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Immune system aging may be affected by HIV infection: the mathematical model of immunosenescence

T. E. SANNIKOVA*, S. G. RUDNEV *, A. A. ROMANYUKHA*, and A. I. YASHIN†

Abstract — In this paper, we analyse the structure of equations in the earlier proposed mathematical model of the dynamics of age-related changes in population of peripheral T lymphocytes. To investigate behaviour of the model solutions in a wide range of values of variables we introduce a linear relation between the rate constants of T lymphocytes proliferation and the values of the mean length of telomeric chromosome fragments spent by naive and memory cells in the course of immune response, as well as the dependence of these parameters on the value of the cell replicative potential. We obtain sufficient conditions for existence, uniqueness, and positiveness of solutions over the whole time interval. The results of numerical calculations illustrate the capabilities of the model for describing accelerated aging mechanisms of the immune system using the example of HIV infection.

In [16], there was proposed the mathematical model of the dynamics of age-related changes in population of peripheral T lymphocytes. T lymphocytes account for most (approximately 75%) of cells in the lymphatic nodes and are responsible for the rate and amplitude of essentially all immune processes and especially antiviral immunity. As compared to other components of the immune defense of an organism, the changes in the T immunity system with age are most pronounced [2] and hence responsible for the rate of the immune system aging as a whole. Thus, the mathematical model of age-related changes in the peripheral T lymphocyte population can be regarded as a model of the immune system aging.

The model parameters in [16] were adjusted by the data obtained from healthy donors of various ages. This allows one, in particular, to assume the constancy of antigen load (the absence of prolonged and severe diseases) and the normal steady functioning of various subsystems and organs of the immune system during lifetime. The next logical step is an attempt to use this model for describing the immune system aging in severe and chronic diseases.

The peripheral T lymphocyte population consists of cells of two types: naive T lymphocytes and memory cells. T lymphocytes that do not participate in an immune response are called naive T lymphocytes. In the course of immune response to an

*Institute of Numerical Mathematics of the Russian Academy of Sciences, Moscow GSP-1, 119991, Russia

†Center for Demographic Studies, Duke University, Durham, NC 27708, USA

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antigen, the specific naive T lymphocytes undergo clonal expansion and differentiation which involves 15–20 cell divisions, the number of cells of given specificity thus increases 10^5- to 10^6-fold. Upon removing the antigen, the main part of these cells (90–95%) die of apoptose during several days, the other cells form the population of memory cells. The memory cells concentration of given specificity is generally much higher than the concentration of the initial population of naive cells, which ensures the higher rate and amplitude of the secondary immune response [19].

The normal function of the immune system in a human over 20 is characterized by a surplus of the produced T memory lymphocytes, which leads to a competition among them and a decrease in the mean lifetime of these cells. With age, the thymus lymphoid tissue contracts and the influx rate of naive T cells decreases, which leads to a decrease in their concentration and causes them to gradually release the occupied niche. Consequently, the excessively produced T memory cells can compete not only for their niche but also for the released part of the naive cells' niche. We assume that the total number of lymphocytes in an organism depends on the volume of the peripheral immune system. If the total number of lymphocytes becomes larger than the lymphatic nodes can accommodate, they are subject to accelerated death. If the total number of lymphocytes becomes smaller, they and, first of all, the memory cells proliferate until the released space is filled [8, 19].

Since the age of 18–20 and over the next 15–20 years there is in a human organism a fast (four- to five-fold) decrease in the amount of lymphoid tissue of the thymus, with the process subsequently slowing down. The quantitative characteristics of the age-related changes in the peripheral organs of the immune system are discussed much more rarely. Analysis of the histological data shows that, with age, the intact peripheral lymphoid tissue (IPLT) is replaced by connective and fat tissues [17].

The lymphocyte division process is accompanied by a gradual shortening of the length of the end parts of chromosomes that are called telomeres. After the telomeres in a given cell contract to a certain length (4000–5000 pairs of bases per cell), the cell loses its proliferative capacity [5]. This critical length is called the Hayflick limit. The telomere length may serve as a measure of the replicative potential of cells and hence is an important characteristic of their immunocompetence [14]. Note that with age there is a decrease in the length of telomeres in hemopoietic stem cells as well [21]. This also reduces the replicative potential of their progenies. A decrease in the rate of the production of naive T lymphocytes and the supply of antigens in an organism, which cause an immune response, result in an increase with age in the fraction of memory cells with a low replicative potential. They force out the naive cells with a higher replicative potential. Normally, the proliferative capacity of lymphocytes decreases gradually over 50–60 years and the critical decrease occurs at the age of 80–90 [7]. The problems of influence of the immune system aging on morbidity and mortality have been studied extensively in [1, 22].

Under the conditions of constant and relatively low antigen load, a decrease in the proliferative capacity of lymphocytes only slightly affects the background process of the cell population renewal. However, when the antigen load increases

considerably as, for example, in the case of chronic relapsing infectious diseases, this factor can substantially change the dynamics of the process described by the model. An increased turnover of T and B lymphocytes caused by the prolonged presence of a pathogen often leads to a substantial impairment of the immune defense and the development of secondary immunodeficiency. Moreover, as a result of enhanced antigen stimulation, the division rate of lymphocytes can increase five- to ten-fold as compared to the normal state [20]. If this process lasts for a long time, the proliferative potential of peripheral T lymphocytes and, primarily, the memory cells decreases and starts to limit the rate of their proliferation well before the beginning of the old age. Finally, part of the memory cells that receive an activation signal has only two or three division cycles, and the rest cells fail to divide at all [4].

