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MEDICAL PHYSICS: MOLECULAR ASPECTS

Actual problems in medical physics have been considered. Features in the cell membrane structure promoting the action of anticancer drugs are studied. The mechanism of an invasive method for measuring the blood pressure is analyzed. The tension distribution in the left ventricle wall was calculated. Conditions that prevent magnetic particles, nanodiamonds, and fullerene molecules, which are used to transport drugs in human body, to aggregate in liquid systems are determined. A molecular mechanism of electric welding of biological tissues has been proposed, as well as a method to study the surface of biological structures, by using ultrasound. The origin of structural changes in human hair under the influence of chemicals is determined.

K e y w o r d s: cellular membranes, arterial pressure, cardiac muscle tension, drug transport, electric welding of biological tissues.

1. Introduction

Medical physics is a branch of science dealing with physical processes running in human body at its various structural levels – molecular, submolecular, cellular, and subcellular, as well as at the levels of the whole body and the system of bodies – under the influence of external factors and the environment [1]. Medical physics uses almost all modern domains of fundamental physics. It is aimed at studying the physical nature of human organism, creating new physical methods for diagnostics and medical treatment on the basis of this knowledge, implementing and maintaining physical methods in the practical clinical work, studying the influence of the environment (in particular, electromagnetic and ionizing radiation) on human body, and developing methods for protecting the organism from adverse effects of external factors.

Medical physics researches were started at the Faculty of Physics of the Taras Shevchenko National University of Kyiv more than twenty years ago, when, by the initiative of Academician L.A. Bulavin, the speciality "medical physics" was created at the Chair of Molecular Physics. A significant number of those researches were carried out in cooperation with specialized medical institutions. The main results of the performed researches are summarized in this work together with the results obtained in other known scientific works dealing with the problems concerned. Certainly, a single paper cannot cover the whole variety of problems arising at the boundary between medicine and physics. However, we hope that the examples presented in this article will be enough to confirm the validity of the formulated extended concept of medical physics [1].

2. Structure and Properties of Cell Membranes: Application in Oncology

It is known (see, e.g., work [2]) that membranes play a key role in the cellular metabolism. The mem-

brane structure reflects the physiological state of a cell and, accordingly, the state of organism as a whole. Therefore, the study of the membrane structure is of high importance in medical physics.

2.1. Diffusion of water molecules in cell membrane suspensions

The matter concerns the action of the antitumor remedy doxorubicin on the state of a tumor cell. In the previous researches [3–6], two types of cells were found: sensitive and resistant to the doxorubicin action. A hypothesis was put forward that plasmatic membranes play an important role in the formation of cell resistance to doxorubicin. In particular, using the method of nuclear magnetic resonance spectroscopy, it was found [4, 5] that, at the level of the plasmatic membrane in Guerin's carcinoma cells, which are sensitive and resistant to the cytostatic action, doxorubicin stimulates a considerable growth in the concentration of strongly bound water. In addition, the general level of membrane hydration increases against the background of a further decrease in both the energy of structured water and the energy change at the interface biopolymer–water. In [6], the evidences were obtained, e.g., for a substantial variation of the free energy of strongly bound water owing to the adsorption interaction with the plasmatic membrane. It was shown that those modifications in the properties of structured water affect structure-functional reconstructions in the plasmatic membranes of tumor cells, which is one of the origins that give rise to the formation of the antineoplastic drug resistance phenotype.

Which is the difference between the membranes of sensitive and resistant cells? In attempting to answer this question, the quasielastic scattering of neutrons in the aqueous suspensions of both cell types was researched in works [7–9]. The corresponding experimental results are exhibited in Fig. 1.

Using the broadening of the quasielastic peak, the self-diffusion coefficient for water was calculated. For the untreated suspensions and the doxorubicin-treated suspensions with cells sensitive to the action of this remedy, the self-diffusion coefficient of water D turned out approximately 1.3 higher than the corresponding value for water without additives. For the treated suspensions with cells resistant to the doxorubicin action, the coefficient D grew by a factor

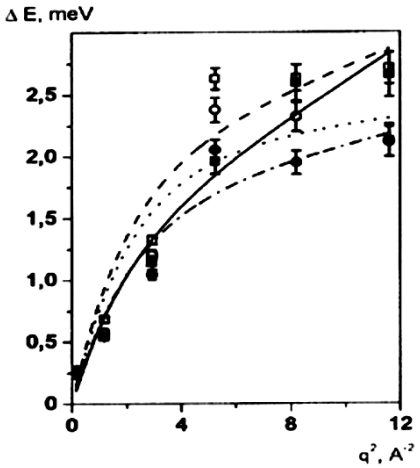

Fig. 1. Dependence of the quasielastic peak broadening ΔE on the squared scattering vector q^2 for an aqueous suspension of membranes

of 1.75 in comparison with that for water without additives.

What can be said about the membrane structure on the basis of those data? The appearance of membranes creates an additional channel for the diffusion of water molecules. One can suppose that, when in a suspension, the membranes form a network, and it is along the chains of this network that the diffusion of water molecules becomes facilitated. Such facilitation can be a result of a certain number of defects in the membrane structure. In this case, the additional increase in the mobility of water molecules for resistant cells can be explained by the growth in the number of those defects.

