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Prospects for Development of Noninvasive Spectrophotometric Medical Diagnosis

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Analysis of the development of modern medical diagnosis and treatment shows that there is a worldwide trend toward introduction into medical practice of sophisticated scientifically substantiated methods minimizing invasiveness, radiation load, and other physiologically and psychologically undesirable effects. Modern electronic, laser, and computer technologies, etc. are used to increase the efficiency of diagnosis and treatment. Population growth and rising incidence of many diseases increase the load on medical personnel, making it necessary to develop highly efficacious medical technologies providing minimal time per examination.

These requirements are fully met by noninvasive (*in vivo*) laser and other optical methods of diagnosis, which have been extensively used in many industrially developed countries for the last 10-15 years [8, 11, 13]. These methods are based on the use of low-intensity (up to 10 mW) optical radiation for examination of organs and tissues. The light reflected by or transmitted through the tissues provides diagnostic information about their state. Processes of linear and quasi-linear interaction of light with optically inhomogeneous and semitransparent media (lymph, soft tissues, etc.) form the physical basis of these diagnostic methods [21]. For example, a light beam falling on skin is partially reflected by it and partially transmitted, reaching the connective and muscular tissues, vascular bed, etc. The transmitted radiation is multiply reflected (scattered) within biological tissues on the boundaries of inhomogeneous anatomical and cellular structures and partially absorbed by different substances (water, melanin, hemoglobin, etc.). A part of the radiation attenuated by absorption and multiple scattering emerges back from the skin surface [13], forming so-called back-scattered radiation flux F_{bs}. A small part of radiation is transmitted through the organ under examination. It forms the transmitted radiation flux F_{τ}. These fluxes can be detected using a photodetector. Different spectral components of optical radiation are absorbed and scattered by different biological tissues and substances. Thus, exposure of various organs and areas of human body to radiation of given intensity and spectral composition with further analysis of the intensities of spectral components of the fluxes F_{bs} and/or F_{τ} provide valuable information about the internal structure of the organ under examination.

The principles outlined above are already implemented in such noninvasive optical diagnostic methods as laser Doppler flowmetry [5, 16], biophotometry [4], optical pulsoximetry [2], fluorescence diagnosis [3, 10, 12], etc. Methods of light scattering and absorption spectroscopy of biological tissues have been described in international literature [14, 15]. These methods are used to obtain information about the content of various natural pigments (melanin, oxy- and deoxyhemoglobin, bilirubin, etc.) in tissues. The diagnostic methods listed above are implemented using similar measuring techniques and equipment (Fig. 1). Measurements are performed in transmitted (Fig. 1a) or reflected (Fig. 1b) light depending on the accessibility of the organ under examination. A single monochromatic radiation source *1* (laser) or a set of sources with different radiation spectra (including white light sources) can be used. Radiation is transmitted to the organ *2* under examination using an optical fiber *3*. A receiving optical fiber bundle *4* transmits the detected fluxes F_{bs} and F_{τ} to a detection/spectral analysis unit *5*. This unit can be implemented as a polychromator with a matrix photodetector, as individual optical filters and photodetectors, or even as a single photodetector used to measure the total radiation. Then, the electrical signal undergoes analog processing (amplification, filtration, etc.) in an electronic unit *6*, is digitized, and is transmitted to a computer *7* for further processing. In some cases

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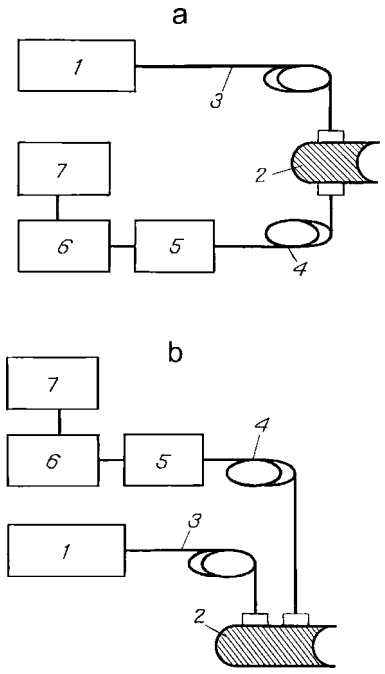

Fig. 1. Diagram of diagnostic equipment for measurements in transmitted (a) and reflected (b) light. Explanation in text.

(for example, in pulsoximetry), the radiation sources (LED) and the photodetector (photodiode) can be arranged directly on the surface of tissue under examination. In this case, there is no need for light-transmitting optical fibers.

