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SIMULATION OF THE FORMATION OF A THERMAL-LASER-ACTION SITE ON EYE TISSUE

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A method of calculating the concentration of a thermally denaturated protein in a site formed on eye tissue under the action of laser radiation is proposed. It is shown that this method allows one to determine the position of the indicated site in relation to the radiation wavelength, the radiant exposure, the focusing of radiation, and the duration of irradiation. The threshold and limiting radiant exposures permissible in the case of irradiation of eyes by IR laser radiation for medical purposes have been determined.

Lasers are widely used in medicine, in particular in ophthalmology. A high-intensity laser radiation exerts a different thermal action on different pathologic sites due to the selectivity of absorption of this radiation by tissues. It is used, e.g., for thermal coagulation of vascular neoplasms in the case of diabetic retinopathy [1] and of tumors in a vascular layer [2] or for heating the cornea of an eye for the purpose of changing its refractivity [3]. In this case, it is necessary to exactly know the localization of the laser-action site and its dimensions as well as the threshold of laser-radiation action at different focusings, wavelengths, and radiation-pulse durations. It is agreed that the threshold energy of a laser radiation is the energy of a laser pulse causing the minimum damage of a tissue that can be observed using a standard ophthalmoscope without recourse to special microscopic, histologic, or fluorescent investigations. On the other hand, it is agreed that a damage is threshold if it denaturates the proteins in a tissue to the level exp (−1) [4].

A damage site arises on eye tissue under the action of laser radiation as a result of the heating of the light-absorbing layer. The cornea is transparent for visible radiation but absorbs IR radiation. The retina is heated as a result of the absorption of visible light by the thin pigmented-epithelium layer at the eye grounds. All tissues absorb a 1.3–1.7-μm radiation. It will be assumed that the temperatures of a tissue heated by a laser radiation are known at every instant of time.

The heat-conduction equation with homogeneous initial conditions and boundary conditions of the third kind on the frontal surface has the form

$$C_i \frac{\partial T}{\partial t} = \frac{1}{r} \frac{\partial}{\partial r} \left(\kappa_i r \frac{\partial T}{\partial r} \right) + \frac{\partial}{\partial z} \kappa_i \frac{\partial T}{\partial z} + \Phi (t)\, q\, (r, z)\,, \tag{1}$$

$$0 \le r \le r_1\,, \quad 0 \le z \le z_5\,, \quad t > 0\,, \quad i = 1, 2, ..., 5\,;$$

$$T\,(0, r, z) = T_{\text{ph}}\,, \quad \frac{\partial T\,(t, 0, z)}{\partial r} = 0\,, \quad T\,(t, r_1, z) = T_{\text{ph}}\,; \tag{2}$$

$$\frac{\partial T\,(t, r, z_5)}{\partial z} = 0\,, \quad \kappa_1 \frac{\partial T\,(t, r, 0)}{\partial z} = -\,\alpha\,[T\,(t, r, 0) - T_0]\,,$$

the heat source in the ith layers of a tissue, having different absorption coefficients, is defined as

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$$q(r, z) = Ek_i \exp(-k_i(z - z_{i-1})) \exp\left[-\sum_{l=1}^{i-1} k_l (z_l - z_{l-1})\right] \varphi\left(\frac{r}{r_0}\right). \quad (3)$$

The influence of the radiation scattering was investigated in [1].

Using a nonuniform space-time grid, we approximated the system of equations (1)–(2) using an economical, local, one-dimensional difference scheme. The numerical method of solving this nonstationary, two-dimensional, heat-conduction equation was described in detail in [1–3].

The denaturation of the retina proteins under the action of a pulsed laser radiation is usually calculated on the assumption that the denaturation reaction

$$\frac{df}{dt} = -K(T) f \quad (4)$$

is irreversible when the relative concentration f of the nondamaged protein in the tissues $f = 1$ at the initial instant of time $t = 0$; $K(T)$ is the denaturation reaction rate determined by the theory of absolute reaction rate:

$$K(T) = \frac{k_b T}{h} \exp\left(-\frac{\Delta G}{RT}\right). \quad (5)$$

Here, ΔG is the change in the free Gibbs energy, which is equal to $\Delta G = \Delta H - T\Delta S$ at a constant pressure, while $\Delta G = \Delta U + P\Delta V - T\Delta S$ at a variable pressure characteristic of nanosecond pulses, where ΔV is the corresponding change in volume caused by the pressure wave formed as a result of the action of a short laser pulse on the tissue [5].