This is the case with severe viral infections, HIV infection is a dramatic example. During HIV infection, the aging of the immune system is four-five times faster than that in the norm [3]. It is interesting to study the mechanisms of the immune homeostasis maintenance under these conditions. Therefore along with the justification of the structure and the characteristic of the properties of solutions to the system of equations in the mathematical model of the dynamics of age-related changes in the peripheral T lymphocyte population, we consider the possibilities of the application of the model to the description of the mechanisms of the immune system accelerated aging in HIV infection.

1. JUSTIFICATION OF THE STRUCTURE OF MODEL EQUATIONS

According to the described scheme of age-related changes in T cell immunity, we assume that:
1. The population of naive cells in the IPLT is replenished with their influx from the thymus.
2. The naive T lymphocytes participate in immune response to various antigens whose total impact on the immune system is generalized by an antigen load notion.
3. As a result of primary immune response, the main part of the formed population of specific lymphocytes dies, the rest part transforms into the memory cells.
4. The specific T memory cells that ultimately replenish their own population participate in an immune response to an already known antigen.
5. The process of cell division is accompanied by a decline in their replicative potential and the replicative potential of their progeny.
6. The concentration of T lymphocytes in the IPLT is maintained by the regulation of the lifetime of memory cells.
7. With age, there occurs a reduction in the IPLT volume, the production rate of naive T lymphocytes in the thymus as well as in the length of telomere repeats in stem cells.

We consider the following model variables:

$N(t)$ is the concentration of naive T lymphocytes in the IPLT at time t [cell/ml];

$P_N(t)$ is the mean length of telomere repeats in the naive T lymphocyte population at time t [b.p./cell];

$M(t)$ is the concentration of T memory cells in the IPLT at time t [cell/ml];

$P_M(t)$ is the mean length of telomere repeats in the population of T memory cells at time t [b.p./cell];

$N^*(t)$ is the rate of naive T lymphocytes influx into the IPLT at time t [cell/day];

$V(t)$ is the IPLT volume at time t [ml];

$P^*(t)$ is the length of telomere repeats in naive T cells produced at time t [b.p./cell].

The mathematical model of the dynamics of age-related changes in the population of peripheral T lymphocytes is constructed in the form of the system of ordinary differential equations. We assume that the immune system cells and antigens in the IPLT volume are distributed uniformly. We consider interactions between them by the mass action law.

The formula for the finite increment in $N(t)$ over the period $[t;t+\Delta t]$ up to terms of 2nd-order infinitesimal with respect to Δt has the form

$$\Delta N(t) = N(t+\Delta t) - N(t) = \frac{N^*(t)}{V(t)}\Delta t - \alpha_1 \frac{L}{V(t)} N(t)\Delta t - \mu_N N(t)\Delta t - \frac{V(t+\Delta t) - V(t)}{V(t)} N(t+\Delta t). \tag{1.1}$$

The first term in the right-hand side of this equation describes an increase in time Δt in the concentration of naive T lymphocytes in the IPLT as a result of their influx from the thymus. The second term describes a decrease in the concentration of naive T lymphocytes as a result of their antigenic stimulation and the multiplication/death processes with the formation of the population of T memory cells. We assume that the transition rate is proportional to $N(t)$ and the specific antigen load $L/V(t)$, where L is the total antigen load (this value is assumed to be constant). The proportionality coefficient α_1 characterizes the sensitivity of naive T lymphocytes to antigen stimulation. The third term describes the natural death of naive T lymphocytes. The value μ_N is inverse to the mean lifetime of these cells in the absence of antigen stimulation. The last term describes changes in $N(t)$ with the volume $V(t)$. Indeed, the conservation law of the number of cells can be written as $N(t)V(t) = N(t+\Delta t)V(t+\Delta t)$, whence we obtain the desired expression for $\Delta N(t)$ upon obvious transformations. If we divide relation (1.1) by Δt and pass to the limit as $\Delta t \to 0$, we obtain the equation for the dynamics of the concentration of naive T lymphocytes in the IPLT:

$$\frac{\mathrm{d}N}{\mathrm{d}t} = \frac{N^*}{V} - \alpha_1 \frac{L}{V} N - \mu_N N - \frac{\mathrm{d}V}{\mathrm{d}t}\frac{N}{V}. \tag{1.2}$$

Analogously we construct the equation for the concentration of T memory cells in the IPLT. In the final form it is written as

$$\frac{\mathrm{d}M}{\mathrm{d}t} = \rho_1 \alpha_1 \frac{L}{V} N + \rho_2 \alpha_2 \frac{L}{V} M + \mu_M (C^* - N - M) - \frac{\mathrm{d}V}{\mathrm{d}t}\frac{M}{V}. \tag{1.3}$$

The first term in the right-hand side of this equation describes an increase in the memory cells concentration as a result of division and differentation of naive T lymphocytes. The coefficient ρ_1 is equal to the mean number of memory cells produced by an immune response from a single naive T cell. The second term describes the multiplication of T memory cells. The coefficient ρ_2 is equal to the number of lymphocytes reduced by unity, which are produced by an immune response from a single memory cell. The value α_2 characterizes the sensitivity of T memory cells to antigen stimulation. We assume that the homeostatic regulation mechanism of the immune system provides the maintenance of the constant concentration of T lymphocytes in the IPLT. This assumption is associated with the structure of the third term in the right-hand side of (1.3). Here C^* is the lower bound of the normal T lymphocyte concentration in the IPLT and μ_M is the specific rate of the death of 'excessive' memory cells. The last term takes into account changes in the memory cells concentration as the IPLT volume changes.