It should be noted that such standardization of equipment does not reduce the quality and content of diagnostic information obtained by the methods listed above. For example, an apparatus of a similar structure (Fig. 1a) was used for measuring the transmission spectra in mammary glands [15]. It was shown that there were reliable differences between near-infrared spectra measured in healthy subjects and patients with breast tumors (mastopathy, carcinomas). The problems of effective mammological examination are rather urgent in modern medicine, so that diagnostic equipment of such type is in high demand.

Noninvasive fluorescence diagnosis is very informative. It is based on detection of forced endogenous fluorescence (FEF) of various fluorochromes (vitamins, pyridine-nucleotide and flavin enzymes, porphyrin, etc.) contained in tissues. In many cases, development of tumors, burns, suppurative inflammations, and other pathological and wound processes leads to a change in the amount of these substances accumulated in tissues. The ratio between the contents of oxygenated and reduced forms of these substances in the tissues is also changed. A corresponding change is observed in the detected FEF spectra. The FEF spectra measured in healthy mucous coat of the stomach and at zones of erosive gastritis are shown in Fig. 2a. These spectra were detected by the method of noninvasive fluorescence diagnosis using a continuous He–Ne laser (10 mW, 632 nm) [19]. It can be seen that gastritis leads to a considerable increase in the intensity of fluorescence in the range of 650-800 nm. Development of malignant tumors can lead to still greater increase in fluorescence (Fig. 2, b and c). It was even suggested [14] to use methods of fluorescence diagnosis in development of a technique for so-called noninvasive optical biopsy, which would make it possible to determine the malignancy of tumors by simple analysis of their FEF spectra. Such a technique is given much attention by manufacturers of medical equipment. In particular, pilot models of devices for optical biopsy (Fig. 3) are undergoing testing in some clinics in the USA. Similar devices (for example, LF-302 laser fluoroscope) have been designed in Germany. It can be expected that soon such devices will be commercially available.

However, there are some doubts concerning the efficiency of fluorescence diagnosis. It was shown in our previous work [19] that the FEF intensity in the red spectral range correlated with the oxygen deficiency in tissues rather than the proliferative cellular activity, which is used as a criterion of tumor development. As a sequence, not only malignant, but also normal cells can fluoresce in the case of a metabolism disorder, a cardiovascular disease, dysbacteriosis [7], etc. For example, consider the FEF spectra detected from three finger pads of a patient with lead intoxication (Fig. 2d). Although these spectra are somewhat different from those shown in Fig. 2 (a-c), they are typical for many clinical cases, including malignant diseases [1]. Therefore, FEF spectra cannot be used for unambiguous diagnosis of malignant diseases if the disease etiology is not known. Moreover, theoretical analysis [6, 10, 17] of the main physical phenomena accompanying the radiation propagation in biological tissues showed that correct quantitative interpretation of the FEF spectra was virtually impossible without knowing the coefficient of light scattering and absorption in tissues [10]. The shape of the spectra depends not only on the fluorochrome content in tissues, but also on the optical properties of tissues, which also change as a disease progresses. Therefore, all spectral methods of diagnosis should include layer-by-layer determination of all transport coefficients for tissues under examination. For example, fluorescence diagnosis should include elements

