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A HYPOTHESIS ON THE STRUCTURE OF THE BIOMEMBRANE LIPID BILAYER

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Abstract A novel biomembrane lipid bilayer imitation has been built, using new Tartu precision space-filling atomic-molecular models. According to this model, the membrane contains trimeric hexagonal-prismatic lipid units, which are bound to one another mostly through weak interactions between hydrocarbon chains, composing a dynamic honeycomb-like general structure. These units, having a cross-section area of 222 $Å^2$, consist of three peripherically placed molecules of fundamental lipids (two-tailed glycero- and sphingolipids) and centrally localized molecules of assistant lipids (sterols, hopanoids, carotinoids, terpenes, etc.) or ice-like water. The units are mostly held together by water bridges and electrostatic interactions between lipid polar groups as well as by van-der-Waals contacts between fundamental and assistant lipids.

It is generally accepted that the main structural component of biomembranes is a lipid bilayer formed by glycero- and sphingolipids having centrally localized apolar hydrocarbon tails and peripherically placed (oriented to the water) polar groups. There are many hypotheses on the biomembrane general structure, but the most popu-

lar one to-day is the fluid mosaic model[1], according to which the lipid bilayer is a sort of a "sea" of lipid molecules with floating "icebergs" of peripherical and integral proteins. This model proposed in 1972 is of considerable value in the explanation of diverse experimental data obtained in cell membrane investigations. Unfortunately, it doesn't provide any knowledge either on the exact spatial architecture of lipid molecular complexes or the reason for the asymmetric nature and large diversity of membrane lipids. The fluid mosaic model has not cast any light on the role played by the lipid bilayer in the processes of ionic permeability, bioenergetics and the transfer of nerve impulses. Nor is there any explanation for the contradictory situation: the chemically active polar groups theoretically ought to interact and fix lipids to one another but factually the latter are very mobile and have a high rate of lateral diffusion.

The aim of the present work was to elucidate the detail structure and exact role of the biomembrane lipid bilayer by means of molecular modelling. Under the supervision of the author of this paper new precision space-filling atomic-molecular models were elaborated in Tartu State University. Due to the extraordinary firmness of connectors and improved theoretical parameters the latter are highly suitable for the modelling of membrane lipids, proteins and other macromolecules[2,3]. Until now only a short paper on

biomembrane modelling with new Tartu models has been published[4].

On the basis of molecular modelling experiments it was demonstrated that according to the ability of complex formation all membrane lipids may be divided into two groups. The first one contains two-tailed* glycero- and sphingolipids. These molecules may be called f u n d a m e n t a l lipids, because owing to strong amphiphilic properties they have an ability to spontaneously form a lipid bilayer. The second group consists of sterols, hopanoids, carotinoids, terpenes, etc., which are cyclic or branched--chain neutral and weakly polar isoprenoid compounds. These molecules have a regulatory or modifying function and we call them a s s i s t a n t lipids. Our experiments with atomic-molecular models revealed that fundamental lipids must possess a very important property - the ability to form trimeric (trimolecular) cyclic complexes, which can include in their central parts molecules of assistant lipids or ice-like water (Fig. 1).

In the above-mentioned complexes three different region are formed: the polar, central and

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* At a glance, c a r d i o l i p i n , having four tails, seems to be an exception. However, actually this molecule represents a hybrid of two two-tailed glycerolipids - phosphatidylglycerins - and it will be thought that in the biomembranes cardiolipin plays almost the same role as two separate molecules of phosphatidylglycerin.

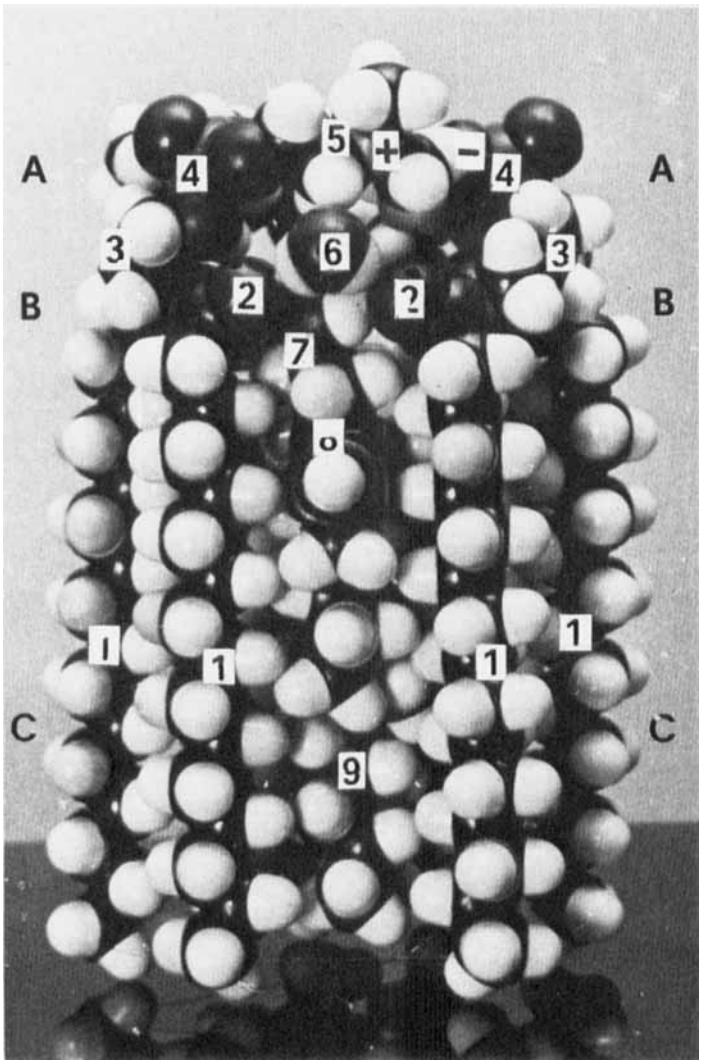

FIGURE 1. A side view of the new space-filling molecular model of trimeric hexagonal-prismatic lipid unit of a biomembrane. Two molecules of lecithin are demonstrated, which are bound to

each other in the polar zone by electrostatic interaction between phosphorylcholine groups and in the central zone by a water bridge between carbonylic oxygen atoms. In the central region of this model a molecule of cholesterol is placed, having a hydroxyl group which is hydrogen-bonded to the carbonylic oxygen atom of the lecithin molecule on the right. Symbols: A - polar zone, B - central zone, C - hydrocarbon zone, 1 - palmitoyl acid residue of lecithin, 2 - carbonylic oxygen atoms of the palmitoyl acid residue of lecithin, 3 - glycerol residues of lecithin, 4 - phosphate residues of lecithin, 5 - choline residue of lecithin, 6 - water bridge, 7 - 3β hydroxyl groups of cholesterol, 8 - - cholesterol corpus, including carbon atoms bound by double bonds, 9 - cholesterol tail, $\oplus$ - positively charged nitrogen atom of the choline residue, $\ominus$ - negatively charged oxygen atom of the phosphate residue.

hydrocarbon zones. In the p o l a r zone three head groups of fundamental lipids are placed. These groups are bound to one another by electrostatic interactions, hydrogen bonds and cationic or water bridges (Fig. 1-3). This zone also contains the largest amount of water molecules and ions of the lipid bilayer.