In the case of a high-intensity laser radiation action, where the electric-field strength is high, one should take into account the influence of this field: $\Delta G = \Delta U + P\Delta V - T\Delta S - \Gamma W$.

When the denaturation reaction is irreversible, the pressure is assumed to be constant, and the influence of the laser-radiation electric field is ignored:

$$\ln f = -\int K(T) dt, \quad (6)$$

$$K(T) = \frac{kT}{h} \exp\left(-\frac{\Delta H - T\Delta S}{RT}\right), \quad (7)$$

where the parameters ΔH and ΔS determine the temperature dependence of the denaturation-rate constant. The eye tissue, as any biological tissue, consists of many bioorganic components, each of which can specifically react to a thermal action. However, calculations of the kinetics of denaturation of the retina and cornea tissues have shown that the reaction-rate constants can be averaged in the case where a thermal action is exerted by an IR laser radiation [6]. For example, ΔS = 364.2 J/(mole·K) and ΔH = 181,900 J/mole for the cornea tissue, ΔS = 889 J/(mole·K) and ΔH = 350,000 J/mole for the rabbit-eye retina, and ΔS = 700 J/(mole·K) and ΔH = 310,000 J/mole for the primate retina [7].

Since the variable temperature $T(t)$ involved in Eq. (5) was determined by numerical solution of the heat-conduction equation (1) in grid nodes, this temperature in the intervals between the nodes j and $j + 1$ will be determined by the linear interpolation

$$T(t) = T_j + \frac{T_{j+1} - T_i}{\tau}(t - t_j), \quad \tau = t_{j+1} - t_j, \quad t_j < t < t_{j+1}. \quad (8)$$

When the temperatures are determined at the nodes j and $j + 1$ of the difference grid, an analytical solution of the thermal-denaturation kinetics equation has the form

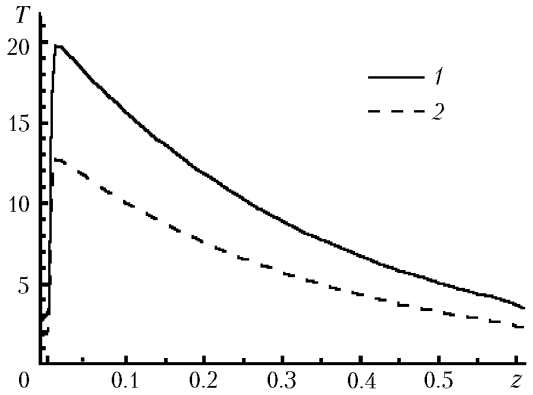

Fig. 1. Distribution of temperatures over the thickness of the eye cornea (0.6 mm) exposed to a holmium-laser radiation at a threshold radiant exposure of 2.9 J/cm^2: 1) temperature at the center of the laser spot (R = 0); 2) temperature at the periphery of the laser spot (R = 0.6 mm). z, mm; T, $^{\circ}$C.

$$\ln \frac{f_{j+1}}{f_j} = \frac{k}{h\,(T_{j+1} - T_j)} \left(\frac{\Delta H}{R}\right)^2 \left[\gamma\left(-2, \frac{\Delta H}{RT_j}\right) - \gamma\left(-2, \frac{\Delta H}{RT_{j+1}}\right)\right] \exp\left(-\frac{\Delta S}{R}\right), \tag{9}$$

where $\gamma(p,\ x) = \int_0^x t^{p-1} \exp(-t)dt$ is an incomplete gamma function with a parameter p [8]. Thus, the solution of the denaturation problem at a known nonstationary temperature field in the reaction-irreversibility approximation is reduced to the construction of a numerical algorithm for calculating an incomplete gamma function with $p = -2$.