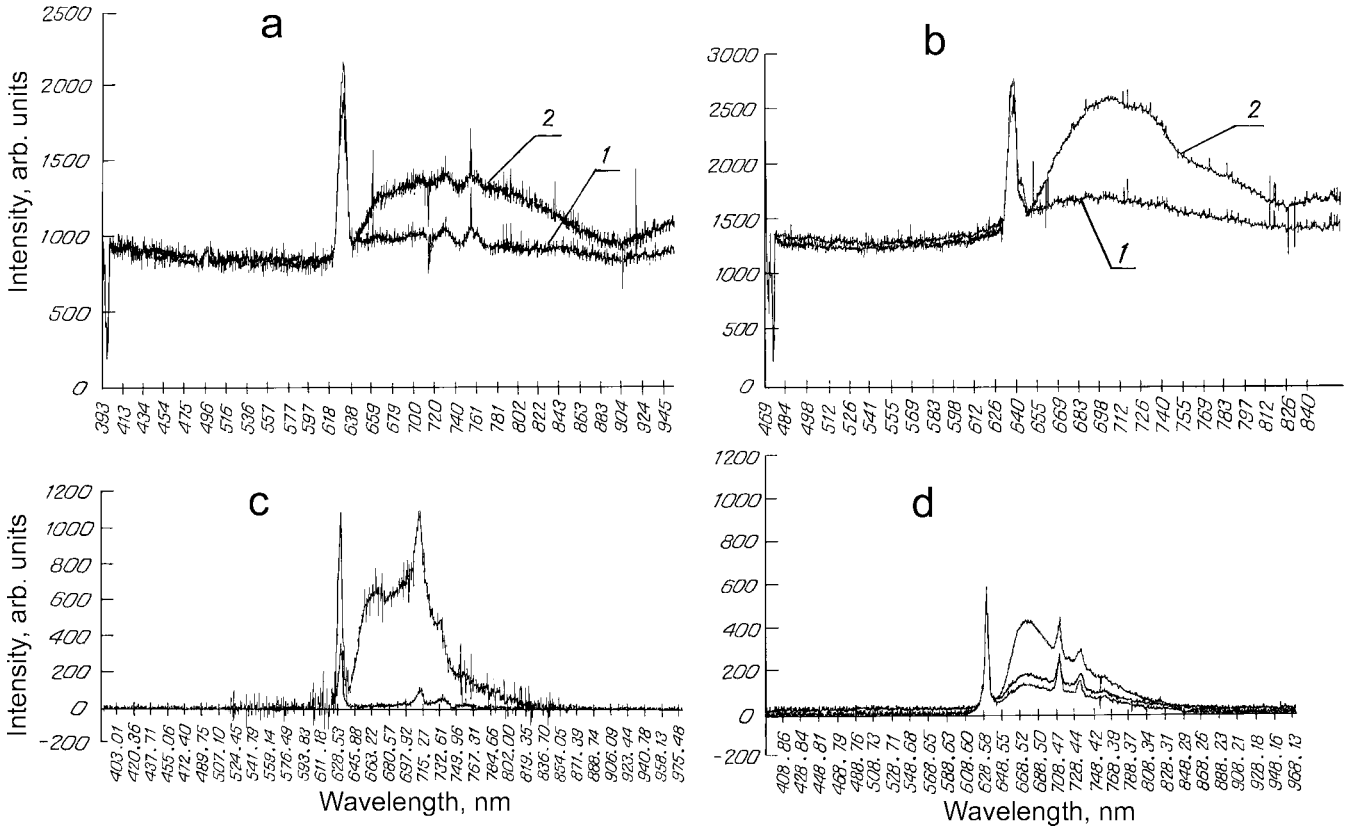

Fig. 2. Examples of induced endogenous fluorescence spectra. a) Mucous coat of the stomach: *1*) healthy mucous coat; *2*) erosive antral gastritis; b) stomach ulcer or carcinoma: *1*) surrounding intact tissue; *2*) lesion focus; c) oral cavity cancer: center of the tumor (upper curve) and surrounding intact tissue (lower curve); d) fingers affected by lead intoxication: three curves for three fingers of the same patient. In all graphs, the abscissa is the wavelength, nm; the ordinate is the intensity, arbitrary units.

of absorption spectroscopy of biological tissues or light scattering spectroscopy.

Nevertheless, even individual FEF spectra contain sufficiently objective information about processes in tissues that can be hardly obtained by other *in vitro* methods. One of the fields of application of the FEF technology is monitoring of the efficiency of treatment of patients with malignant tumors [1]. A curve illustrating the dynamics of changes in the fluorescence contrast coefficient of a tumor in the process of remote gamma-therapy (RGT) is shown in Fig. 4. Jumps in the contrast coefficient observed in the first days of treatment indicate the tissue response to the first sessions of RGT. Toward the end of the treatment session, the contrast coefficients for the tumor and intact tissue become closer to each other, which shows that the irradiation doses were selected correctly.

Another field of application of a number of methods of noninvasive optical diagnosis is angiology. Normal vital activity depends on the parameters of blood circulation in tissues. Hemoglobin is a pronounced optical chromophore, which facilitates detection of circulation parameters by optical methods. Doppler frequency shift measurements [16] are already widely used in clinics for estimating the parameters of blood microcirculation and perfusion [5]. Optical pulsoximetry has found wide application in resuscitation for detection of arterial blood saturation and pulse rate [2]. There is a recent trend toward development of methods of multispectral diagnosis, which make it possible to determine the content of various hemoglobin fractions: oxyhemoglobin, methemoglobin, carboxyhemoglobin, myoglobin, etc. [14]. These methods provide measurements at any point of the human body. Calculations can be performed without reference to pulse waves and blood circulation. The methods of multispectral diagnosis make it possible to monitor exchange processes in tissues. For example, they provide monitoring not only of the