The c e n t r a l zone is formed by three glycerol residues or sphingosine head groups and also contains water and polar groups of assistant lipids, for example, 3β OH-groups of cholesterol (Fig. 1,4,5). Both water and hydroxyl groups are bound by hydrogen bonds to the carbonylic oxygen atoms of glycero- or sphingolipids. Some water molecules form single or double bridges between the neighbouring lipid

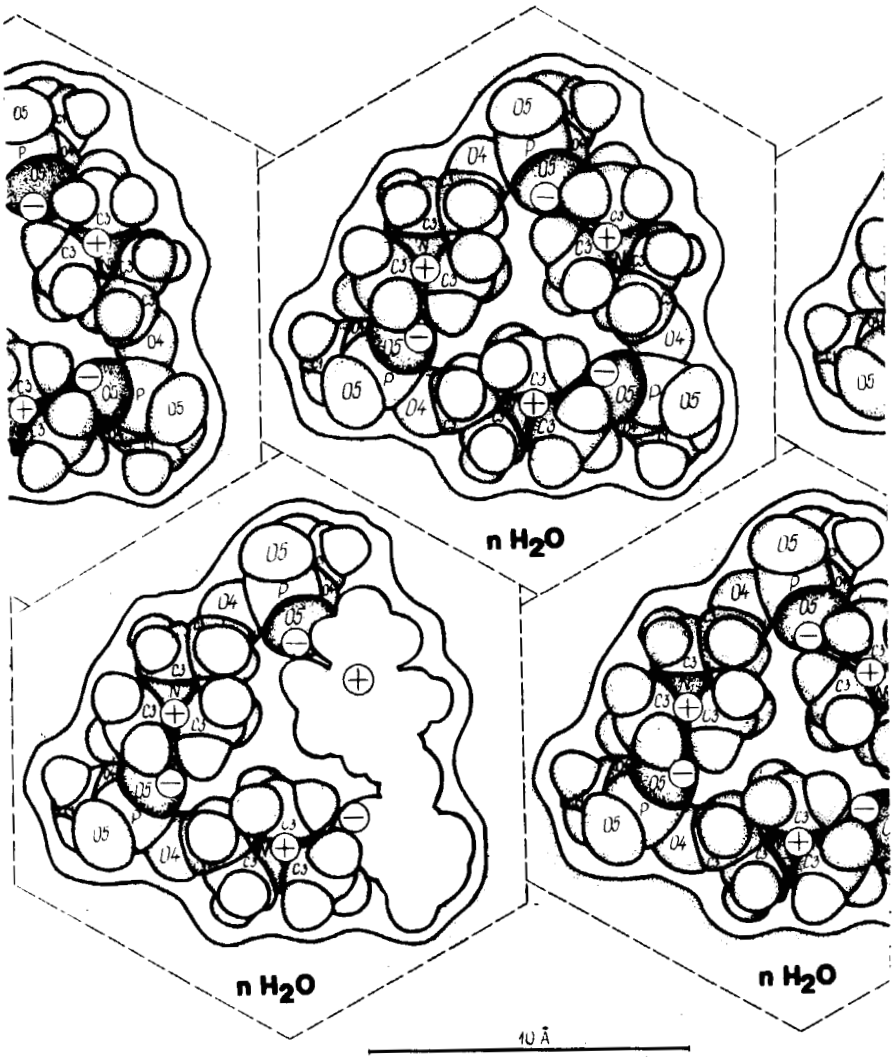

FIGURE 2. A cross-section (parallel to the biomembrane plane) of the lipid bilayer's p o l a r z o n e with closed polaropores (a detailed view), imitated by new molecular models. The trimeric hexagonal-prismatic lipid units are marked by dotted lines. The polar

groups - phosphorylcholine residues of three lecithin molecules - are within each unit like triangular cycles bound by electrostatic interactions between the negatively charged (-) oxygen atoms of the phosphate groups and the positively charged (+) nitrogen atoms of the ammonium groups. To facilitate the recognizing of the polar groups, one of them is represented as "empty" (with no inner structure). Symbols: nH_2O - water molecules, N - nitrogen atom of the ammonium group, C1 - carbon atom of the glycerol residue, C3 - carbon atom of the methyl group, P - phosphorus atom of the phosphate group, O4 and O5 - oxygen atoms of the same group.

molecules of the complex. These water bridges may be one of the most important factors in the forming of these lipid complexes.

In the peripherical part of the h y d r o c a r b o n zone 6 hydrocarbon chains (fatty acid or its aldehyde residues and sphingosine tail groups in eubacteria and eucaryotes, and phytanol residues in archaebacteria) are localized, which are bound to the central zone by ester, amide, ether or single -C-C- links (Fig. 1,6,7). The central part of this zone usually contains assistant lipids, for example the corpus and tail of the cholesterol molecules, having van-der-Waals contacts both to one another and to the neighbouring hydrocarbon chains. The planes, going through the cyclic parts of cholesterol molecules, cross in the center of the lipid complex at the angle 120°. The narrow lateral part of the corpus of the cholesterol molecule containing double bonds between 5 and 6 carbon atoms, has a peripherical localization - near