We construct the dynamic equation for the mean length of telomere repeats of naive T lymphocytes and memory cells. An increment in the total length of telomere repeats in the naive T lymphocyte population over the period $[t;t+\Delta t]$ has the form

$$\begin{aligned} P_N(t\ +\ \Delta t)N(t+\Delta t)V(t+\Delta t) - P_N(t)N(t)V(t) \\ = N^*(t)P^*(t)\Delta t - (\alpha_1 LN(t) + \mu_N N(t)V(t))P_N(t)\Delta t \end{aligned} \tag{1.4}$$

where the first term to the right of the sign of equality characterizes an increase in the total length of telomere repeats at time Δt as a result of the influx of T lymphocytes from the thymus. The second term characterizes a decrease in the total length of telomere repeats as a result of the transition of naive T lymphocytes to the memory cells and the natural death of the naive cells [see the first and third terms in the right-hand side of (1.2)]. We rewrite relation (1.4) as

$$\begin{aligned} \frac{P_N(t+\Delta t) - P_N(t)}{\Delta t} = \frac{P_N(t)N(t)V(t) - P_N(t)N(t+\Delta t)V(t+\Delta t)}{N(t+\Delta t)V(t+\Delta t)\Delta t} \\ + \frac{N^*(t)P^*(t)\Delta t - (\alpha_1 LN(t) + \mu_N N(t)V(t))P_N(t)\Delta t}{N(t+\Delta t)V(t+\Delta t)\Delta t}. \end{aligned} \tag{1.5}$$

Passing to the limit as $\Delta t \to 0$, we get

$$\frac{\mathrm{d}P_N}{\mathrm{d}t} = -\frac{P_N}{NV}\frac{\mathrm{d}}{\mathrm{d}t}(NV) + \frac{N^*P^*}{NV} - \alpha_1\frac{LP_N}{V} - \mu_N P_N. \tag{1.6}$$

From (1.2) it follows that

$$\frac{\mathrm{d}}{\mathrm{d}t}(NV) = \frac{\mathrm{d}N}{\mathrm{d}t}V + \frac{\mathrm{d}V}{\mathrm{d}t}N = N^* - \alpha_1 LN - \mu_N NV. \tag{1.7}$$

Thus,

$$\begin{aligned} \frac{\mathrm{d}P_N}{\mathrm{d}t}\ &= -\frac{P_N}{NV}(N^* - \alpha_1 LN - \mu_N NV) + \frac{N^*P^*}{NV} - \frac{\alpha_1 LP_N}{V} - \mu_N P_N \\ &= (P^* - P_N)\frac{N^*}{NV}. \end{aligned} \tag{1.8}$$

Therefore the equation for the mean length of telomeres in naive T lymphocytes in the ILPT has the form

$$\frac{\mathrm{d}P_N}{\mathrm{d}t} = (P^* - P_N)\frac{N^*}{NV}. \tag{1.9}$$

The increment in the total length of telomeres in the population of T memory cells over the period $[t;t+\Delta t]$ is representable as

$$\begin{aligned} P_M(t+\Delta t)M(t+\Delta t)V(t+\Delta t) - P_M(t)M(t)V(t) \\ = \rho_1\alpha_1 LN(t)(P_N(t)-\lambda_N)\Delta t + \rho_2\alpha_2 LM(t)(P_M(t)-\lambda_M)\Delta t \\ -\alpha_2 LM(t)\lambda_M\Delta t + \mu_M V(t)(C^* - N(t) - M(t))P_M(t)\Delta t. \end{aligned} \tag{1.10}$$

The first term in the right-hand side of this equation describes an increase in the total length of telomere repeats in the T memory cells population as a result of the proliferation and differentiation of naive T lymphocytes; $(P_N(t)-\lambda_N)$ is the mean length of telomeres in T memory cells, which are formed from naive T cells at time t (λ_N is the mean number of the pairs of bases by which the length of the telomeres of the naive T lymphocytes is reduced as a result of an immune response). The second term describes the change in the total length of telomeres in T memory cells as a result of their own division, where $(P_M(t)-\lambda_M)$ is the mean length of telomeres in the progeny of dividing memory cells, which were formed at time t. The third term describes the shortening of the mean length of telomeres in dividing memory cells as a result of an immune response. The fourth term in the right-hand side of (1.10) describes the changes caused by the homeostatic regulation of the total number of T memory cells in the ILPT [see equation (1.3)]. If we transform relation (1.10) and pass to the limit as $\Delta t \to 0$, we get

$$\begin{aligned} \frac{\mathrm{d}P_M}{\mathrm{d}t} = -\frac{P_M}{MV}\frac{\mathrm{d}}{\mathrm{d}t}(MV) + \rho_1\alpha_1(P_N-\lambda_N)\frac{LN}{MV} + \rho_2\alpha_2(P_M-\lambda_M)\frac{L}{V} \\ -\alpha_2\lambda_M\frac{L}{V} + \mu_M(C^* - N - M)\frac{P_M}{M}. \end{aligned} \tag{1.11}$$