In actuality, the process of formation of a laser-damage site is reversible:

$$\frac{df}{dt} = -K\,(T)\,f + K_{\text{re}}\,(T)\,(1-f)\,, \tag{10}$$

where $K_{\text{re}}(T)$ is the rate of the reduction reaction.

At physiological temperature, the rates of the damage and reduction reactions are equal. At a higher temperature, the rate of the direct reaction is higher than the rate of the inverse reaction by several orders of magnitude, which makes it possible to disregard its contribution.

This assumption is warranted for short laser pulses. However, the use of it for calculating the threshold energy of a long pulse (whose duration exceeds 1 sec) leads to a paradoxical result — the complete denaturation $f = 0$ is attained for a finite time at a pulse energy as small as is wished. This points to the fact that, in the case of long thermal actions, the assumption that the reaction considered is irreversibile is incorrect. The rate of the reduction reaction $K_{\text{re}}(T)$ (i.e., the rate of healing of a microscopic burn at the eye grounds) is insufficiently understood, and its temperature dependence is unknown.

However, to calculate the process of formation of a laser-action site, we need not know the rate constant of the irreversible reaction. It will suffice to write the reaction kinetics equation in a form satisfying the dynamic-equilibrium requirement: the concentration of the nondamaged protein at physiological temperature remains unchanged. In this case, the calculation of the concentration is based on the solution of the equation

$$\frac{df}{dt} = -\left[K\,(T) - K\,(T_{\text{ph}})\right] f\,, \tag{11}$$

where T_{ph} is the physiological temperature.

This computational method is free of the above-indicated disadvantage and satisfies the natural asymptotic condition — the irradiation by a zero-power radiation does not lead to the formation of a damage site at the eye

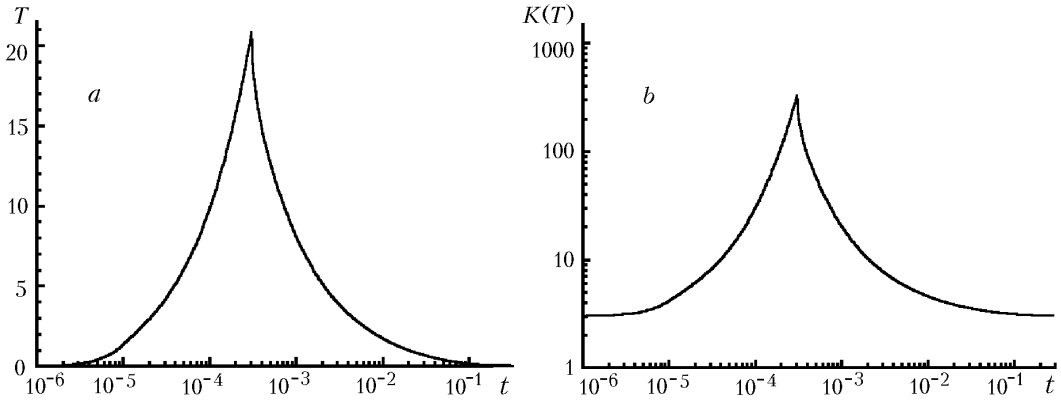

Fig. 2. Time dependence of the temperature (a) and the protein-denaturation rate constant (b) at a threshold laser-radiation action on the eye cornea; the pulse duration is 300 μsec. t, sec; T, ^{o}C; $K(T)$, sec^{-1}.

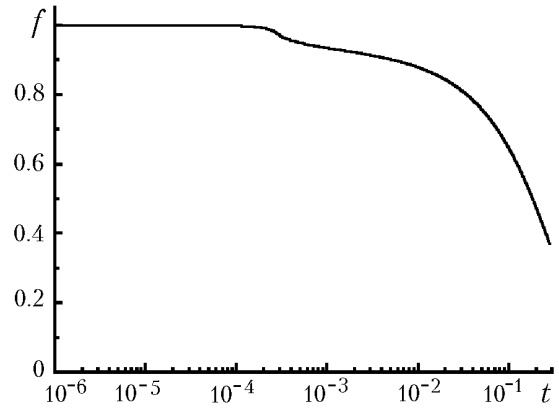

Fig. 3. Change in the concentration of the nondamaged protein in the cornea tissues calculated at temperatures shown in Fig. 2. t, sec.

grounds at any duration of irradiation. In this case, the denaturation kinetics is calculated by numerical integration of Eq. (7).