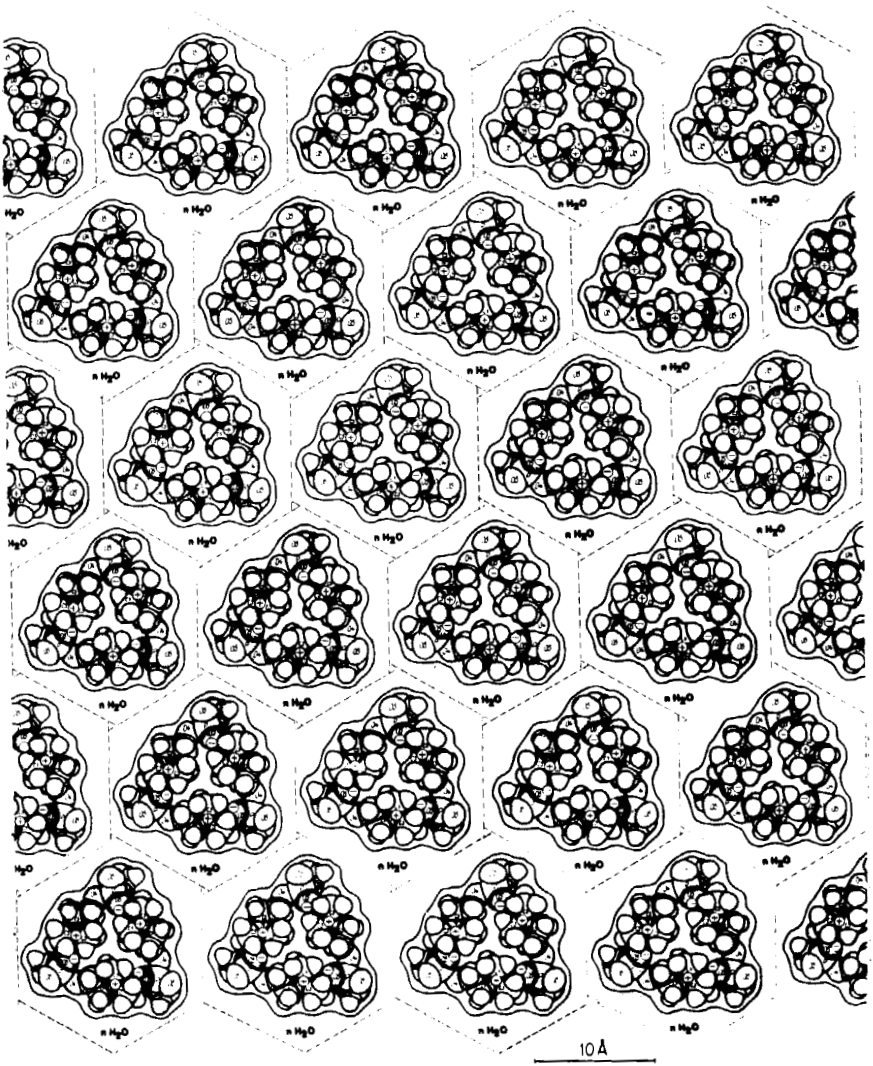

FIGURE 3. A cross-section of the lipid bilayer's polar zone with closed polaropores, a general view (cf.Fig. 2,8,9).

the interlipid water bridges. The wide lateral part of the cholesterol molecule, containing the angular methyl groups, is turned to the center of the lipid complex.

In some places ("the defect areas") of the biomembranes the hydrocarbon zone contains i c e - l i k e w a t e r structures instead of assistant lipids. The main elements of these structures are hexagons formed by 6 water molecules, bound to one another by hydrogen bonds in the form of 4-6 discs (in the lipid monolayer) or 8-12 discs (in the lipid bilayer). These water prisms or cylinders appear to be pieces of ice 1 having along the c-axis channels with the diameter of 3 Å, which are probably filled by free water molecules. These channels have been called "shafts"[5], however, we propose to use the term "s h a f t" to signify not the central channel alone, but the latter together with the surrounding sheet of water molecules, i.e. the whole ice-like structure included into the membrane lipid complex. The arising of ice-like structures in the membrane hydrocarbon zone can be facilitated by the negatively charged hydroperoxyl groups ROO^-, frequently formed under the influence of oxygen within the region of hydrocarbon chain double bond.

The t h i c k n e s s of lipid complex zones is different as it depends on the membrane's chemical composition, the average up-down strech of the polar zone being 5 Å, that of the central zone - 3 Å and that of the hydro-

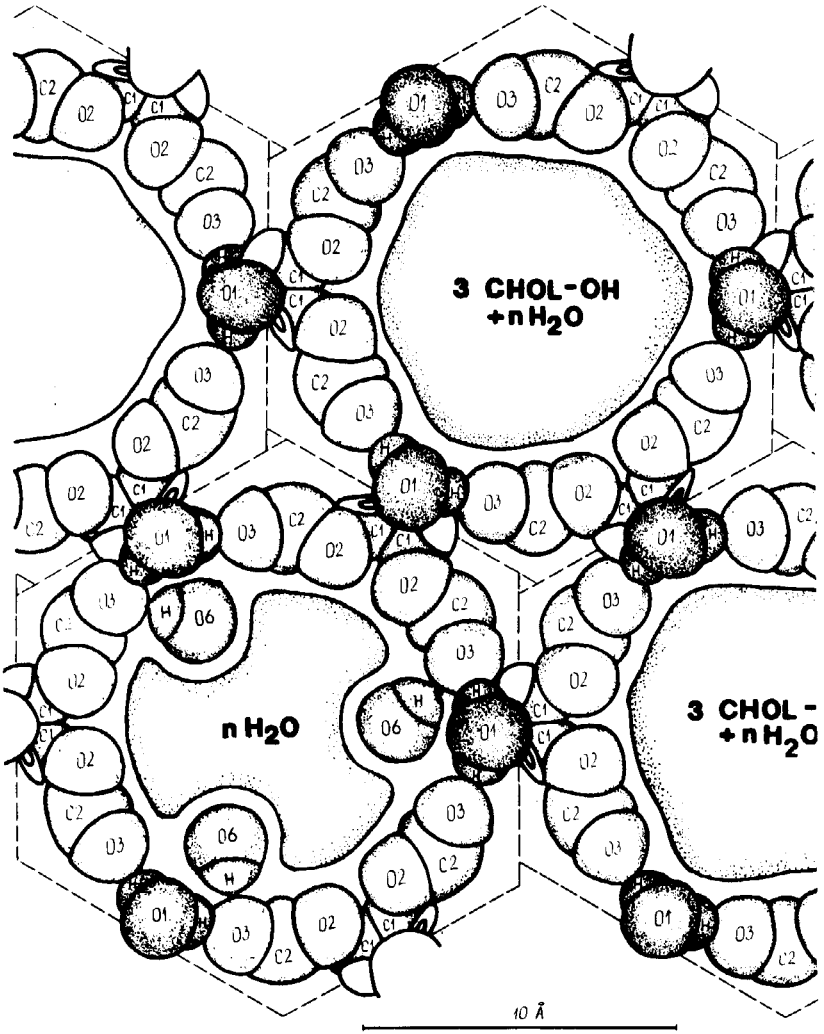

FIGURE 4. A cross-section of the central zone of biomembrane glycerolipid units (a detailed view). Symbols: 3CHOL-OH - hydroxyl groups of three cholesterol molecules (in a generalized form), H-O1-H - water bridge, O2 - oxygen atom in the ether link, O3 - carbonylic oxygen atoms of the fatty acid residues, O6-H - 3β hydroxyl

group of cholesterol which is hydrogen-bonded to the carbonylic oxygen atom, C2 - carbon atom of the carboxyl group of the fatty acid residue.

carbon zone - 20 Å. Thus, the thickness of the monolayer containing trimeric lipid units is generally 28 Å and that of the bilayer - 56 Å.

The cross-section of the lipid complex hydrocarbon zone has a form of a h e x a g o n , having in each corner an element of the hydrocarbon chains. The cross-sectional area of this hexagon is 222 $Å^2$. All the corners are 120°, but the sides are not equal: there are three short ones (8.5 Å), formed between the hydrocarbon chains of the same lipid molecule and three long ones (10.0 Å), formed between the chains of the neighbouring molecules.

