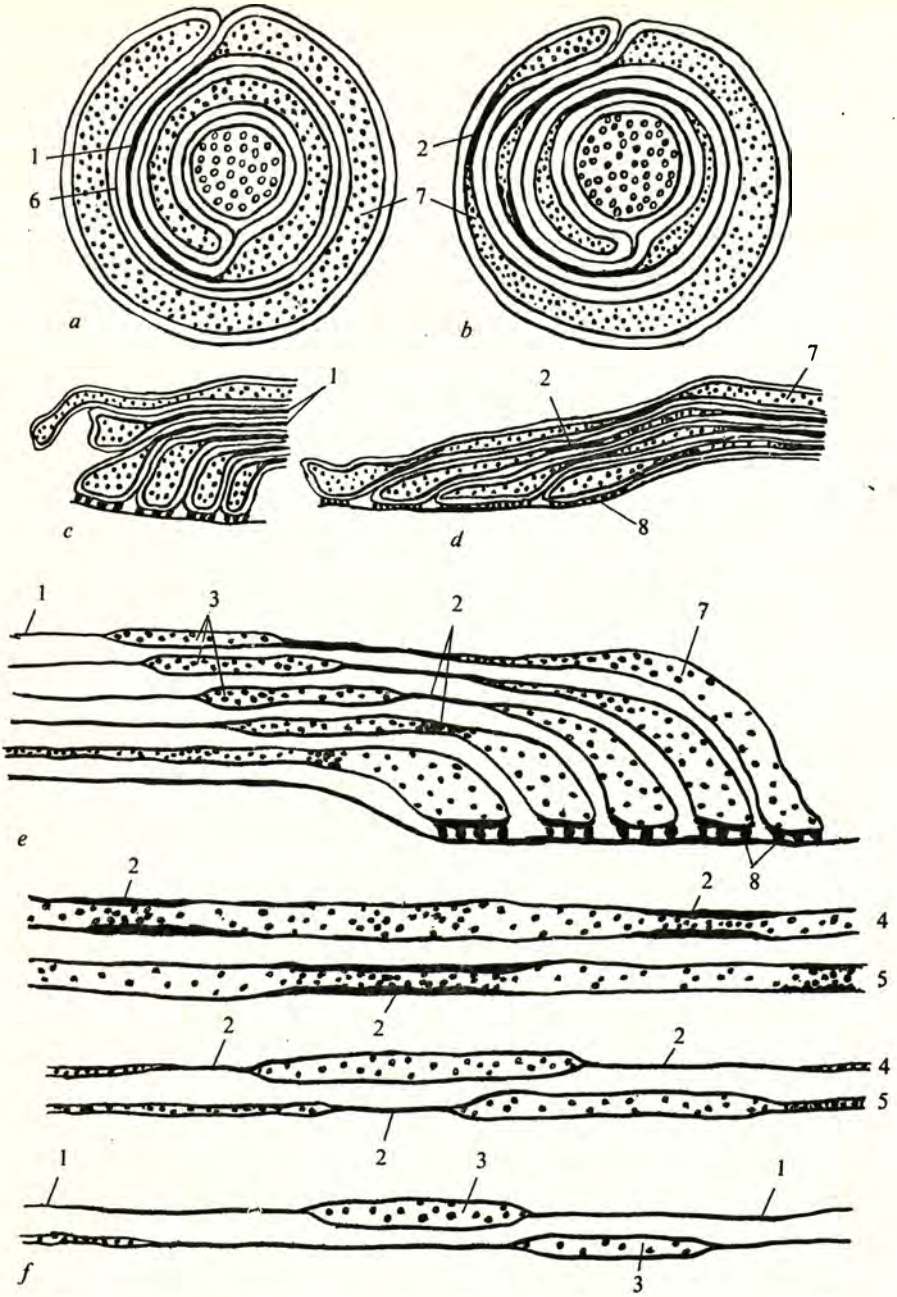


Fig. 4. Diagrammatic representation of dense line and myelin structure formation

a — conventional concept of indiscrete formation of myelin continuous dense lines; *b* — diagram generalizing the data on discrete formation of main dense lines (1) by means of local "inside-out" junction fusion (2); *c* — diagram of compact myelin in a developed node; *d* — diagram of junctions-forming myelin in a developing node; *e* — cleft-node structure in a developing myelin sheath; *f* — diagram of formation of cytoplasmic islands (3) of clefts and main dense lines by two gliocyte flat layers (4, 5); 6 — intermediate dense lines; 7 — lemmocyte plasma; 8 — axonal-glial junctions