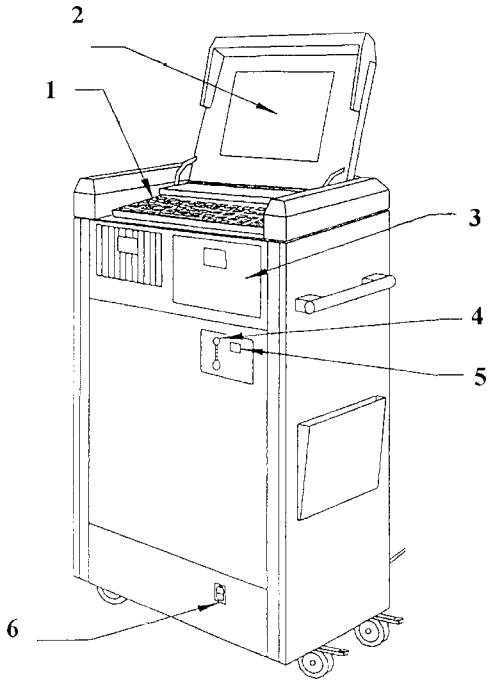

Fig. 3. OBS/L system for optical biopsy (USA): *1*) keyboard; *2*) display; *3*) disk drives; *4*) optical fiber adapter; *5*) radiation power meter; *6*) power switch.

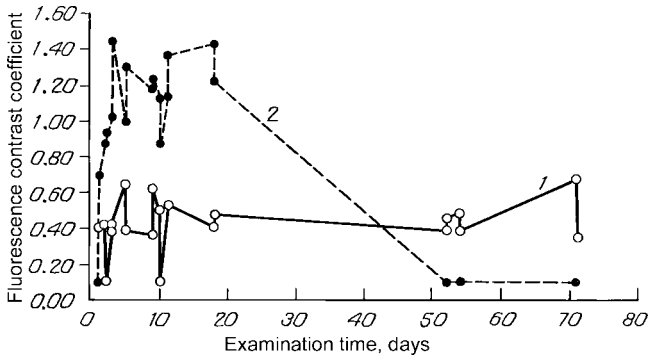

Fig. 4. Dynamics of changes in the fluorescence contrast coefficient of a tumor in the process of remote gamma-therapy: *1*) surrounding intact tissue; *2*) lesion focus.

Fig. 5. Dynamics of the mean level of blood oxygenation (upper curve) and blood volume (lower curve) (ordinate, arbitrary units) during a functional occlusion test. The abscissa is the time, min.

oxygen supply of arterial blood, but also of the mean parameters of oxygenation for the entire vascular bed of the part of the body under examination.

Optical methods can be also used to assess the neural reflex response to external factors. For this purpose, optical diagnosis is combined with various functional tests. Monitoring of changes in blood circulation makes it possible to assess the level and duration of the response, the latent period duration, etc. This is a rather simple method for differentiating organic and functional disorders of peripheral blood circulation and the peripheral nervous system. For example, it was shown in [8, 11] that optical methods provided detection of small changes in blood volume in tissues caused by laser therapy. Multispectral methods provide still greater capabilities. The dynamics of changes in the mean level of blood oxygenation and the total blood volume in tissues of a finger during an occlusion test is illustrated in Fig. 5. Real-time noninvasive measurements were performed using an Istok-EOS Spektrotest device. It can be seen that the blood saturation with oxygen is reduced by occlusion (upper curve), while there is a simultaneous small increase in the blood volume (lower curve) caused by reflexive capillary dilation under conditions of oxygen deficiency. Reactive postocclusion hyperemia occurring upon completion of the test can be also observed in the curves (at 24-25 min). The curves measured in patients with vascular stasis or congestion differ considerably from those measured in healthy subjects.

The methods of noninvasive optical diagnosis considered above are rather efficacious and should in the near future find wide application in medical practice. Devices implementing these methods are forming a new segment of the market of medical equipment. Thorough analysis of the problems of construction of optical noninvasive diagnostic equipment [9, 17, 18] enabled us to make several conclusions about the prospects of its development.

1. Such noninvasive optical diagnostic methods as oximetry, scattering and absorption spectroscopy, fluorescence diagnosis, photoplethysmography, etc. can be considered as branches of a multipurpose diagnostic technology, which can be effectively used in medical

practice along with such conventional diagnostic technologies as X-ray diagnosis, ultrasonic diagnosis, laboratory investigations, etc.