According to the form of the hydrocarbon zone cross-section, the outer shape of the lipid complexes formed by three molecules of fundamental lipids with assistant lipids is hexagonal--prismatic. The area of the prism's faces correlates to the lengths of the cross-sectional hexagon's sides: there are respectively three larger and three smaller faces. Thus the lipid complexes may be called t r i m e r i c h e x a g o n a l - p r i s m a t i c units of the membrane lipid bilayer. Since usually the polar groups of lipids are bound to one another within the region of the same lipid unit only van-der-Waals interactions occur between different units. The best packing should follow, when

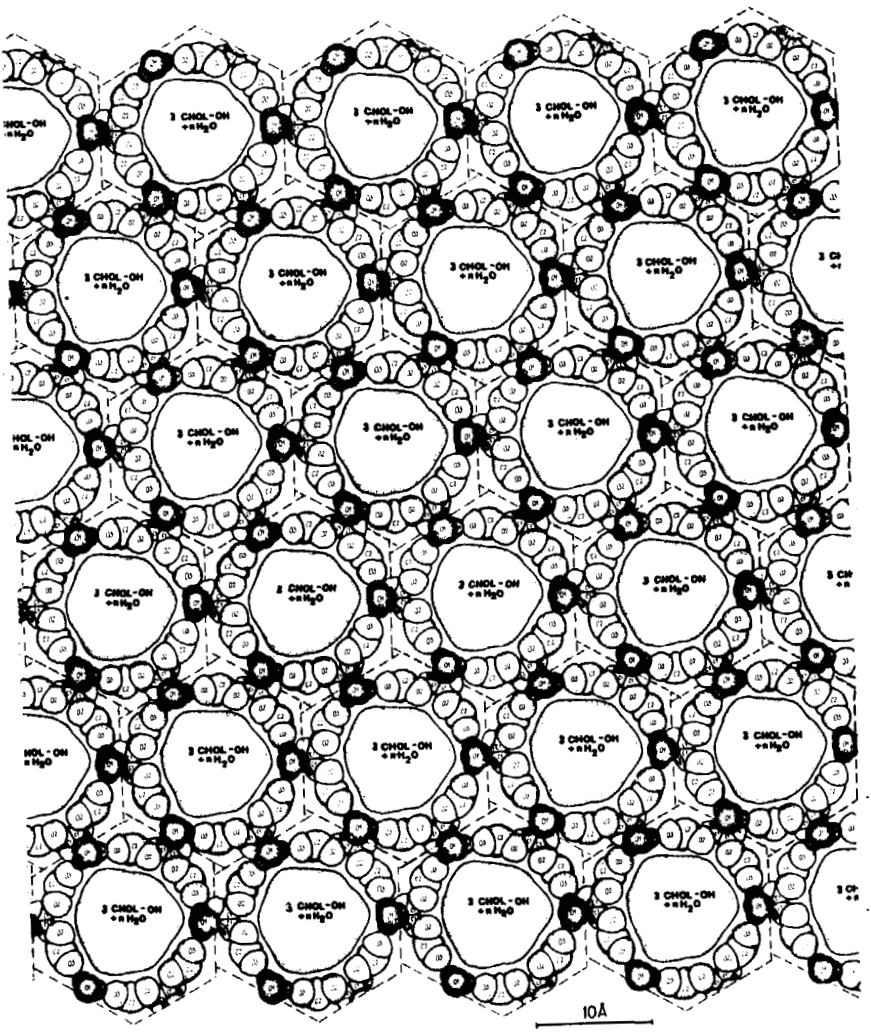

FIGURE 5. A cross-section of the c e n t r a l z o n e of biomembrane glycerolipid units, a general view (cf. Fig. 4).

a large face of one lipid complex is in contact with a small face of the other one and vice versa. This packing will, as a rule, be not disturbed, when a part of the lipid units is replaced by polypeptide chains or proteins. Therefore the structure of the lipid bilayer, containing trimeric hexagonal-prismatic units with the inclusion of proteins, may be called the honeycomb-like model of the biomembranes.

As concerns the functional role of the lipid complexes, the units, formed by combining fundamental and assistant lipids, prove to be relatively inert barrier - structural units of the biomembranes. But the lipid units including ice-like structures - shafts - , may function as lipid channels. Respective to the zones, the channels have polaro-, centro- and hydrocarbopores. The narrowest and most rigid part of the channel in the centropore having a diameter of about 10 Å. The head groups in the polar zone of lipid units may undergo considerable conformational rearrangements, and so they represent three-gate regulators opening or closing the polaropores (Fig. 2, 3,8-10). Polar groups of various lipids are bound to one another by different forces: in cholinolipids (lecithin, sphingomyelin, plasmalogen) they are electrostatic interactions, whereas in aminophosphatides (phosphatidylethanolamine and -serine) and glycolipids they are

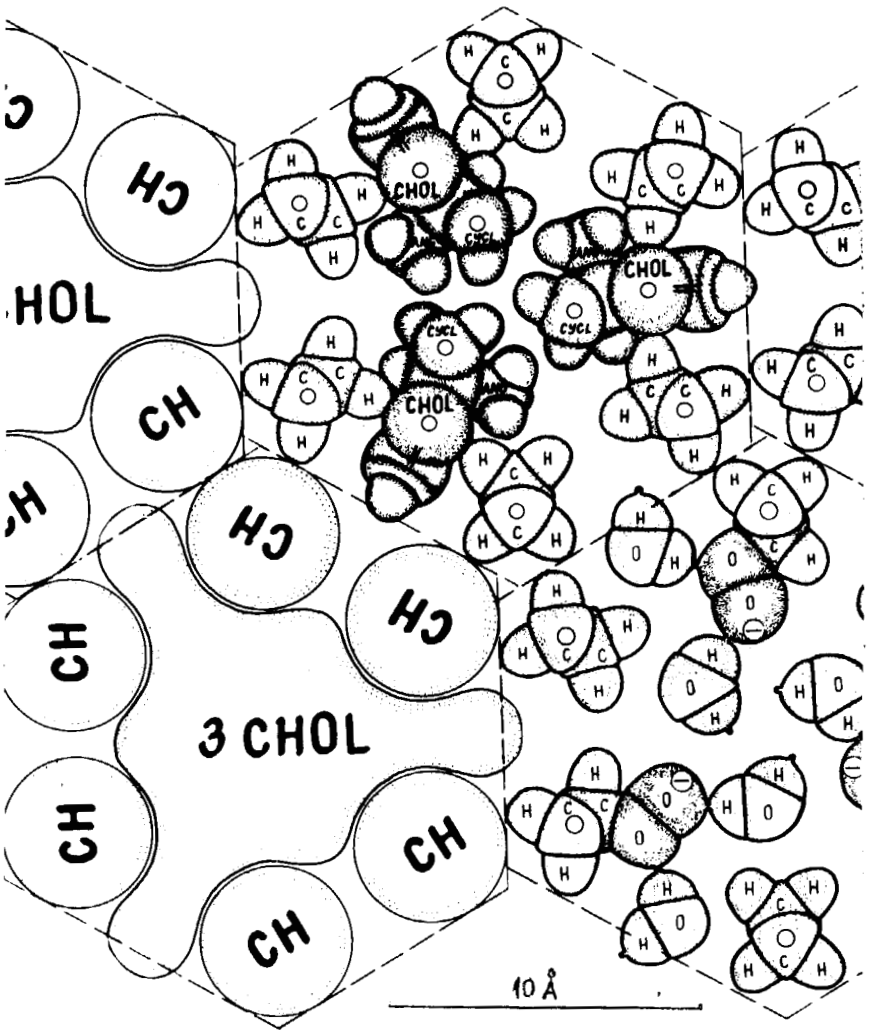

FIGURE 6. A cross-section of the hydrocarbon zone of the biomembrane's lipid units on the level of 5-6 carbon atoms bound by double bonds, a detailed view. Symbols: CH - saturated hydrocarbon chain, CHOL - - cholesterol, 3 CHOL - three molecules of cholesterol in a generalized form, ANG - side of cholesterol with angular methyl groups,