2.2. Membrane defects and membrane fusion

The origin of defects in membranes was analyzed in works [10–14]. Aqueous solutions of membrane suspensions were studied using the methods of small-angle neutron and x-ray scattering and the $P-V-T$ method. The temperature dependence of the large period of D was obtained (Fig. 2).

The experiment was interpreted in the framework of the supervacancy theory [15, 16]. Namely, the specific defects, supervacancies, seem to appear in the membrane structure at a certain temperature. They are voids with the volume equal to that of a lipid molecule. The appearance of supervacancies in the

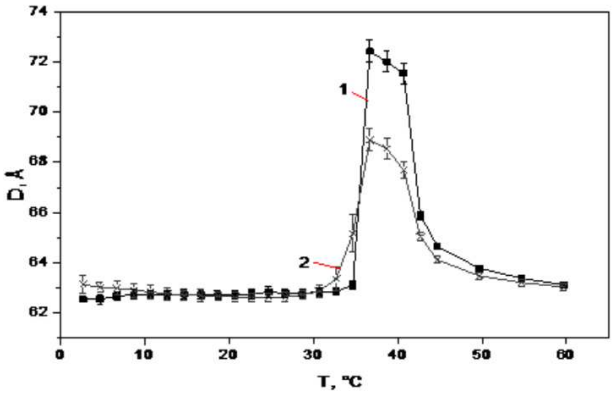

Fig. 2. Temperature dependence of the large period for the aqueous suspension of membranes [11]

membrane structure means the formation of a certain transient phase.

The temperature, at which the jump of the large period was observed, was identified with the temperature, at which the formation of supervacancies began. The further temperature elevation results in a growth of the supervacancy number and, finally, gives rise to the membrane fusion.

The obtained results allowed reasonings made earlier on the mechanism of doxorubicin action to be specified. In particular, the membrane structure in tumor cells corresponds to a transient phase, and the increase of the diffusion coefficient of water at the action of doxorubicin on resistant cells is associated with the membrane fusion.

2.3. Membrane elasticity

The normal functioning of a cell is possible provided the certain values of intracellular pressure. The stability of those values is provided by the membrane elasticity. In work [17], a method to determine the elastic modulus of a membrane was proposed, which is based on the measurement of the torsion stiffness of biological tissue. It was found that the membranes are characterized by nonlinear elasticity. Nonlinear elasticity is one of the means used by the cell to counteract the dehydration.

3. Mechanisms of Tension Emergence in Biological Tissues: Applications in Cardiology

There are numerous literature sources (see, e.g., works [18, 19] and others) that study a situation where, under the action of various external factors, there arise mechanical tensions in tissues composing the organism. One of those factors is the muscle excitation. Muscle tensions considerably affect physiological processes in organism, in particular, the processes studied by cardiology.

3.1. Invasive method of arterial pressure measurement

The specific feature of this method [20] is known to consists in that a catheter is introduced into a vascular channel. The catheter presence in the vessel changes the character of blood flow, resulting in an error at the pressure measurement. How large is this error?

The answer to this question was given in work [21]. The vessel was considered as a cylindrical channel in an elastic medium, and blood as an ideal incompressible fluid. A cylindrical tube (the catheter) is introduced into the channel. In the framework of this model, the Euler equations were solved. The solution was sought in the form of a one-dimensional wave. For the vessel cross-section that coincided with the catheter end, boundary conditions describing the continuity of the fluid velocity and pressure were given. As a result, the following formula was obtained for the pulse pressure:

$$p = p' \frac{3b^2 - a^2}{2b^2 - a^2}, \tag{1}$$

where p is the pressure measured by the invasive method, p' the true pressure, b the vessel radius, and a the catheter radius. The substitution of numerical values for a and b into formula (1) brings us to a conclusion that the relative error of the pulse pressure measurement by the invasive method exceeds 50%.

3.2. Stressed state of the left heart ventricle

From the medical practice, it is known [22] that the heart attack damages the inner surface of the left ventricle of heart the most often. A probable origin of this phenomenon was analyzed in work [23], where the stresses arising in the ventricular wall at the systole were calculated. In the literature, similar calculations were carried out earlier as well (see, e.g., work [24] and others). In calculations, the left ventricle was simulated as a hollow thin-walled cylinder. The appearance of stresses in the ventricular walls was supposed

to be a consequence of the blood pressure growth in the ventricle. The results of corresponding calculations brought about a conclusion that those stresses are stretching and directed perpendicularly to the radius, being identical by magnitude across the ventricular wall. The corresponding plot is shown in Fig. 3 by the solid curve.

In work [23], another model of a hollow cylinder, with a thick wall, was also used taking into account that the average values of the outer and inner ventricle sizes amount to 5.1 and 3.7 cm, respectively. One more difference of the calculation model used in work [23] consisted in the account of additional stresses emerging owing to the non-uniform distribution of deformations in the ventricular wall at the muscle contraction. It was demonstrated that these additional stresses can be regarded as following from the formation of a wedge-like dislocation. Therefore, while calculating stresses in the ventricle, the methods of disclination theory [25] were applied. Moreover, since the ventricle dimensions considerably change in the systole phase, the calculation was carried out in the framework of the finite deformation theory [25]. The results obtained are illustrated in Fig. 3, where points denote the distribution of stresses $\sigma_{\varphi\varphi}$ acting along the ventricular wall at the systole phase.