By way of example, we will consider the threshold parameters of irradiation in the case of action of a holmium-doped yttrium aluminum garnet laser (Ho:YAG laser, λ = 2.06 μm) on the cornea [9]. The threshold energy measured in [9] (at a duration of a holmium-laser pulse of 100 μsec and a laser-spot diameter of 1.8 mm) was 2.9 J/cm^2. At this wavelength, the absorption coefficient of the cornea tissues k = 2820 m^{-1}.

The nonstationary temperature field in the cornea at the above-indicated laser-radiation parameters was calculated by the method described in [1, 3], and the concentration of the nondamaged protein was determined by the method proposed. Figure 1 shows the axial distributions of temperatures over the cornea thickness, at the center of a laser spot, and at the periphery of the spot — at a distance of 0.6 mm from its center. At the indicated pulse duration, the threshold temperature is the temperature exceeding the physiological temperature by approximately 20 deg.

The physiological temperature of the human cornea T_{ph} = 35.4^{o}C [10], and the denaturation-rate constant is equal to approximately 1 sec^{-1} at thermochemical constants ΔH = 181,900 J/mole and ΔS = 364.2 J/(mole·K). As for the rate constant at temperatures higher than the physiological temperature, Fig. 2a shows the change in the temperature on the cornea surface at a threshold action of a holmium-laser pulse of duration 300 μsec. The corresponding change in the rate constant is shown in Fig. 2b. It is seen from this figure that the rate constant of the denaturation proceeding during the laser pulse is two times higher than the denaturation-rate constant at physiological temperature.

The values of f are calculated until f = exp (–1). This is attained in the following way. The initial calculation data are temperatures determined as time functions in accordance with the mathematical model of [1, 3] for an arbi-

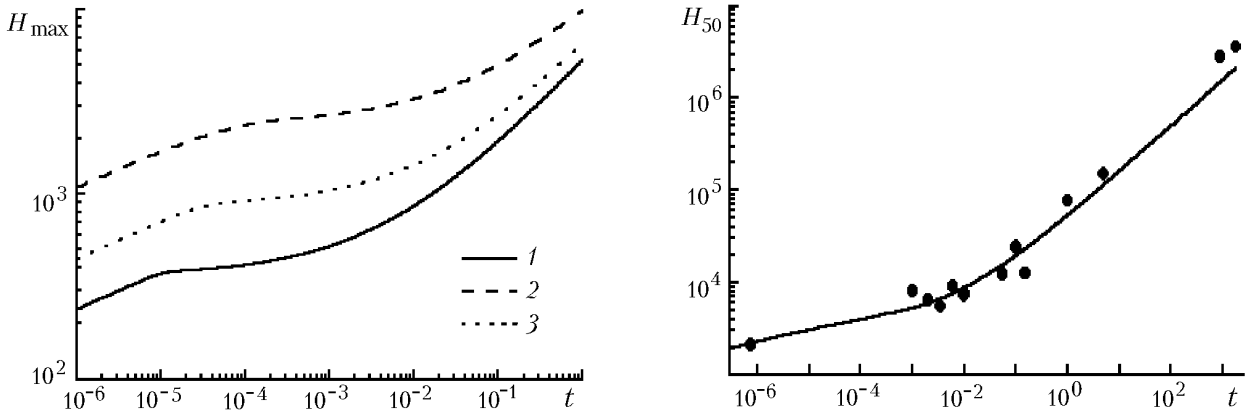

Fig. 4. Time dependence of the limiting permissible radiant exposure H_{max} calculated for three types of lasers at a pulse duration of 0.3 sec (H_{max} is ten times lower than H_{50}): λ = 10.6 μm and $k = 10^5$ m^{-1} (1), 1.91 μm and 10^4 m^{-1} (2), 2.09 μm and 3000 m^{-1} (3). t, sec; H_{max}, H_{50}, J/m^2.