CYCL - side of cholesterol with atomic cycles, = - side of cholesterol with atoms bound by double bonds, HOH - water, COO^- -hydroperoxyl group bound to the hydrocarbon chain.

hydrogen bonds.

It is interesting to note that the polar groups of lipids can be bound to one another in most of the biomembrane regions not only in an intra- but also intercomplex way, i.e. within the regions between lipid units.These structures may be called i n t e r m e d i a l c o m - p l e x e s (Fig. 8,9,11). The intracomplex association of the polar groups can easily be transformed into the intercomplex one and vice versa. These transformations represent two different t r i g g e r s t a t e s of lipid bilayers. The cholinolipids are likely to perform these shifts most easily because the N^+- -atoms of choline residues can bind to the O^-- -atoms of phosphate residues by electrostatic interactions. The angle of the long axis rearrangement of phosphorylcholine residues on the plane of the lipid bilayer in case of trigger state transformations is nearly 50° (Fig.10,11).

The above-mentioned conformational changes of the lipid polar groups and corresponding transformations of the membrane trigger states are caused by various factors.Thus, when a positively charged "strange" molecule reacts (in a special receptor site) with the polar groups of cholinolipids, then the N^+ atomic groups of choline residues will be repulsed or O^- atomic

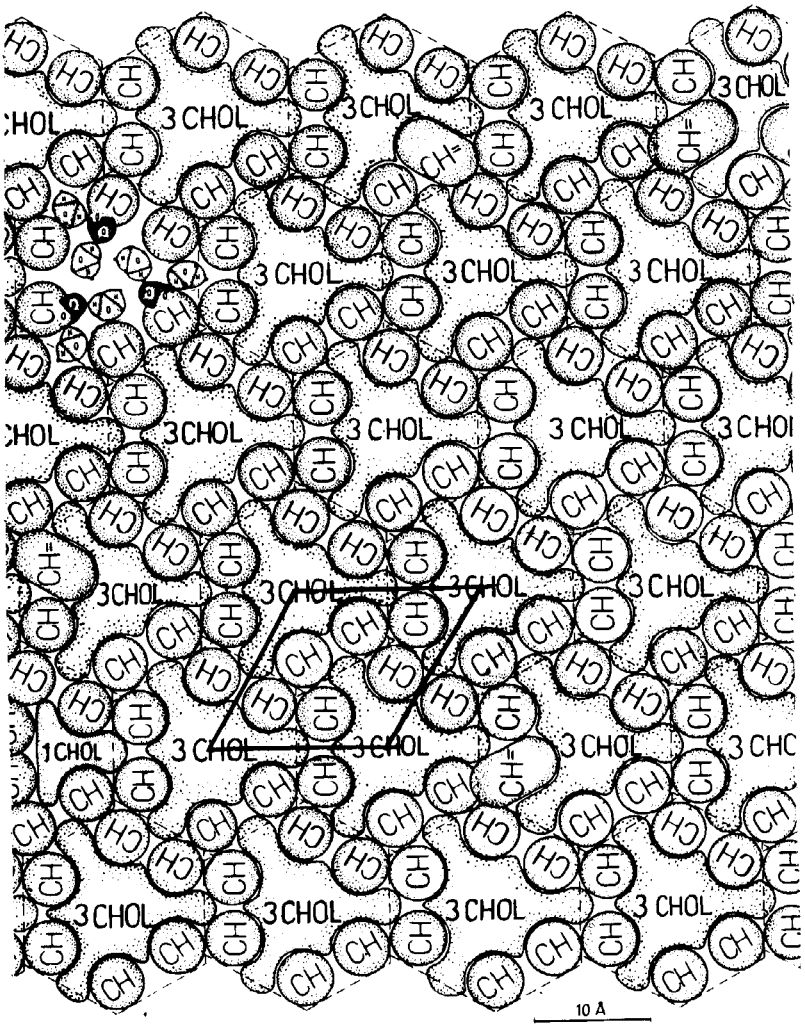

FIGURE 7. A cross-section of the hydrocarbon zone of the biomembrane's lipid units, a general view (cf. Fig. 6). The hexagonal packing of these units is marked by a rhomb. Symbol: CH= - unsaturated hydrocarbon chain.

groups of phosphate residues will be attracted (Fig. 12). The N^+ and O^- atoms of the phosphoryl-choline groups, changing their localization, then interact with the corresponding charged regions of the neighbouring lipid units, and short-living intermedial complexes of polar groups will be formed. Such a conformational shift of the lipid polar groups will quickly spread in several directions on the membrane plane.

It was shown that the molecular modelling with new space-filling models allowed to represent a d e t a i l e d m o d e l of the lipid structures in biomembranes. To our knowledge no work has yet been published, giving an exact picture of the biomembrane lipid structure. Franks[6] built a space-filling (CPK) model of the lipid bilayer, which was based on the experimental data about hydrated mixtures of lecithin and cholesterol. This model has many common points with the structure described in the present paper: a perpendicular ("palisade") orientation of the cholesterol molecules and hydrocarbon chains, the placing of the cholesterol hydroxyl group in the central zone and lecithin polar groups on the bilayer plane. But in this work lateral contacts between lipids were not modelled (probably because of some technical problems). In the article of Forslind and Kjellander[7] an interesting structure model for the membrane lipids was derived from the conformational properties of ice-like water. Unfortunately, the use of only skeletal models in this work did not allow exact