The main conclusion of calculations performed in work [23] consists in that there arises a region of compressive stresses in the ventricular wall near the inner surface, as one can see from Fig. 3. The capillaries become compressed at that, so that the blood supply is complicated. As a result, there emerges a danger of blood stagnation in the indicated region, which favors the heart attack.

3.3. Indirect action of antiaggregants

The medicamentous therapy of patients with heart valve prosthesis implies the application of antiaggregant preparations. However, in this case, the risk of disorders in the gastrointestinal tract induced by the damage of mucosa increases for elderly age patients. There are a few antiaggregant preparations: Warfarin, Cardiomagnyl, and Ticlopidine. For which of them is the probability of mucosal damage the lowest?

The composition of mucosa includes the basal membrane. Under the action of stresses that arise at

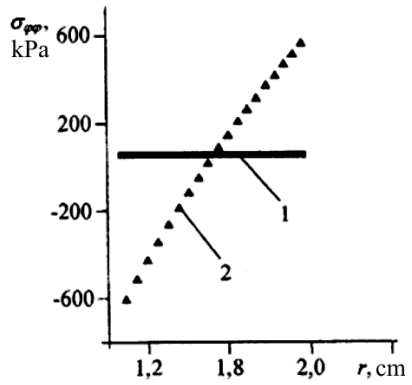

Fig. 3. Distribution of stresses in the left ventricle wall [23]

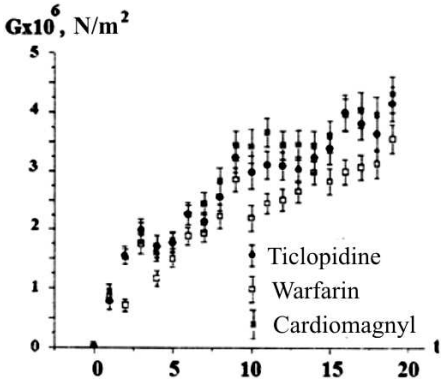

Fig. 4. Time dependences of the shear modulus G for the aqueous solution of collagen with antiaggregant additives [27]

muscular contractions, the membrane structure can be destroyed. The larger the elastic modulus of membrane tissue, the higher are those stresses. Hence, the probability of the structure destruction grows with the elastic modulus. The mechanical properties of a membrane are governed by a collagenic network entering its composition. Accordingly, the problem concerned is reduced to the question: How do the aggregants indicated above affect the elastic modulus of the network?

In work [27], following the procedure described in work [28], the shear modulus G of the aqueous solution of collagen with antiaggregant additives was measured (see Fig. 4, where t is the time reckoned from the start of the network formation). It is evident that the lowest value of the shear modulus is observed for the solution with Warfarin. This fact allows us to assert that the danger of indirect action will be the smallest if this preparation is used.

4. Magnetic Fluids and Their Applications in Oncology

By definition, magnetic fluid systems (ferrofluids) are suspensions containing magnetic particles with a typical dimension of 1–15 nm. A number of promising methods to treat oncological diseases, which are based on the application of magnetic fluids, were proposed. Hyperthermia of tumor tissues [29] is one of them. In the framework of this method, the temperature in a confined region of human body can be elevated by absorbing the electromagnetic radiation of the corresponding frequency (0.1–0.5 MHz). Attempts were made to deliver magnetic particles, which absorb the electromagnetic radiation well enough, to the damaged zone and hold them there. It turned out that this hyperthermic procedure can be successfully applied to the therapy of oncological diseases, especially in combination with chemo- and radiotherapy. In order to suppress the uncontrollable growth of pathological cells, it is enough that the temperature of a damaged region be raised above 43°C; to a high probability, healthy cells will remain undamaged at such temperatures [30]. In works [31–33], the application of this method to treat oncological diseases was reported.

Recently, a new method to treat oncological tumors with the use of magnetic particles has been considered; this is the neutron capture therapy. Its essence is as follows. Substances containing the stable boron isotope ^{10}B are introduced into pathological cells. Afterward, the cells are irradiated with a flux of thermal neutrons. As a result, the boron atom, having captured a neutron, transforms into a radioactive isotope, which will decay to form a lithium nucleus, an α-particle, and a γ-quantum. In this case, the lithium nucleus and the α-particle, the mean free paths of which are small and comparable with the size of biological cells, are considered to perform the major medical action. If those compounds are localized only in pathological cells, one may quite soundly expect that the neighbor healthy cells will remain almost undamaged.