However, at the stage of active myelination (5th-7th day of development) patterns were observed that suggest a different process of myelin formation. The supposition of exact conformity of the number of myelin lamellae along the whole length of the myelin segment remains one of the unsubstantiated morphological aspects of myelination. The hypothesis of lemmocyte or mesaxon revolving around the axon demands such conformity. At the same time, while examining rat myelination, we observed patterns which testify the possibility of local self-assembly of myelin-like membrane structures in immediate proximity to myelin and their building into myelin in the internodal segment zone.

This process can be observed in the central zones of a myelin segment, at some distance from nodes and clefts. Glioplasma's inner layer invaginations into the axon that are often observed in this region, are abundant in vacuole-like structures which flatten, while the inner surfaces of their membrane are drawn together, forming something like a tight "inside-out" junction (Fig. 9). As a result, stick-like or racket-like membrane structures with developed basis are formed and approach with their main lines the compact myelin at a distance equal to the width of intercellular gap and gradually build into it from within. Such pictures were regularly observed in the 5 to 7-day-old animals, i.e. during the most active growth of the myelin sheath thickness. In all probability, at this stage of development the process of myelin sheath thickening may occur by way of membrane structures building into it on the principle of self-assembly. Such observations were not infrequent. Some researchers have also described the phenomenon of membrane structure formation in glial cell cytoplasma, which build into the myelin sheath [20, 23]. It should be pointed out that the process of self-assembly of lipid membrane structures (myelin blocks) was observed in our investigations only in the zone of glioplasma's inner layer located near the axolemma. This fact possibly suggests a high concentration of lipid components in this zone and their transportation from axoplasma through membranes.

The processes of interactions of both membrane surfaces observed in our research possibly suggest that during the studied period of nerve fibre development the degree of gliocyte membrane adhesion increases, which is manifested by the formation of membrane junctions and their fusion. According to the widely recognized concept of the mechanism of myelination, the essence of the process is in mesaxon elongation accompanied by the increase in the number of turns (in winding) and in lemmocyte concentric layers drawing together. Myelination starts near the site where mesaxon originates and spreads out gradually and unifirmly along the entire helix of a gliocyte tongue [18, 19].

It is possible for non-myelin nervous fibres to form local membrane junctions between the turns of glial winding. This ability had been demonstrated long before the notion of frequent occurrence of membrane junctions in the nervous system was developed [17]. The author observed the formation of a patchy (mosaic) pattern due to glial membrane adhesion, accompanied by filling up of the intercellular gap under the action of a stimulating hypotonic medium. At present glial membrane junctions are well-known [15]. Electrotonic interrelation between glial cells was also described [18]. The phenomenon of gliocyte membrane adhesion was described also in the zone of myelin fibres mesaxon [9]. A difference in local adhesive properties of glial membranes of myelin lamellae in some mutant and normal mice was discovered, when attempts were made to segregate the myelin intermediate and main dense lines [12]. The attention of researchers was drawn to the great heterogeneity and time straggling of the process of segregation. They also found out that after this clearly marked dense-line segregation there are still non-segregated serial sites in myelin, propagating

radially towards the lamellae groups (radial myelin component). In the figures presented by the authors these remaining non-segregated dense lines loci do not differ at all from the serial membrane junctions described above, which demonstrate the cooperative and long-range nature of adhesive membrane processes.

The data obtained by us on heterogeneity and time straggling of myelin dense line formation on the basis of membrane junctions seem to be in conformity with the data presented in literature.

While considering the main and intermediate dense lines as gigantic intercellular junctions, it is extremely important to discuss the gliocyte adhesive membrane proteins participating in the formation of these junctions. There are the same antigens as in myelin on the outer and inner side of gliocyte membrane. They appear in gliocyte at different stages of its differentiation and then remain in myelin [11]. The intermediate dense line is shown to contain proteolipid protein (PLP). The latter is a highly hydrophobic macromolecule which has components released by membranes [6, 21]. These features make it possible to suggest that PLP may take part in providing the membrane outer surface protein adhesion. A second component in this process might be high-molecular Wolfgram — a protein which can also be located in the intermediate dense lines [18].