From (1.3) it follows that

$$\frac{\mathrm{d}}{\mathrm{d}t}(MV) = \frac{\mathrm{d}M}{\mathrm{d}t}V + \frac{\mathrm{d}V}{\mathrm{d}t}M = \rho_1\alpha_1 LN + \rho_2\alpha_2 LM + \mu_M V(C^* - N - M). \tag{1.12}$$

Substituting this equation in (1.11) and simplifying the relation obtained, we arrive at the equation for the dynamics of the mean length of telomeres in the T memory cell population:

$$\frac{\mathrm{d}P_M}{\mathrm{d}t} = \rho_1\alpha_1(P_N - P_M - \lambda_N)\frac{L}{V}\frac{N}{M} - (\rho_2+1)\alpha_2\lambda_M\frac{L}{V}. \tag{1.13}$$

The rate of the influx of naive T lymphocytes (N^*) from the thymus as well as the functions of age-related changes in the length of their telomeres (P^*) and

the ILPT volume (V) are represented as the linear functions of the exponents with negative powers:

$$N^*(t) = N_0^* \mathrm{e}^{-k_T t} \tag{1.14}$$

$$P^*(t) = (P_0^* - P_H)\mathrm{e}^{-k_P t} + P_H \tag{1.15}$$

$$V(t) = (V_0 - V_{\min})\mathrm{e}^{-k_V t} + V_{\min} \tag{1.16}$$

where N_0^*, P_0^*, and V_0 are the initial values at the zero instant corresponding to the age of 20, P_H is the value of the Hayflick limit, which is taken to be constant, and $V_{\min}$ is the minimum IPLT volume. Combining (1.2), (1.3), (1.9), and (1.13), we obtain the system of nonlinear ordinary differential equations for the dynamics of age-related changes in the peripheral T lymphocyte population:

$$\begin{aligned}
\frac{\mathrm{d}N}{\mathrm{d}t} &= \frac{N^*}{V} - \alpha_1 \frac{L}{V} N - \mu_N N - \frac{\mathrm{d}V}{\mathrm{d}t}\frac{N}{V} \\
\frac{\mathrm{d}M}{\mathrm{d}t} &= \rho_1 \alpha_1 \frac{L}{V} N + \rho_2 \alpha_2 \frac{L}{V} M + \mu_M (C^* - N - M) - \frac{\mathrm{d}V}{\mathrm{d}t}\frac{M}{V} \\
\frac{\mathrm{d}P_N}{\mathrm{d}t} &= (P^* - P_N)\frac{N^*}{NV} \\
\frac{\mathrm{d}P_M}{\mathrm{d}t} &= \rho_1 \alpha_1 (P_N - P_M - \lambda_N)\frac{L}{V}\frac{N}{M} - (\rho_2 + 1)\alpha_2 \lambda_M \frac{L}{V}
\end{aligned} \tag{1.17}$$

where the functions N^*, P^*, and V are given by expressions (1.14)–(1.16). We add to the system of equations (1.17) the initial conditions:

$$N(0) = N^0, \qquad M(0) = M^0, \qquad P_N(0) = P_N^0, \qquad P_M(0) = P_M^0. \tag{1.18}$$

Note that the equations for the dependent variables N and M result from the assumptions made at the beginning of this section and the conservation laws of the number of cells, whereas the equations for P_N and P_M are derived from (1.2) and (1.3) by the balance relations for the total length of telomeres. The derived system of equations mostly coincides with that suggested in [16], except that in the second term of the right-hand side of the equation for P_M the value ρ_2 (from the empirically derived equation for P_M in [16]) is replaced by $(\rho_2 + 1)$. Besides, by virtue of the fact that the length of the telomeres of stem cells is bounded below by the Hayflick limit, the formula for $P^*(t)$ is changed. A similar change is introduced for the value $V(t)$ [see (1.16)], where $V_{\min} > 0$ is an arbitrarily chosen and small enough value. The computational results show that these refinements do not introduce appreciable changes in the dynamics of solutions to the system of the model equations in the age range of interest as compared to the results obtained in [16] (data is not shown).

When constructing the model equations we implicitly assumed that the values of the parameters α_i, $i = 1,2$, and λ_i, $i = N,M$, are constant and independent of one another. However, this assumption is valid only for cell populations with high proliferative potential. When this potential decreases, the value α_i decreases, which

leads to a decrease in λ_i because the number of cell divisions reduces. Consequently, in order to study the behaviour of the model solutions in a wide range of values of the variables, it is necessary to take into account a dependence between α_i and λ_i, for example, in the form $\alpha_i/\lambda_i =$const. We further assume that this relation is valid and when decreasing the proliferative cell potential the value α_i decreases in proportion to $(P_i - P_H)/(P_i^0 - P_H)$, where P_i and P_l^0 are the lengths of the telomeres in the i-th type cells ($i = N, M$) at the instant t and the initial instant, respectively.