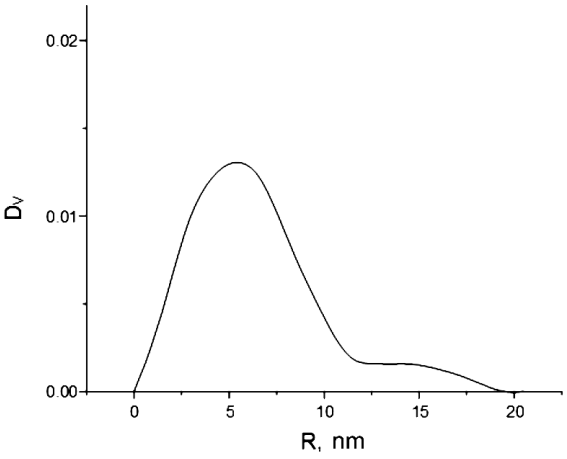

Fig. 5. Size distribution function of particles in a ferrofluid [44]

It is of importance that the boron and gadolinium atoms have extremely large values of interaction cross-section with thermal neutrons. They are several orders of magnitude larger than the neutron cross-sections of hydrogen, oxygen, and nitrogen atoms, which enter the composition of biological molecules [34, 35]. Therefore, the main task of the neutron capture therapy consists in the search for means for the targeted delivery of required medical remedies.

One of the ways to provide the accumulation selectivity with respect to substances containing boron or gadolinium at the cellular level is the application of magnetically controlled agents in the form of magnetic fluid systems. For instance, in work [36], a possibility for the magnetite ferrofluid stabilized with sodium oleate to be used as a magnetically controlled carrier for the preparation of calcium metaborate, which is an effective neutron capture agent, was considered. It is evident that the required properties of magnetic particles can be realized if the latter remain isolated. To prevent their agglomeration, surfactant stabilizers are introduced into suspensions.

How does the structure of the magnetic fluid systems stabilized by surfactants change? This problem was studied in works [37–46]. Small-angle neutron scattering in ferrofluids stabilized with dodecylbenzene sulfonic, oleic, and myristic acids was researched. On the basis of those measurements, the distribution of particles over their sizes was calculated. In Fig. 5, the corresponding distribution function D_V obtained in the case where the dodecylbenzene sulfonic acid was used as a stabilizer is shown. The figure testifies that there are two groups of particles in the ferrofluid: with average sizes of 6 and 16 nm. The former value corresponds to isolated magnetic particles, and the latter to their clusters. From Fig. 5, one can also see that the number of clusters is insignificant in comparison with the number of isolated par-

ticles. It was found that particles almost do not aggregate in the magnetic fluid systems if the stabilizer fraction is lower than 25%. Hence, monocarboxylic acids are more suitable to be used for the ferrofluid stabilization.

5. Nanodiamonds and Their Application to Regenerative Medicine

An important role played by diamonds in regenerative medicine stems from their ability to form substrates for tissue growing. For example, in work [47], a report was made about nanodiamond monolayers which were used as substrates for growing neurons. Platforms are created from composite materials, which are polymeric systems armored with nanodiamonds (see, e.g., work [48]) .

From this point of view, the biologic compatibility of nanodiamonds is their important advantage. Nonmodified, surface-functionalized, and conjugate nanodiamonds were used to interact with various types of cell cultures and some tissues [49–53]. Cytotoxicity tests carried out with crystallites of various dimensions demonstrated that nanodiamonds about 100 nm in diameter with a well-determined diamond structure are nontoxic for many kinds of cultivated animal cells. No substantial influence of nanodiamonds on the property of blood plasma (the protein structures and the blood coagulability) was revealed [54].

Bearing in mind the application of nanodiamonds described above, it is important to know the surface structure of nanoparticles, as well as the structure of aggregates formed by nanodiamonds. For this purpose, regularities in the formation of such aggregates and fluid systems were studied [55] with the use of the small-angle neutron scattering method. The average size of nanoparticles was found to equal 3 nm. The surface of particles was established to be in the graphene state. The aggregates were demonstrated to have a fractal structure, which forms a gel phase at high concentrations.

6. Targeted Transport of Medical Preparations

The application of magnetic particles to the targeted transport of drugs in organism has considerable advantages, which consist in that the drug delivery to specific regions of the body becomes possible. As a result, the total amount of medical substances in other parts of the body can be reduced.

The internal transport of iron oxide particles substantially depends on their size [29]. If particles with a diameter larger than 200 nm are introduced, they can be easily absorbed in the spleen and, finally, removed by cells of the phagocytic system. At the same time, fine particles less than 10 nm in diameter are removed through nephritic ducts. Therefore, particles with the diameter ranging from 10 to 100 nm are optimum for the intravenous introduction and have the longest blood circulation time. The way of magnetically driven delivery of preparations that use nanoparticles as carriers is a promising method of cancer treatment, which allows the by-effects of traditional chemotherapy to be avoided. Iron oxide nanoparticles covered by a stabilizer with phosphatic groups with the attached medical preparation mitoxantron were used in chemotherapy [36].

Great expectations are associated with the application of nanodiamonds for the delivery of medical remedies [56]. A low cytotoxicity determines the potential of their medical and biological applications. Interaction with various cell kinds (and some tissues) was studied for both nonmodified nanodiamonds and nanodiamonds with biomolecular compounds [48, 57–60]. In those researches, the biocompatibility of nonmodified nanodiamonds was determined by the physical and chemical properties of the surface (for example, surface chemistry, charge, size, and aggregation degree). At the same time, in the case of modified nanodiamonds, those properties are determined by the attached molecules. The low cytotoxicity of nanodiamonds makes them promising as carriers to deliver drugs into certain human organs.