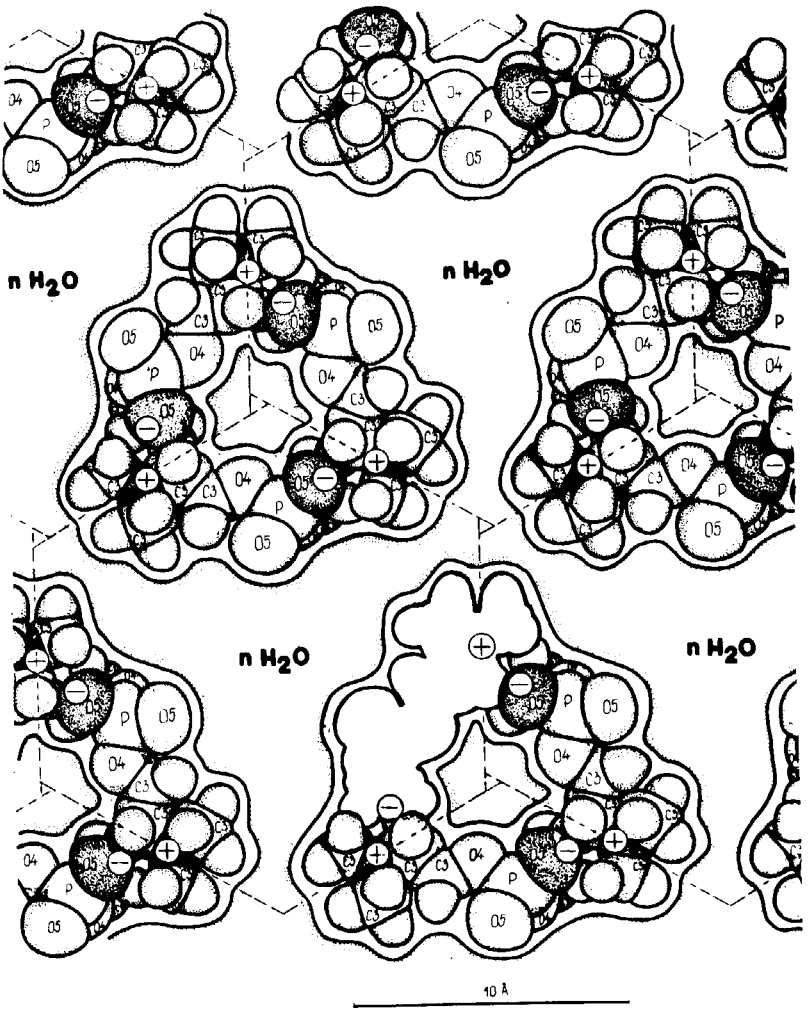

FIGURE 8. A cross-section of the biomembrane's polar zone with open p o l a r o p o r e s and closed intermedial complexes, a detailed view (cf. Fig. 2,3,9-11).

three-dimensional molecular modelling. In addition, it is not clear, why the lipid polar groups must preferably interact with water molecules but not with one another. Forslind and Kjellander[7] suppose that the cholesterol hydroxyl group makes a hydrogen bond to the phosphate oxygen atom, but the formation of this bond to the carbonyl oxygen atom is more likely, because the latter is closer to the hydrophobic zone where the main part of the cholesterol molecule localizes. Eventually, if indeed the polar groups of lipids are fixed in the ice-like structures, it is difficult to explain the high rate of lateral diffusion of membrane lipids. In the works of other authors the description of general membrane architecture is absent, although the localization of the lipid polar groups (dipols) in the membrane plane, the joining of the lipid molecules by water bridges and the tight packing of the phospolipids and cholesterol are given[8-13]. A conception of Singer and Nicolson[1] about the biomembrane structure and function is based on the experimental data about the mobility of lipid molecules, but these authors could not show, how a high rate of the l a t e r a l d i f f u s i o n is possible in the state of considerable reactivity of the polar groups to one another and water. The honeycomb-like membrane model reveals that the high rate of the lipid lateral diffusion is possible only in this case when polar groups interact with each other and water not diffusely but mosaicly and cycli-

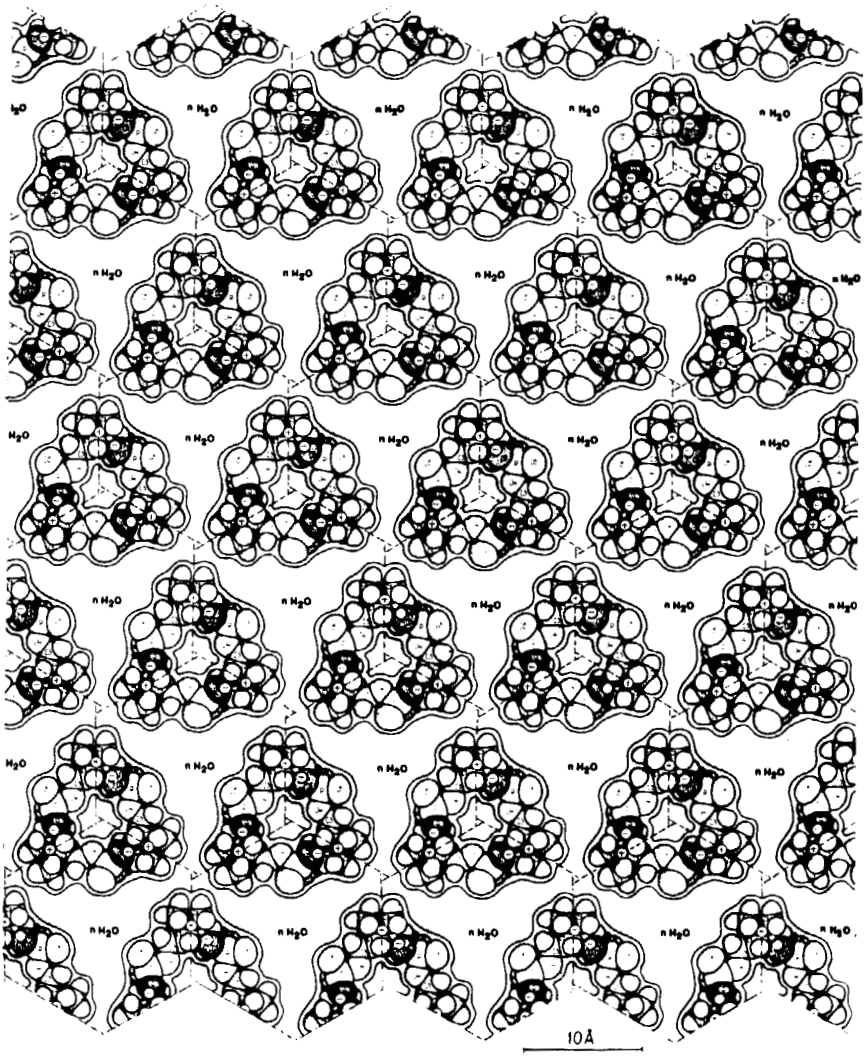

FIGURE 9. A cross-section of the biomembrane's polar zone with open p o l a r o p o r e s and closed intermedial complexes, a general view (cf. Fig. 2,3,8,10,11).

cally in separate trimeric lipid units. Then these units composed of glycerolipids will have only weak hydrophobic van-der-Waals contacts and therefore are characterized by great mobility. The rate of diffusion of lipid complexes will be higher, when the van-der-Waals interactions are looser, for example, when unsaturated fatty acids are included into the hydrocarbon zone. The mobility of the sphingolipid complexes is apparently lower because on the level of the central zone the units are bound by the network of the hydrogen bonds[14,15].