2. ANALYTIC TREATMENT

We assume that all the parameters and the initial conditions in the Cauchy problem (1.17)–(1.18) are positive. To prove the existence and uniqueness of its solutions we take advantage of the following theorem [13].

Suppose that in the Cauchy problem

$$\frac{\mathrm{d}X(t)}{\mathrm{d}t} = F(t, X(t)) \tag{2.1}$$

$$X(t_0) = X^0 \tag{2.2}$$

the function $F(t,X(t)) = (F_1(t,X(t)),\dots,F_n(t,X(t)))^T$ is determined and continuous on some open set Γ in the space $R_+ \times R^n$ with coordinates $(t, x_1(t),\dots,x_n(t))$, together with all the functions of the form $\partial F_i(t,X(t))/\partial x_j(t)$, $i, j = 1,\dots,n$. Then for any point $(t_0, X^0) \in \Gamma$, there exists the solution $Y(t)$ of the system (2.1), which is defined over an interval $(t_0 - \triangle, t_0 + \triangle)$ and satisfies the condition $Y(t_0) = X^0$. This solution is continuous and unique.

We consider the domain $\Gamma = ((t, N, M, P_N, P_M) : t > 0,\ N > 0,\ M > 0,\ P_N > 0,\ P_M > 0)$. The hypotheses of the theorem are valid for our system if for any $t > 0$ we have $N(t) \neq 0$ and $M(t) \neq 0$.

Transforming the first equation in the system (1.17), we get

$$\begin{aligned}\frac{\mathrm{d}N}{\mathrm{d}t} &= \frac{N^*}{V} - \Big(\alpha_1 \frac{L}{V} + \mu_N + \frac{1}{V}\frac{\mathrm{d}V}{\mathrm{d}t}\Big)N \\ &= \frac{N_0^* \mathrm{e}^{-k_T t}}{(V_0 - V_{\min})\mathrm{e}^{-k_V t} + V_{\min}} - \left[\frac{\alpha_1 L - k_V(V_0 - V_{\min})\mathrm{e}^{-k_V t}}{(V_0 - V_{\min})\mathrm{e}^{-k_V t} + V_{\min}} + \mu_N\right] N. \end{aligned} \tag{2.3}$$

Let

$$A(t) = \frac{N_0^* \mathrm{e}^{-k_T t}}{(V_0 - V_{\min})\mathrm{e}^{-k_V t} + V_{\min}}, \qquad B(t) = \frac{\alpha_1 L - k_V(V_0 - V_{\min})\mathrm{e}^{-k_V t}}{(V_0 - V_{\min})\mathrm{e}^{-k_V t} + V_{\min}} + \mu_N.$$

Then we can write

$$\frac{\mathrm{d}N}{\mathrm{d}t} = A(t) - B(t)N. \tag{2.4}$$

The solution of this equation has the form

$$N(t) = \mathrm{e}^{-\int_0^t B(\tau)\mathrm{d}\tau}\left[\int_0^t A(\tau)\mathrm{e}^{\int_0^\tau B(\zeta)\mathrm{d}\zeta}\mathrm{d}\tau + N^0\right]. \tag{2.5}$$

Since all the parameters in the system of equations and the initial conditions are positive, for all $t > 0$ we have $A(t) > 0$. Taking into account that $N^0 > 0$, we obtain $N(t) > 0$ for any $t > 0$.

Let us consider the second equation in the system (1.17):

$$\begin{aligned}\frac{\mathrm{d}M}{\mathrm{d}t} &= \rho_1\alpha_1\frac{L}{V}N + \rho_2\alpha_2\frac{L}{V}M + \mu_M(C^* - N - M) - \frac{\mathrm{d}V}{\mathrm{d}t}\frac{M}{V} \\ &= \frac{\rho_1\alpha_1 LN}{(V_0 - V_{\min})\mathrm{e}^{-k_V t} + V_{\min}} + \mu_M(C^* - N) \\ &\quad + \left[\frac{\rho_2\alpha_2 L + k_V(V_0 - V_{\min})\mathrm{e}^{-k_V t}}{(V_0 - V_{\min})\mathrm{e}^{-k_V t} + V_{\min}} - \mu_M\right] M. \quad (2.6)\end{aligned}$$

Whence,

$$\frac{\mathrm{d}M}{\mathrm{d}t} = E(t) + G(t)M$$

where

$$E(t) = \frac{\rho_1\alpha_1 LN}{(V_0 - V_{\min})\mathrm{e}^{-k_V t} + V_{\min}} + \mu_M(C^* - N)$$

$$G(t) = \frac{\rho_2\alpha_2 L + k_V(V_0 - V_{\min})\mathrm{e}^{-k_V t}}{(V_0 - V_{\min})\mathrm{e}^{-k_V t} + V_{\min}} - \mu_M.$$

The solution of equation (2.6) has the form

$$M(t) = \mathrm{e}^{\int_0^t G(\tau)\mathrm{d}\tau}\left[\int_0^t E(\tau)\mathrm{e}^{-\int_0^\tau G(\zeta)\mathrm{d}\zeta}\mathrm{d}\tau + M^0\right]. \quad (2.7)$$

Since $M^0 > 0$, for $M(t)$ to be positive, it is sufficient to satisfy the condition $E(t) > 0$ for any $t > 0$. This relation is valid if for any $t > 0$ we have $N(t) \leqslant C^*$.