Recently, the influence of nanodiamonds on alive cells has been studied experimentally [61]. It was shown that nanodiamonds can really serve as either carriers of drugs to healthy cells or poisonous substances to tumor cells. No negative consequences are observed in this case for healthy cells, similarly to what takes place when the traditional ways of delivery are used. Materials used at present to deliver preparations can induce the tissue inflammation, which is able to block the activity of anticarcinogenic medicines and even accelerate the tumor growth, which does not occur if medical preparations are transferred by nanodiamond crystallites. In order to enhance the material efficiency, the researchers com-

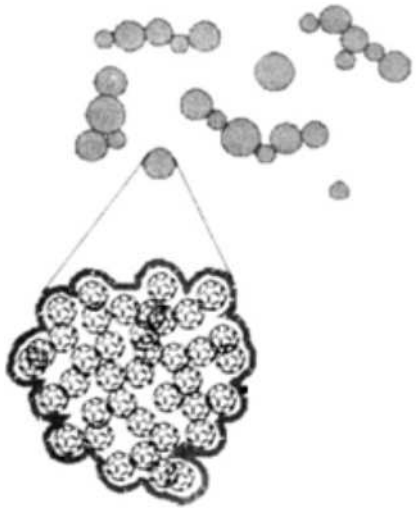

Fig. 6. Structure model for the fluid mixture "water–fullerene C_{60}" proposed on the basis of neutron experiment results [62]

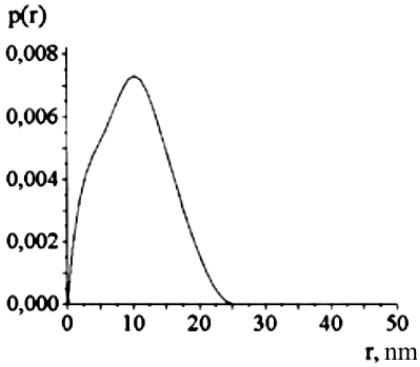

Fig. 7. Size distribution function as a result of the simulation of neutron scattering in the system C_{60}–NMP–H_2O, by using the method of indirect Fourier transformation [62]

bined separate nanodiamond crystallites, each a few nanometers in diameter, into aggregates 50–100 nm in length. When arriving at the place, the cluster will decay into separate particles and slowly release the preparation adsorbed on the surface. Unlike the modern means aimed at the local delivery of medicines by encapsulating them in liposomes and polymersoms, nanodiamond clusters do not damage healthy cells. Their dimensions are one hundredth as large as those of liposomes. Nevertheless, on their surface, they can carry the amount of medical preparation that is several times larger [61]. Nanodiamonds can freely circulate over the body and much more easily penetrate through biomembranes into cells.

The application of fullerenes is also promising for the transport of remedies. The structure of fullerene molecule allows a radioactive isotope to be put inside. The introduction of such molecules into tissue makes it possible to selectively affect the damage of tumor tissue [62].

Fullerene molecules are also used independently as a medical preparation for the treatment of neurodegenerative disease. In this case, they play the role of traps for radicals, which results in a reduction of the number of dead neurons.

The described properties of fullerenes also manifest themselves in fullerene-containing fluid systems. Those systems were studied in works [63–65]. The small-angle neutron scattering, $P-V-T$, and mass spectroscopy methods were used, as well as optical methods. Since the useful (in the medical meaning) properties of fullerenes reveal themselves in the best way, when fullerene molecules are isolated from one another, main attention in the cited works was concentrated on the aggregation issues. The average size of aggregates in the systems "water–fullerene" was determined to equal 72 nm. By its shape, the aggregate is an ellipsoid with an elongation coefficient of 1.65. The coagulation process in those systems was also studied, and the corresponding half-period of coagulation was determined. The structure model of the system "water–fullerene" was built (Fig. 6).

The mechanisms responsible for the stability and aging of this system were considered. As was already mentioned, the biological activity decreases if fullerene is in the cluster state. The high solubility of fullerenes in polar liquids stimulated the research of fluid systems "polar liquid–fullerene" and "polar liquid–fullerene–water". In Fig. 7, the corresponding distribution of particles over their dimensions is exhibited. According to it, the average particle size equals 18 nm.

According to the results of mass spectrometry researches, fullerene clusters include from 2 to 5 monomers. The addition of water favors a reduction of the monomer number in the cluster.

7. Visualization in Medical Physics

7.1. Contrast media

It is known that images in the nuclear magnetic resonance (NMR) tomography are obtained with the help of magnetic properties of protons, water molecules,

and molecules of organic substances located in cells and body's tissues. This method is applied to obtain three-dimensional noninvasive images of human body. In a number of clinical cases, contrast agents turn out necessary to reveal certain types of diseases. The role of such agents consists in that the time of magnetic relaxation of water protons becomes shorter at their presence in some organism regions, which enhances the contrast between adjacent image sections. In the last years, the aqueous suspensions of magnetite nanoparticles stabilized by a dextran layer have been started to apply for this purpose [66]. At present, two types of magnetic nanoparticles are used in medicine as contrast agents in NMR tomography. They have an inorganic core from iron oxide (magnetite, maghemite) covered with a polymer like dextran. These are lumiren, iron oxide particles covered with silicone to a diameter of 300 nm, and endorem, magnetite nanoparticles 150 nm in diameter stabilized by dextrin [29, 67].