The honeycomb-like membrane model gives an explanation to the role of cholesterol and other assistant lipids in the bilayer: they serve as structural centers of the barrier lipid units. The new model also allows us to understand the well-known fact about the reducing influence of cholesterol on the cross-sectional area of lipids[8,16]. Indeed, the packing of molecules in the trimeric hexagonal-prismatic complexes is maximally tight: from the general area of lipid units 222 $Å^2$ each molecule of cholesterol occupies 37 $Å^2$ and hydrocarbon chain 18.5 $Å^2$.

The problems of lipid bilayer permeability may also be elucidated with the help of a honeycomb-like membrane model. Although it is widely known that the lipid part of the biomembrane is easily penetrated by water and small apolar molecules and in some cases also by ions, there is no reasonable idea about concrete

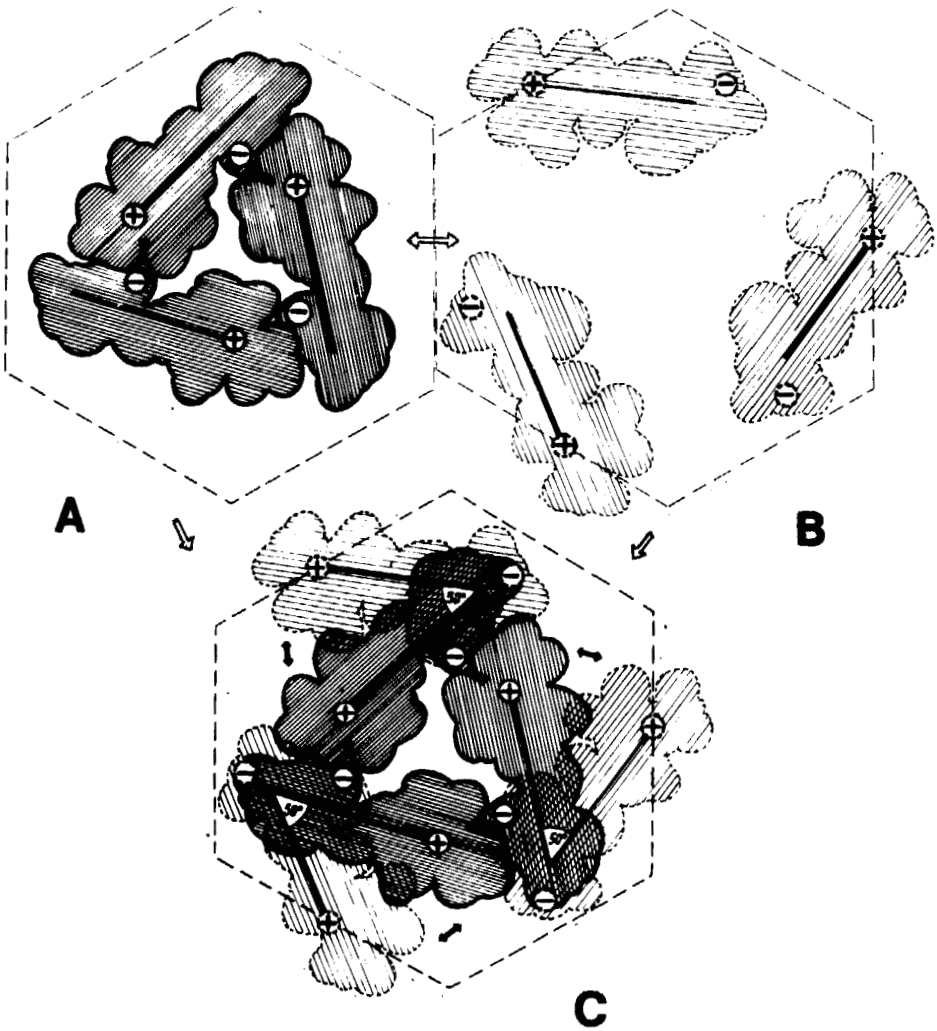

FIGURE 10. A p o l a r o p o r e . Symbols: A - open, B - closed, C - amplitude of shifts of the gate polar groups (50°).

lipid channels. Ivkov et al.[17,18] supposed that in the bilayer between clusters of lipid molecules "dynamic defects" occur (15-30 per cent of the total membrane area!), but the molecular architecture of these defects is not described. Only Hosur and Govil[19,20] as well as Govil and Hosur[21] have represented detailed descriptions of the molecular defects in the lipid bilayer structure, which may serve as ionic channels. However, from these works it is not clear, what the molecular mechanisms of the defect formation are and how the defects fit in the surrounding regular lipid structure. Some authors underline the importance of ice-like water in the biomembranes, but no concrete structures of this water and their contacts with lipids are described[7,22-24]. According to the new honeycomb-like membrane model it is apparent that each trimeric hexagonal-prismatic fundamental lipid unit may (in case of the absence of the assistant lipid core) serve as a channel. The diameter 10 Å of the centropore allows many small apolar compounds to move through the lipid channel. The excellent spatial fit of the water shaft to the center of the trimeric fundamental lipid complex resembles inverted clathrates and seemingly enables the relatively frequent occurrence of the ice-like defect structures. The central part of the water shafts represents a narrow microchannel with a diameter of about 3 Å, which is permeable for free water and other small molecules (oxygen, nitrogen, etc.). The chains of hydrogen-