We consider equation (1.7). If we solve the linear differential equation $\mathrm{d}x/\mathrm{d}t = N^*(t) - \mu_N x$, where $N^*(t) = N_0^*\exp(-k_T t)$, and use the majorization theorem [11], we thus get

$$N(t)V(t) \leqslant \frac{N_0^*}{\mu_N - k_T}\mathrm{e}^{-k_T t} + \left(N^0V_0 - \frac{N_0^*}{\mu_N - k_T}\right)\mathrm{e}^{-\mu_N t}.$$

Taking into account the equality $V(t) = (V_0 - V_{\min})\exp(-k_V t) + V_{\min}$, we have

$$\begin{aligned}N(t) &\leqslant \frac{1}{[(V_0 - V_{\min})\mathrm{e}^{-k_V t} + V_{\min}]}\left[\frac{N_0^*}{\mu_N - k_T}\mathrm{e}^{-k_T t} + \left(N^0V_0 - \frac{N_0^*}{\mu_N - k_T}\right)\mathrm{e}^{-\mu_N t}\right] \\ &= \frac{1}{V_0 - V_{\min} + V_{\min}\mathrm{e}^{k_V t}} \\ &\quad \times \left[N^0V_0\mathrm{e}^{(k_V - \mu_N)t} + \frac{N_0^*}{k_T - \mu_N}\left(\mathrm{e}^{(k_V - \mu_N)t} - \mathrm{e}^{(k_V - k_T)t}\right)\right]. \quad (2.8)\end{aligned}$$

We denote the right-hand side of this inequality by $f(t)$, and $f(0) = N^0$. It is not difficult to see that the function $f(t)$ monotonously decreases with increasing t if the conditions $k_V \leqslant \mu_N$ and $k_V \leqslant k_T$ are simultaneously satisfied ($\mu_N \neq k_T$). In this case, for $N(0) \leqslant C^*$ we obtain $N(t) \leqslant C^*$ and hence $M(t) > 0$ for any $t > 0$. A similar proposition can be proved for the case $\mu_N = k_T$, but the proof is cumbersome and therefore is not presented here.

The positiveness of P_N and P_M is established in the same way as in the investigation of the basic mathematical model of infectious disease [12]. Let us show that, given the condition $P_0^* - P_H > 0$, the inequality $P_N(t) \geqslant P_H$ holds for any $t > 0$. Suppose this is not the case. Then in view of the continuity of P_N, there exists the point $t_0 > 0 : P_N(t_0) = P_H$, and $\mathrm{d}P_N/\mathrm{d}t|_{t=t_0} < 0$. From the third equation of the system (1.17), with allowance for (1.15), we have

$$\frac{\mathrm{d}P_N}{\mathrm{d}t}(t_0) = (P_0^* - P_H)\mathrm{e}^{-k_P t_0}\frac{N^*(t_0)}{N(t_0)V(t_0)} > 0. \tag{2.9}$$

There is a contradiction. Consequently, given the above condition, we have $P_N(t) \geqslant P_H$. Analogously, when the condition $P_M^0 - P_H > \lambda_N$ is satisfied, we obtain $P_M(t) \geqslant P_H$ for all $t > 0$.

We can show that the right-hand side of (1.17) is majorized by the system of linear differential equations. Therefore the local solution can be extended to include the whole time interval studied. We consider, as an example, the first equation in the system (1.17):

$$\frac{\mathrm{d}N}{\mathrm{d}t} = \frac{N^*}{V} - \alpha_1\frac{L}{V}N - \mu_N N - \frac{\mathrm{d}V}{\mathrm{d}t}\frac{N}{V} \leqslant \frac{N_0^*}{V_{\min}} + k_V N. \tag{2.10}$$

The procedure is analogous for the second equation. In addition, it can be easily shown that the functions $P_N(t)$ and $P_M(t)$ are bounded above. Thus, we have the following assertion.

Proposition 2.1. *In the case of the positive parameters and the initial conditions, as well as the validity of the inequalities $k_V \leqslant \mu_N$, $k_V \leqslant k_T$, and $N(0) \leqslant C^*$, there exists a unique solution to the Cauchy problem* (1.17)–(1.18)*, which is defined over the whole interval $t > 0$, $N(t) > 0$ and $M(t) > 0$. If, besides, the conditions $P_0^* - P_H > 0$ and $P_M^0 - P_H > \lambda_N$ are satisfied, for all $t > 0$ we have $P_N(t) > P_H$ and $P_M(t) > P_H$.*

3. MODELLING THE ACCELERATED AGING OF THE IMMUNE SYSTEM IN HIV INFECTION

The rates and the character of the processes responsible for the dynamics of the peripheral T lymphocyte population in the course of HIV infection substantially differ from those of the processes responsible for the dynamics of the normal aging of the immune system. Of major importance are the differences:

Table 1.
Initial conditions and model parameters, which correspond to the normal aging of the immune system.