2. The diagnostic methods considered in this work are based on the same principles of technological and methodological implementation. On the other hand, they are used for investigation of phenomena that are similar from the viewpoint of physics. All these methods provide monitoring of the biochemical content and morphological structure of tissues, organs, and fluids of the living human body. They are used for measuring quantitative, relative, and dynamic parameters characterizing tissue biochemistry and morphology. These measurements are performed using multistage indirect methods. These methods resemble conventional laboratory methods for photometric analysis, but they are noninvasive. They are known collectively under the name of noninvasive spectrophotometric diagnosis or noninvasive spectrophotometry.

3. All medico-biological parameters of biological tissues are indirectly determined from the parameters of secondary radiation emerging from biological tissues (reflected, scattered, etc.). Therefore, a diagnostic system implementing these indirect methods should provide solution to inverse problems of light-scattering medium optics. Diagnostic information (secondary radiation parameters) collected and processed by such systems should provide unambiguous calculation of the main optical properties of multicomponent biological tissues with a given accuracy.

Thus, taking into account the common features of the methods under consideration, large amounts of collected data, and sophisticated algorithms used for processing the diagnostic information, it can be concluded that development of multipurpose computer-assisted diagnostic systems is the most promising trend in the development of equipment for noninvasive spectrophotometry. Such systems should implement all diagnostic methods considered above and provide combined processing of the entire amount of information obtained. Development of such systems should lead to a considerable increase in the content, accuracy, and reliability of diagnostic information. The cost of a multipurpose system should also be lower than the total cost of devices implementing different diagnostic methods.

It should be noted that in many respects the potentialities of domestic medical engineering industry are not inferior to those of foreign manufacturers. Russian scientists and engineers even hold the leading position in the world in development of some types of optical diagnostic equipment. For example, laser tomographs developed at the Nizhni Novgorod State Medical Academy and the Institute of Applied Physics, Russian Academy of Sciences, received much recognition both nationwide (State Prize Award) and worldwide [20]. However, the absence of special state projects and insufficient funding hinder the development of domestic equipment for optical noninvasive diagnosis. As a result, current priorities of domestic developers can soon be lost, and it may become necessary to import noninvasive diagnostic technologies [8].

Currently used domestic standards for development, testing, serial manufacture, and introduction into practice of new medical equipment also do not promote fast development of domestic noninvasive spectrophotometry. It is beyond doubt that medical equipment should undergo complete engineering and medical testing according to GOST R 15.013-94 before it is adopted for clinical use. However, to receive financing for development of medical equipment, it is necessary to demonstrate the efficiency and good commercial prospects of the technology used. This is often impossible without considerable preliminary financing necessary for development and testing of pilot models, preparation of technical documentation, etc. Thus, developers of medical equipment are often caught in a vicious circle in which the required financing can be received only after development and testing of the product.

Thus, it seems expedient to adopt a less strict procedure for admitting such low-risk diagnostic technologies as noninvasive spectrophotometry for clinical use. Leading medical and scientific centers can be allowed to use low-risk diagnostic technologies prior to their official clinical testing. At first, these technologies can be used simply in the background mode for additional monitoring of patient's state without changing the treatment procedure. This would make it possible to accumulate valuable information about the efficiency of the technology developed. This information would be very useful for the developers, physicians, and experts of the Committee for New Medical Equipment of the Ministry of Health of Russian Federation. Scientific centers could increase financing of the models that had proved their efficiency. This would intensify the development of especially promising technologies. On the other hand, early access to new technologies could accelerate the development of optimal methods of their clinical application. The developers could also assess with more certainty the efficiency of the pilot models developed. This would facilitate the task of experts of the Committee for New Medical Equipment and make it easier to receive further financing required to introduce the developed equipment into

serial manufacture. It should be noted that GOST R 15.013-94 formally admits such testing procedure for individual production (see Note 1). In our opinion, this standard should be complemented with corresponding regulations concerning devices for scientific research and a list of low-risk medical technologies that are admitted for use in special scientific centers at the stage of development of pilot models.

The GOST standards for laser medical equipment, All-Russian Production Classifier, etc., also require some revision. In particular, recently adopted GOST R 50267.22-02 (Medical Electrical Equipment. Part 2. Particular Requirements for the Safety of Diagnostic and Therapeutic Laser Equipment) and GOST R 50723-94 regulating laser safety do not even mention diagnostic laser equipment. The OK 005-93 Classifier registers such equipment under production code 944281: Devices for Diagnosis Using Ultrasound, Infrared, and Ultraviolet Radiation. For some reason, visible light range is not mentioned. The list of such examples of inadequacy of currently used standards could be continued.

Nevertheless, the technological capabilities of domestic medical engineering and industry of medical equipment are still rather high, and we hope that our country will hold a leading position among the manufacturers of high-efficiency noninvasive spectrophotometric and laser diagnostic systems.

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