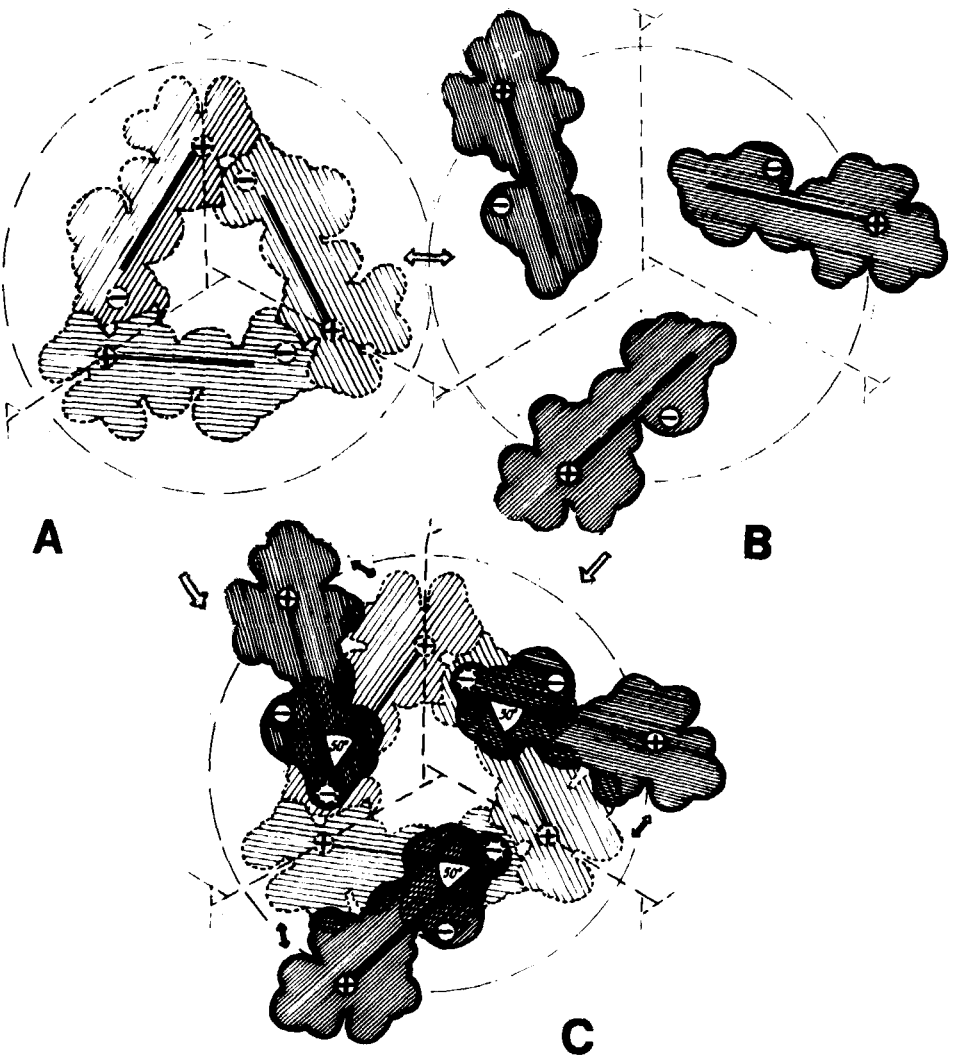

FIGURE 11. An intermedial complex. Symbols: A - closed, B - open, C - - amplitude of shifts of the gate polar groups (50°).

-bonded water molecules in shafts may serve as a p r o t o n c o n d u c t o r s y s t e m -- according to the mechanism, proposed by Eigen and De Maeyer[24,25]. This idea will be very useful for bioenergetics, because no ways of proton transport through the biomembranes have yet been identified. The ice-like defect structures may in some cases be used for penetration by other ions. Thus, for instance, the lipid units in which hydrocarbon chains bear hydroperoxyl groups ROO- may serve as cationic (especially calcium) channels[26,27].

The permeability of the lipid channels depends on the molecular composition of the membrane complexes, especially on the character of lipid head groups opening and closing the polaropores. Therefore, since the moving of molecules from the extracellular fluid towards the cell is different in comparison with that in the opposite direction, there must be differences of lipid structures between the membrane's inner and outer monolayer. Indeed, a l i p i d a s y m m e t r y in biomembranes was identtified. For example, it was shown that cholinolipids (lecithin, sphingomyelin) prevail in the outer lipid monolayer of the eucaryotic cells, and aminophosphatides (phosphatidylethanolamine and -serine) in the inner monolayer[28-33]. This may be so because the phosphorylcholine groups of the cholinophosphatides interact with one another only because of electrostatic forces, which are more sensitive for the regulation of the

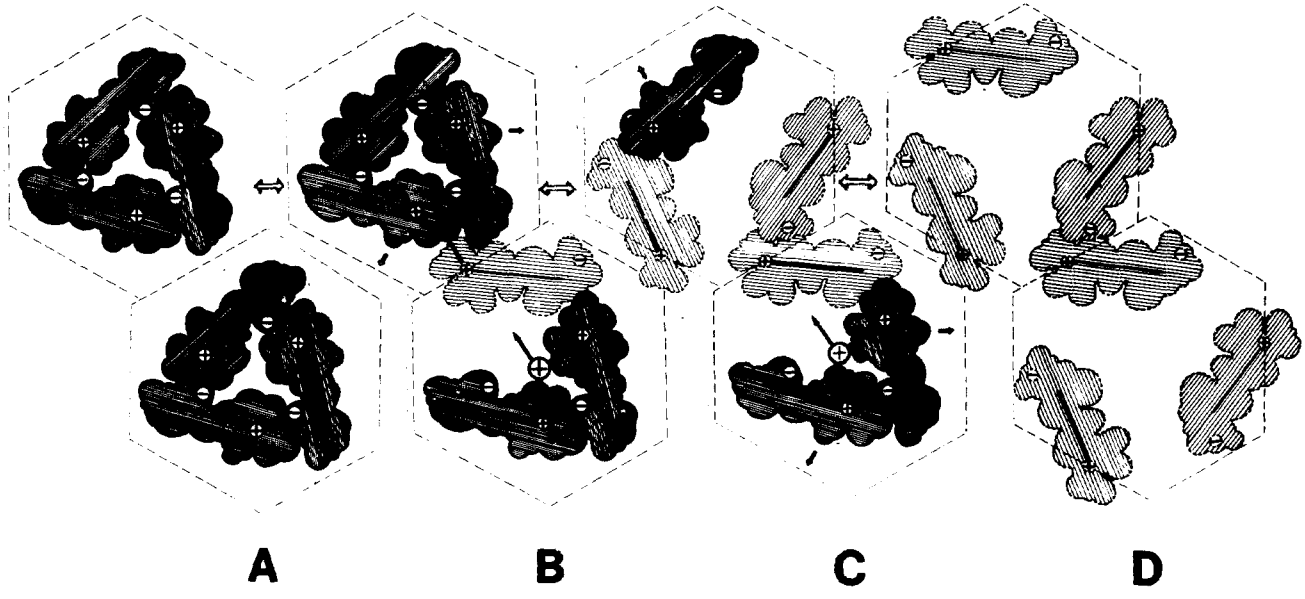

FIGURE 12. An induction of the co-operative o p e n i n g of the polaropores by exogenic factors (for example, by a neurogenic mediator). Symbols: A - closed polaropores (the first trigger state). B - shift of one polar group under the influence of mediator's (+) - charge (actually shifts of three groups occur simultaneously), C - induction of the opening of the neighbouring polaropore by one polar group, D - open polaropores (the second trigger state), inducing the formation of intermedial complexes (cf. Fig. 11).

metabolic exchange between the cell and the environment in comparison with the polar groups of aminophosphatides bound by more static and fixed hydrogen bonds. The preference of cholinolipids in the outer layer may be also due to their better barrier function, because they contain more residues of the saturated fatty acids and more easily complex with cholesterol[29,31,32].

The above-described conformational shifts of membrane lipid polar groups (especially of cholinolipids in the outer layer) may represent a basis for the molecular mechanism of the formation of n e r v e i m p u l s e s . It is shown that this process is accompanied by the shift of charged atomic group and ions[34,35]. The opening-closing of the three-gated entrances into the lipidochannels and the work of the proton-conductor system of ice-like structures (shafts) as well as the transformation of membrane trigger states (Fig. 10-12) - are all electrodynamic processes making for the rapid cooperative transfer of the information and physiological effects.

To sum up, the honeycomb-like biomembrane model, built as a result of experiments of molecular modelling, is a useful means for solving a number of important problems in membranology.

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