Parameter	Physical meaning	Dimension	Value
α_1	The rate constant of naive T lymphocytes proliferation	ml/g	1.5×10^4
α_2	The rate constant of T memory cells proliferation	ml/g	1.5×10^4
μ_N	The constant of the natural death rate of naive T lymphocytes	1/day	1.8×10^{-4}
μ_M	The constant of the death rate of T memory cells as a result of competition for an IPLT site	1/day	0.05
ρ_1	The mean number of T memory cells produced during an immune response from a single naive T lymphocyte	dimens-ionless	100
ρ_2	The mean number of T memory cells produced during an immune response from a single T memory cell	dimens-ionless	1.1
λ_N	The mean length of the telomeric fragment of a naive T lymphocyte, which is lost as a result of an immune response	b.p./cell	1400
λ_M	The mean length of the telomeric fragment of a T memory cell, which is lost as a result of an immune response	b.p./cell	500
C^*	The lower bound of the normal concentration of T lymphocytes in the IPLT	cell/ml	2.5×10^9
k_T	The constant of the reduction rate of the naive T lymphocyte production in the thymus	1/day	1.1×10^{-4}
k_V	The constant of the contraction rate of the IPLT volume	1/day	2.7×10^{-5}
k_P	The constant of the shortening rate of the telomere length in the precursors of naive T lymphocytes	b.p./day	1×10^{-5}
L	Antigen load	g/day	1.25×10^{-6}
N_0^*	The rate of production of naive T lymphocytes in the thymus at the age of 20	cell/day	4×10^8
V_0	The IPLT volume at the age of 20	ml	1500
$V_{\min}$	The 'minimum' IPLT volume	ml	100
P_0^*	The mean length of telomeres in naive T lymphocytes produced at the age of 20	b.p./cell	8.3×10^3
N^0	The concentration of naive T lymphocytes in the IPLT at the age of 20	cell/ml	1.9×10^9
M^0	The concentration of T memory cells in the IPLT at the age of 20	cell/ml	6.45×10^8
P_N^0	The mean length of telomeres in naive T lymphocytes at the age of 20	b.p./cell	8.8×10^3
P_M^0	The mean length of telomeres in T memory cells at the age of 20	b.p./cell	7.4×10^3
P_H	The Hayflick limit	b.p.	5×10^3

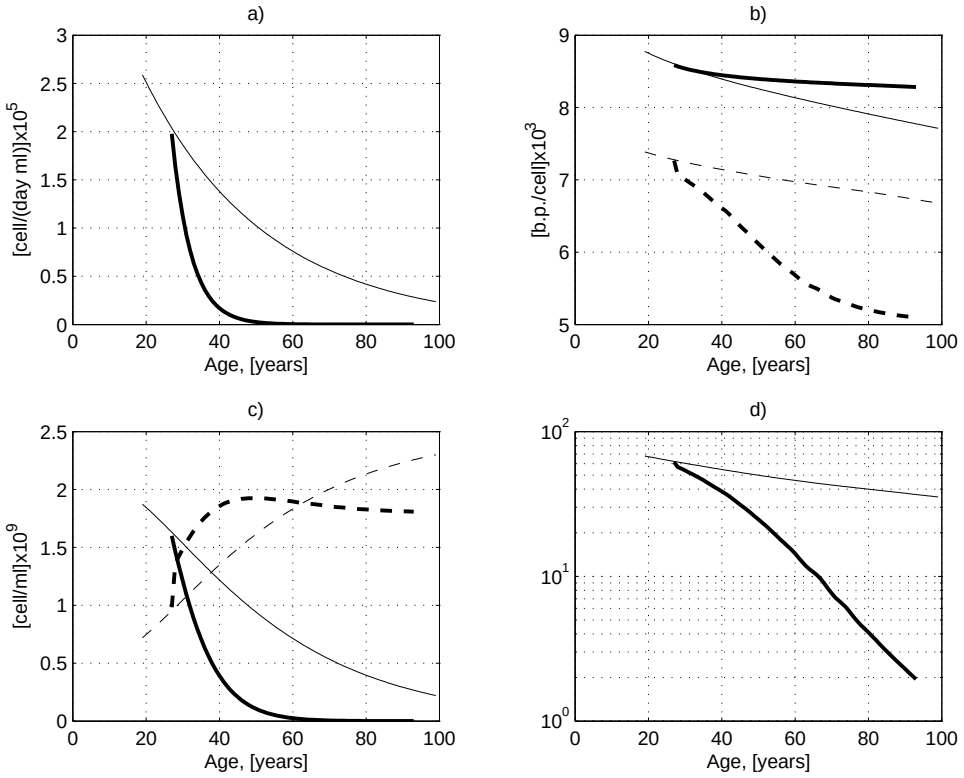

Figure 1. Solution of the system of equations in the mathematical model of the dynamics of age-related changes in the peripheral T lymphocyte population. Thin lines indicate the results of modelling the normal aging, thick lines- the results of the accelerated aging in HIV infection. (a) The rate of naive T lymphocytes influx from the thymus; (b) the dynamics of the telomere length in naive T lymphocytes (solid lines) and in T memory cells (dotted lines); (c) the dynamics of the concentration of naive T lymphocytes (solid lines) and T memory cells (dotted lines) in the IPLT; (d) the mean specific replicative potential of T lymphocytes (the maximum number of divisions per cell).

–The influx rate of naive T lymphocytes from the thymus substantially decreases. The estimates in [9] show that at the terminal stage of HIV infection this value decreases five and more times. The considerable part of the newly forming cells can be infected by the virus and hence is not able to multiply.