The princinpal protein of the main dense lines is myelin basic protein (MBP). The main dense lines do not form in mutant mice in the absence of MBP [5]. This suggests that MBP may participate in the membrane inner surface protein adhesion provision, i.e. in the formation of "inside-out" membrane junctions during myelination. The concept of myelination as a process of membrane junction formation allows us to consider this particular and highly specialized phenomenon from a wider biological stand. The general biological and evolutionary essence of this process is of considerable significance.

The importance of myelination for perfecting axon functions during phylogenetic and ontogenetic development is well known. Less attention is paid to the importance of this process for lemmocyte itself in the study of myelogenesis. Lemmocyte is known to be a unique cell. It is a matter of common knowledge that within one day the lemmocyte produces membranes to the weight which exceeds several times its own mass [13]. The consequences of this are very important. The formation of a multi-layer helix of exceedingly thin flat tongues leads to a considerable increase in gliocyte surface area (S) with relatively little change in its cytoplasmic volume (V). However, such increase in the relative surface area S/V is equivalent to a considerable decrease in the thermodynamic stability of the structure. From this follows, first, that the increase in the number of gliocyte cytoplasmic layers is apparently limited. Second, the structure of these glial processes must be highly unstable. This can actually be detected in experiments with homeostasis disturbance of isolated nerve fibre external medium [24]. How gliocyte "manages" to attain considerable stability of multi-layer thick fibre sheath is of great interest for many researchers [18]. It is known that in conditions of permanently varying external medium parameters single isolated cells find it difficult to keep up their integrity and the intracellular homeostasis of their inner contents. Structural stability of the system in multicellular aggregates in tissue culture or in multicellular organisms increases at the expense of decreased total cell surface area bordering on the external medium, i.e. at the expense of decreased S/V, and also in connection with the formation of intercellular junctions. It is only the formation of intercellular junctions that secures the organization and stability of multicellular associate and the formation of the system internal medium (intercellular gaps). Membrane junctions fill up

intercellular gaps and facilitate a partial segregation of the associate enternal medium from the external one. This also decreases the intensity of the external medium influence on live structures. The intercellular junctions integrating the cells mechanically and metabolically contribute to their increased total stability and increase the system's compensatory abilities. The response of cells acquires cooperative nature and long-range abilities [24].

It is this picture of membrane junction formation and gliocyte tongue aggregation that makes the basis of myelination. In connection with this, myelination might be supposed to be the necessary reactive compensatory process which helps to maintain the thermodynamic stability of gliocyte lamellae and preserve its integrity. A number of investigators also consider myelination to be a lemmocyte and oligodendrocyte response to a certain "signal" of the axon [1, 8, 10]. It is quite possible that the factor ("signal") causing this protective reaction — myelination — is a common initial bioelectric axon activity and the associated with it considerable changes in the medium homeostasis in axon-glial and glio-glial intercellular gaps. It has been previously shown that disturbances of intercellular space medium homeostasis connected with axon bioelectric activity lead to membrane junction formation [24]. Conformational restructuring of superficial proteins of the membranes proper, as well as of intercellular gap proteins is accompanied by their increased adhesive properties, gluing up and drawing together of adjacent membranes.

As regards myelination, it has also been shown that the axon signal is localized on the membrane surface and is associated with the external proteins as it can be removed by means of tripsin [1]. This feature has much in common with the factor causing axon electrophysiological action upon the glia [17] in non-myelin fibres. In this case the "signal" also comes from the axolemma surface and is also associated with protein as it can be removed by tripsin. The author's supposition is that such an effect can testify to the formation of axoglial membrane junctions. It has also been noted that for myelination to occur, components of extracellular matrix secreted by lemmocyte into the intercellular gap are necessary [1]. The important part of axoglial junctions in premyelin transfer has been repeatedly shown [7, 18].

Thus, the material presented supplements the traditional concepts of myelination with new data on the part played by the membrane junctions in this process. These data enable us to visualize the myelin sheath as a gigantic complex membrane junction. Its formation is probably of reactive nature and is directed towards increasing the thermodynamic stability of the differentiating neuro-lemmocyte structure.

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