Magnetic fluid systems are also used as contrast media in X-ray tomography. In work [68], an X-ray contrast preparation which includes a magnetite ferrofluid on the basis of tetradecane was described.

7.2. Markers

An important property of nanodiamonds is their extremely intense fluorescence, which can be observed with a naked eye in a suspension containing only 0.004 wt.% of nanodiamonds. The mechanism of this phenomenon is associated with the presence of nitrogen-vacancy defects in the crystal lattice of diamond [69]. Fluorescent nanodiamonds are coming into use in biomedical diagnostic procedures, because the efficiency of this technique has already been verified [70]. Hydrophobic fluorescent nanodiamonds open new ways in the visualization of cell membranes and other hydrophobic components of biological systems. Such color centers of the defect origin can be ideal markers and serve as an alternative to molecular dyes.

Besides fluorescent properties, diamonds have a unique Raman scattering signal which follows from the phonon mode of sp^3-carbon at a wave number of 1332 cm^{-1}. This signal is not overlapped by the majority of Raman signals from biosystems and, hence, is a perfect marker for the biovisualization [71]. Examples of the visualization of bacteria (e.g., *Escherichia coli*) by revealing the signal of diamond Raman scattering were presented in work [72].

7.3. Visualization of transition layers in ultrasonic diagnostics

It is known that, in order to visualize images obtained with the help of ultrasonic research, a model of organism is used, which presents it as an inhomogeneous continuum. In the framework of this model, the organism is considered as a set of regions with different acoustic characteristics. At the boundaries between those regions, there are transition layers with a specific structure. However, in the mentioned model, the existence of those layers is ignored, because their thickness is often smaller than the acoustic wavelength.

In work [73], a method was proposed, which allows the data of ultrasonic research to be used for the determination of dimensions and acoustic parameters of the transition layer. It is known that information about the internal structure of organism is transferred by the sound signal: it is contained in the reflection coefficient V. In work [73], the following formula was obtained for this quantity:

$$V = \frac{i\rho' c' \frac{\rho'' c'' - i\rho' \omega h'}{i\rho' c' + \frac{\rho'' c'' \omega h'}{c'}} - \rho c}{i\rho' c' \frac{\rho'' c'' - i\rho' \omega h'}{i\rho' c' + \frac{\rho'' c'' \omega h'}{c'}} + \rho c}, \tag{2}$$

where ω is the cyclic frequency; ρ and ρ'' are the densities of the media separated by the transition layer; c and c'' are the sound velocities in them; h', ρ', and c' are the thickness, density of the transition layer, and sound velocity in it, respectively; and i is the imaginary unity. This formula was derived in the approximation $h' \ll \lambda$, where λ is the sound wavelength. Hence, the application of this method makes it possible to reveal the existence of thin transition layers. According to formula (2), for this purpose, it is necessary to measure the reflection coefficients V at different frequencies.

7.4. Influence of a magnetized coating on the quality of MRT images

The deposition of a magnetized coating onto an examined object changes the magnetic properties of the latter. How does this procedure affect the quality of a magnetic resonance tomography (MRT) image? For

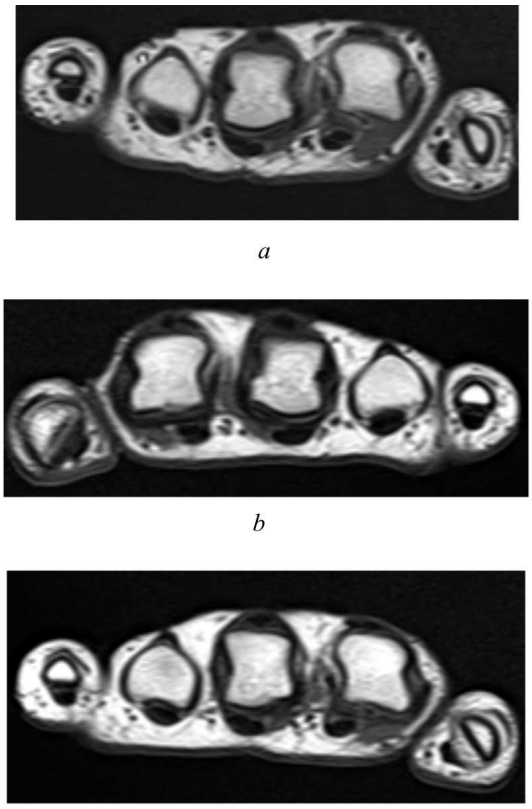

Fig. 8. MRT images of human hand: in the absence of glycerol (*a*), with non-magnetized glycerol (*b*), and with glycerol subjected to a constant magnetic field of 0.4 mT for 25 min (*c*)