–The mean lifetime of T lymphocytes decreases 3.6 times and is about 33 days, which is due to a considerable increase in the proliferation and death rate of peripheral T lymphocytes [10].

–The intensive division of peripheral T lymphocytes leads to the exhaustion of their replicative potential, which is manifested in a five-fold increase in the shortening rate of the telomere length. At the late stages of HIV infection (i.e. about 10 years after contamination) the length of the telomeres of mononuclear cells in peripheral blood becomes shorter, on average, by 1500 b.p. than that in the age norm [3].

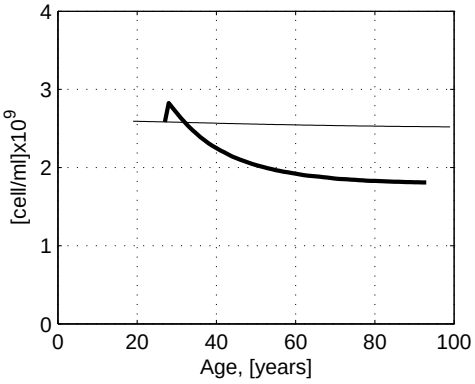

Figure 2. The dynamics of the T lymphocyte concentration in the IPLT in normal aging (thin line) and in HIV infection (thick line).

–As a result, the population of peripheral T lymphocytes proves incapable of self-maintenance and their concentration decreases.

Figures 1 and 2 present the results of modelling the immune system aging in the norm (the values of the parameters and the initial conditions for this case are given in Table 1) and in HIV infection. In accordance with the above differences, to describe the dynamics of the peripheral T lymphocyte population in HIV infection we added to the right-hand side of the equation for M the term of the form $-\mu M$ describing the phenomenon of the accelerated death of T memory cells in HIV infection ($\mu = 0.02$). It is easy to see that this addition does not affect the form of the equation for P_M. The constant of the reduction rate of naive T lymphocyte production in the thymus (k_T) was five times as much as the norm (see Table 1), the antigen load L was eight times as much, and $\rho_2 = 50$. We assume that the onset of HIV infection corresponds to the age of 27. As seen, the model solutions with the above set of the parameters adequately reproduce the available data on the accelerated aging of the peripheral T lymphocyte population in HIV infection (see Figs. 1a–1c). In addition, Fig. 1d illustrates a sharp decline in the mean specific replicative potential of peripheral T lymphocytes [i.e. the value of the form $(N(P_N - P_H) + M(P_M - P_H))/\lambda(N + M)$ in HIV infection as compared to normal, where λ is the average length of T lymphocytes telomeric fragments lost per one division cycle; in our numerical experiments we used the value $\lambda = 50$]. Interpretation of the data describing a decrease of the average lifetime of T cells in HIV infection will be considered in the future works.

Figure 2 shows the dynamics of the total concentration of peripheral T lymphocytes in norm (thin line) and in HIV infection (thick line). On the background of the steady maintenance of the constant cell concentration in normal conditions there is a fast initial increase, which follows the pattern seen in an acute immune response, and a subsequent progressive decrease in the cell concentration in HIV infection. This pattern is in good agreement with the current concepts of AIDS development.

4. DISCUSSION AND CONCLUSIONS

Using the balance relations, we constructed the mathematical model of the peripheral T lymphocyte population aging. As compared to the earlier published version of the model, this model takes into account the effect of a decrease in the telomere length on the cell proliferation rate. The constructed model quantitatively describes the normal age-related changes in the peripheral T lymphocyte population in adults. An example of the extensive study of the normal age-related changes in the telomere length in a wider age range and with allowance for the inhomogeneity of the T lymphocyte population, is given in [18].

Unlike the normal aging process, prolonged and severe diseases are characterized by an abrupt increase in the antigen load and the accelerated aging of the immune system. To study the behaviour of the model solutions in a wide range of values of the dependent variables, we introduced a linear relation between the rate constants of the peripheral T lymphocytes proliferation and the mean length of the telomeric fragments of chromosomes in naive and memory cells, which are spent in the cell division process. The constructed model allows one to semi-quantitatively describe the main regularities of the immune system aging in HIV infection. In particular, the phenomenon of lymphoadenopathy (an increase in the lymphatic tissue volume at the initial stage of infection) and a subsequent decrease in the peripheral T lymphocyte concentration at later stages of infection are described. Since the model describes the dynamics of the lymphocyte concentration in peripheral lymphoid tissue rather than in blood, for an exact quantitative description it is necessary to know the dynamics of the change in the volume of the peripheral lymphoid tissue, which is beyond the scope of this study. The dynamics of the shortening of the telomere length of peripheral memory lymphocytes qualitatively reproduces the available clinical data. Further analysis of the key mechanisms for the maintenance of the peripheral lymphoid tissue homeostasis under pathological conditions is necessary to establish a quantitative correspondence.

Moreover, it should be particularly emphasized that without resort to the description of the viral infection mechanisms (examples of modelling the HIV infection dynamics in blood, see [6, 15]) it was possible to reproduce the main features in the pathological process of progressive immunodeficiency in HIV infection as the responses of the system of homeostasis maintenance to an increased antigen load.

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