Fig. 5. Experimental and calculated values of the threshold radiant exposure H_{50} in the case of action of a CO_2-laser radiation (λ = 10.6 μm) on the eye tissues at an exposure duration t ranging from $7\cdot10^{-7}$ to 1800 sec. The points are experimental data. H_{50}, J/m^2; t, sec.

trary initial radiant exposure. In numerically solving the concentration equation (11), the iteration is performed by division of a segment in two. The iteration process converges fairly rapidly to the desired threshold radiant exposure. The calculation gives the values of the temperatures and concentrations at a threshold radiant exposure for a given laser-radiation wavelength.

Figure 3 shows the change in the concentration of the protein at the center of a laser spot on the cornea surface, calculated at temperatures presented in Fig. 2a. It is seen from the graph presented that the denaturation process is not terminated at the instant the laser-pulse action ceases; it proceeds during the whole period of cooling, i.e., until the temperature decreases to the physiological temperature. In the example considered, at the instant the temperature reaches a maximum (300 μsec) the concentration of the nondamaged protein decreases only by 3% and the threshold concentration is attained in 0.3 sec. The time of cooling is mainly determined by the laser-spot size.

The threshold energy H_{50} calculated by the method proposed represents a base for calculating the limiting permissible radiant exposure H_{max} that is lower than the threshold radiant exposure by a coefficient of hygienic reserve, which is assumed to be tenfold. However, it was shown in [1, 11] that, because of the low absorption of the tissues of the frontal part of the eye, the probability of thermal damage of the retina is fairly high in the wavelength range 1.6–1.75 μm (near-IR range) since this radiation is focused at the eye grounds. Because of this, the coefficient of hygienic reserve in the above-indicated IR range was taken to be equal to 15. The dependences of the threshold energy H_{50} calculated under these assumptions and the limiting permissible radiant exposure H_{max} calculated for three laser-radiation wavelengths on the laser-pulse duration are presented in Fig. 4. These three wavelengths are generated by two types of pulsed solid-state lasers and continuous-wave CO_2 lasers and correspond to practically all the absorption bands of the eye media — from 3000 to 10^5 m^{-1}. The calculation data agree with the experimental ones obtained at different durations of pulses. It should be noted that the threshold radiant exposures were measured for pulsed lasers only at pulse durations of no larger than 0.1 sec, while a large number of experimental data were obtained for continuous-wave CO_2 lasers at pulse durations ranging from $7\cdot10^{-7}$ to 1800 sec. All these experimental data fit in the calculation curve shown in Fig. 5.

Thus, the method proposed for numerically determining the concentration of the thermally denaturated protein in tissues exposed to laser radiation allows one to determine both the threshold and limiting permissible radiant exposures in the case where a laser radiation is used for medical purposes.

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NOTATION

C, heat capacity per unit volume, J/(m^3·K); E, radiant flux, W/m^2; f, relative concentration of protein; G, Gibbs energy, J/mole; H, enthalpy, J/mole; H_{50}, threshold radiant exposure, J/m^2; H_{max}, limiting permissible radiant exposure, J/m^2; h, Planck constant; k, absorption coefficient, m^{-1}; k_b, Boltzmann constant; K, rate constant, sec^{-1}; P, pressure, N/m^2; r, radial coordinate, m; R, universal gas constant; r_0, laser-beam radius, m; S, entropy, J/(mole·K); t, time, sec; T, temperature, K; q, heat release per unit volume; W/m^3; U, energy, J/mole; V, volume, m^3; W, electric-field strength, V/m; z, axial coordinate, m; α, heat-transfer coefficient on the cornea surface, W/(m^2·K); γ, gamma function; Γ, coefficient of structural sensitivity; κ, heat conduction, W/(m·K); λ, wavelength, μm; Φ, radiation-intensity distribution as a function of time; φ, radial distribution of radiation intensity. Subscripts: 0, ambient air; re, reduction reaction; ph, physiological value; i, serial number of a radiation-absorbing layer; j, index related to time; l, index of summation.

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