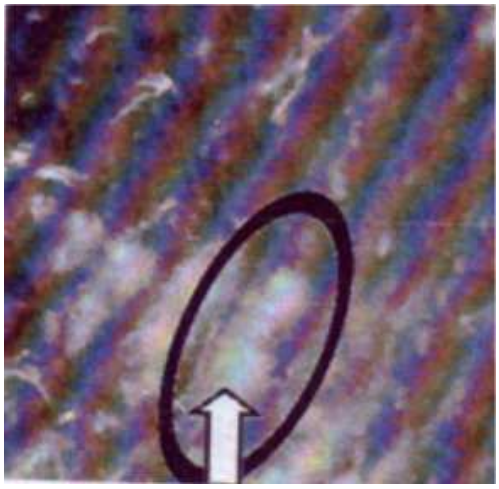

Fig. 9. Appearance of damp epidermis after the electric current application (at 6x magnification) [81]

this purpose, glycerol was used, which was preliminarily subjected to the action of a 0.004 T magnetic field for 30 min. In Fig. 8, an MRT image of human hand is shown, which was obtained with the help of a Toshiba Vantage Octave 1.5 T tomograph. The images were processed using the software package RadiAntDICOMViewer (64-bit).

From Fig. 8, one can see that the images corresponding to the glycerol-free state and the states with magnetized and non-magnetized glycerol differ from each other by the granularity degree. The influence of the glycerol magnetization on the image quality is explained by the orientation of glycerol clusters under the influence of a magnetic field.

8. Structure and Properties of Keratin Fibrous Proteins: Application to Clinical Diagnostics

The structure of keratin fibrous proteins (KFPs), e.g., hair, and their properties, as well as the properties of every component in alive organism, depends on the general state of organism. Therefore, while studying the KFP structure, the researcher has an opportunity to obtain information about changes in other components of organism. An obvious advantage of such researches consists in that the KFPs, e.g., hair, is a specimen, which is ready to be studied *in vitro* and can be obtained in a nontraumatic way. One of the promising way in this direction is the development of early diagnostics methods, e.g., for oncologic deseases, by studying the variations in the structure and the physical and chemical properties of KFPs induced by pathological states.

In works [74–77], the KFP structure was studied from a purely practical viewpoint. Nevertheless, the corresponding data can be useful, when analyzing the relation between the KFP structure and various pathologies. The wide- and small-angle X-ray diffraction methods, the acoustic interferometric method, and calorimetric measurements were applied. Some experimental results are illustrated in Fig. 9.

On the basis of this experiment, a new model was proposed for the KFP structure. Its specific feature is the existence of disordered regions between the fibrils. The structure of those regions has the following peculiarities. First, there are a considerable number of supervacancies and voids in them, with one of the dimensions of the latter being equal to the rigid seg-

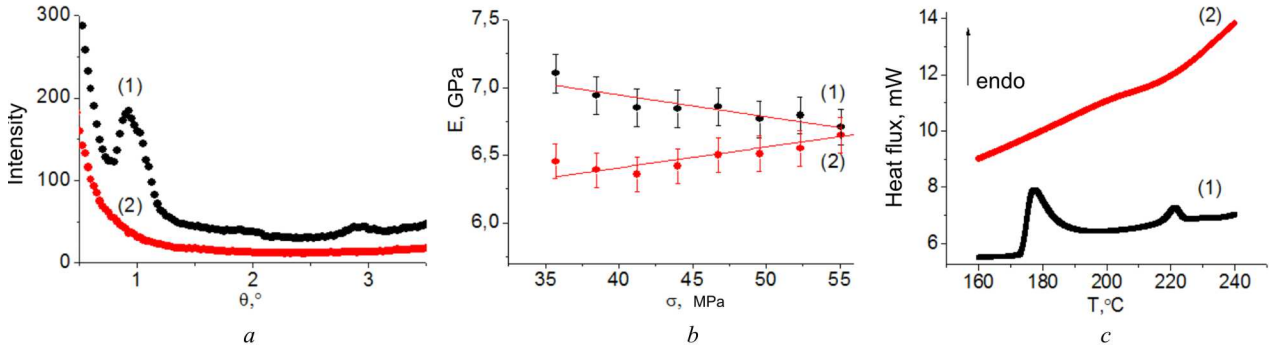

Fig. 10. Small-angle X-ray diffraction patterns (*a*), pressure dependence of the Young modulus (*b*), and thermograms for hair before (1) and after (2) the treatment with thioglycolic acid [77] (*c*)

ment length. Second, the disordered intrafibrillar region in a keratin fiber (which is hair) consists of two domains, the dimension of which in the direction perpendicular to the fiber axis equals 45 Å. Every domain contains folded chains, the rigid segments of which are mainly oriented in the direction perpendicular to the fibril axis and the flexible segments form folds.

When a keratin fiber contacts with the aqueous solution of thioglycolic acid, acid molecules diffuse in hair and accumulate mainly in the intrafibrillar regions. Therefore, after the dissolved substance is washed out from the fiber, the structures of crystalline and intrafibrillar regions in the treated KFP remain almost the same as for the untreated one. The observed structural changes mainly take place in the disordered regions inside the fibrils. To be more specific, at the action of thioglycolic acid on the keratin protein, domains that compose the disordered intrafibrillar regions become destroyed, the number of supervacancies in those regions increases, and rigid segments become mainly oriented toward the fibril axis. There emerge disulfide bonds between the oriented segments, which fix the new positions of KFP segments.

9. Molecular Mechanism of Electric Welding of Biological Tissues: Application to Surgery

The development of methods to join alive biological tissues is one of the challenging tasks for modern surgery. The existing traditional ways, such as using suture materials, metallic retention bridges, and adhesives, have definite shortcomings. For instance, if retention sutures are used, there appears a danger of disturbed blood circulation in the joint region, and microorganisms migrate along the retention sutures, which gives rise to the development of suppurative complications. The emergence of allergic reactions to foreign bodies is also probable. Similar shortcomings are also typical, when metallic retention bridges are applied. Methods of biological tissue adhesion did not become widespread, because they did not ensure the joint reliability. The method of electric welding of biological tissues [78], which was invented at the E.O. Paton Institute of Electric Welding of the NAS of Ukraine, is free from the mentioned shortcomings. Nowadays, this method of joining biological tissues became widespread in clinical practice (see, e.g., work [79]).

While studying the molecular mechanism of electric welding, the main question which is to be answered first of all consists in explaining how the joint tissues keep together after the electrodes are removed. The corresponding explanation was given in work [80]. In a rough approximation, the tissue structure can be imagined as cells separated by an intercellular substance. If a current runs through the tissue, the temperature of the latter grows. As a result, the structure of the cells and the intercellular substance becomes destroyed. After the current stops, a new structure is formed in the connective tissue, which is a network created by collagen fibers entering the composition of intercellular substance. The experimental research of the formation kinetics of this network confirmed the adequacy of the proposed mechanism.

In work [81], the physical peculiarities of the electric welding of skin layers were studied. A model was proposed, which is based on the fact that the elec-

tric welding processes run in the near-surface skin layers and depend on the relationship between the collagen and keratin matrices. If an electric current runs, a intermediate phase can be formed, which consists of keratin structures surrounded by a system of lipids (in Fig. 10, this region is marked by an arrow).

10. Afterword

Traditionally, every paper on that or another problem should end with a conclusion, where new information on the nature of a researched phenomenon obtained in that work is briefly summarized. However, in our opinion, the review character of this work and a significant number of problems considered here make this traditional approach inexpedient, because in so doing, we would repeat again the issues that were already discussed (in brief!) in the main body of the paper. For this reason, the final section of the work is called Afterword rather than Conclusions.

As was already mentioned above, medical physics started its first steps in Ukraine about 20 years ago. Since then, under the supervision and with a direct participation of Academician of the NAS of Ukraine L.A. Bulavin, the research workers of the Chair of Molecular Physics at the Faculty of Physics of the Taras Shevchenko National University of Kyiv performed a cycle of works dealing with medical physics problems. The research workers of the Chair of Physics of Functional Materials at the same faculty were also incorporated into this activity under the supervision of Corresponding Member of the NAS of Ukraine M.P. Kulish. They started to intensively develop the radiation medical physics and teach it to students.

It is evident that since medical physics arose at the boundary between physics and medicine, the development of medical physics without the participation of physicists is impossible. It is medicine that puts problem to be solved before medical physics. Accordingly, a number of works discussed in this paper were carried out in the close cooperation with the research and development institutes headed by Academicians of the NAS of Ukraine V.F. Chekhun and G.V. Knyshov and the Chair of Medical and Biological Physics at O.O. Bogomolets National Medical University headed by Corresponding Member of the National Academy of Pedagogical Sciences of Ukraine Prof. O.V. Chalyi.

When writing this paper, the authors, simultaneously with the analysis of the researches performed within the scope of that or another problem, intended to summarize the results of the work carried out at the Chair of Molecular Physics in cooperation with the mentioned scientific teams for the last twenty years. Having this aim in view and considering the number of problems considered in this paper, as well as the limited length of the latter, we were forced to concentrate a more attention on the works published by the members of the mentioned teams, in no case discarding the results obtained by other researchers.

Although it is not the practice to discuss the following issue in scientific physical papers, we nevertheless consider it pertinent to recall that medical physics in Ukraine arose in the 1990s, under the conditions when Ukraine's economy was almost totally disintegrated. Therefore, when developing this branch of science, the huge difficulties associated with the depreciation of material resources, the bureaucracy of officials, a practically complete absence of the financing, the misunderstanding of the importance of the problems concerned from some physicists, and so forth had to be overcome. If Ukraine really has certain achievements in medical physics, which is evidenced by this paper, this is exclusively due to the energy and persistence of Academician of the NAS of Ukraine L.A. Bulavin, the founder of the Ukrainian medical physics.

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МЕДИЧНА ФІЗИКА: МОЛЕКУЛЯРНІ АСПЕКТИ

Р е з ю м е

Стаття являє собою огляд стану актуальних проблем медичної фізики. Вивчено особливості структури клітинних мембран, що сприяють дії протипухлинних засобів. Проаналізовано механіку інвазивного способу вимірювання артеріального тиску. Розраховано розподіл напружень в стінці лівого шлуночка серця. Визначені умови, що запобігають агрегації в рідинних системах магнітних частинок, наноалмазів та фулеренових молекул, завдяки яким відбувається перенесення лікарських засобів в організмі людини. Запропоновано молекулярний механізм електрозварювання біологічних тканин. Запропоновано спосіб дослідження поверхонь біологічних структур за допомогою ультразвуку. Визначено природу структурних перебудов, що відбуваються у волосі під дією хімічних речовин.