Mathematical modeling of the effect of ionizing radiation on the immune system of mammals

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This review is devoted to the use of mathematical modeling to study the effect of ionizing radiation on the immune system of mammals and on the development of autoimmune diseases resulting in destruction of the tissues of the organism. The models are systems of nonlinear differential equations whose variables are the concentrations of the basic components of the humoral immune reaction and of the cellular autoimmune reaction. The dose of acute exposure and the dose rate of chronic exposure are the variable parameters of the models. Numerical and analytical (where possible) study of the models has shown that they are consistent with the experimental and clinical data. It has proved possible to use these models not only to explain a number of regularities, but also to make some predictions, in particular, about the effectiveness of shielding the thymus to prevent autoimmune diseases and about the possibility of the latter becoming more acute when the radiation background is increased. The models can be used to plan and analyze experiments on immune and autoimmune processes in mammals subjected to various radiation conditions. Study of the models has led to expressions which can be used to calculate the critical radiation doses and dose rates above which autoimmune reactions become a danger. This allows correction of the radiation safety standards. Thus, the studies reviewed here demonstrate the fruitfulness of using mathematical modeling for studying the effect of radiation on living organisms. © *1996 American Institute of Physics.* [S1063-7796(96)00501-6]

INTRODUCTION

The modern development of science is characterized by the exchange of research methods between different fundamental sciences, leading to the development of new areas of research. For example, biophysics has been created at the junction of biology, physics, mathematics, and chemistry. One area of biophysics is the mathematical modeling of biological systems.[1–9]

Today the techniques of mathematical modeling are finding ever broader application in research on the effect of ionizing radiation on the mammalian organism. This problem is important primarily because of the unfavorable ecological environment created in some regions of the Earth by accidents at nuclear power plants and earlier atmospheric tests of nuclear weapons. In addition, in recent decades the development of nuclear power and the use of radioactive materials in industry, science, and medicine has meant that ever larger numbers of people are exposed to sources of ionizing radiation as a part of their professional activity. The problem of evaluating the consequences of exposure to radiation also arises in ensuring safety in long space flights.

Mathematical modeling is an important tool in this research for the following reasons. In the construction of a model, the experimental observations and existing theories are systematized, generalized, and analyzed, and an accurate cause–effect formulation is derived for the biological or biophysical hypothesis on which the model is based. By studying models it is possible to distinguish key variables or parameters, to evaluate the relative importance of the regulatory mechanisms taken into account in the modeling, and to determine the bifurcation values of coefficients giving the boundaries of the domains of different dynamical behavior of systems. All this is of great theoretical importance. In addition, mathematical models can be used to quantitatively predict the reaction of the mammalian organism to various radiation conditions. This is particularly important when the experimental reproduction of such conditions is difficult or when an experiment would require a great deal of time and resources.

The present review is devoted to studies in which mathematical modeling has been used to investigate the effect of radiation on a vitally important system of the mammalian organism: the immune system. Special attention has been paid to mathematical models of the dynamics of humoral immunity (Sec. 1) and also to models of autoimmune illnesses in mammals exposed and not exposed to radiation (Sec. 2).

1. RADIATION AND IMMUNE DEFENSES

1.1. Current ideas about immunity

One of the effects of ionizing radiation on mammals is a lowering of the defenses of the organism to infection. It is exo- and endoinfections which, as a rule, complicate the course of radiation sickness and in some cases cause the death of the exposed mammal.[10] These harmful consequences of radiation are caused by post-radiation changes of the immune system, the system defending mammals and other vertebrates from genetically alien matter (antigens).[11–16] Antigens may be macromolecules (proteins, carbohydrates, nucleic acids), bacteria, viruses, cells of foreign organs and tissues, or cells of malignant tumors. When an antigen encounters an organism it first induces nonspecific

reactions. Phagocytes—blood granulocytes and tissue macrophages—migrate to its site. These cells are capable of absorbing molecular antigens, viruses, and even entire bacterial cells, and also of splitting them into fragments.

The primary specific immune reaction is humoral immunity. Humoral immunity involves the production of protein molecules—antibodies—by certain cells of the organism. Antibodies can specifically bind to an antigen and hasten its expulsion from the organism.

At present, five basic classes of antibodies (immunoglobulins) are known: *IgG, IgM, IgA, IgD, and IgE.* They differ from each other in chemical construction and function. Immunoglobulins of the first two classes play the most important role in the immune reactions developing in an organism with an infectious disease. The *IgG* molecule consists of four chains (two identical heavy ones and two identical light ones) connected to each other by disulfide bonds. Each half of the molecule contains an antigen-binding region (the active center of the antibody). It is formed in a small region of the light and heavy chains and has the form of a shallow "crater" in which part of the antigen molecule (the antigenic determinant) enters when the antigen–antibody complex is formed. *IgG* molecules are most effective in neutralizing the toxins produced by sickness-causing organisms. The *IgM* molecule consists of ten light and ten heavy chains. There are ten active centers. However, only five of them can actively combine with an antigen. *IgM* antibodies play an important role in the early stages of infectious diseases.

The quantity characterizing the ability of an antibody to bind with an antigen is the association constant K. It is equal to the ratio of the rate constants for the direct and inverse interactions of the antigenic determinant and the active center of the antibody in the formation of the antigen–antibody complex.

The widely accepted theory of antibody production is the clonal selection theory of Burnet.[11] According to this theory, the organism of an adult mammal contains a population of "antigen-sensitive" cells. Only a small fraction of them (10^{-5} of the total) can be stimulated by an antigen. After stimulation, the antigen-sensitive cells (small lymphocytes) are transformed into rapidly dividing blast cells. The division (proliferation) of the latter is accompanied by a change of form with a more and more complete protein-synthesis apparatus. The final stage of development is the mature plasma cell which does not divide. It rapidly produces antibodies, and after a certain time it dies.

Studies have shown that the "antigen-sensitive" cells are the descendants of bone-marrow stem cells which follow a route of differentiation to the side of the haematopoietic lymphoid line, and then are "trained" in the bursa of Fabricius in birds or in an analogous organ in mammals. These lymphocytes are called B cells. B lymphocytes carry receptors on their surface. These receptors are antibody molecules of certain classes or fragments of them. On the average, there are $\sim 10^5$ receptors on a B cell. Experimental observations indicate that B lymphocytes are not inert cells regarding the synthesis of immunoglobulins in the absence of an antigen. Immunoglobulins are constantly being produced in B lymphocytes. Some are secreted outside as antibodies, and some become surface receptors which, in turn, can also be separated from the cell surface. However, the rate of antibody production by B lymphocytes is considerably lower than that by plasma cells. It should be noted that the association constants of the receptors of a B cell and of the antibodies synthesized by it and its descendants are the same.

It is considered a proven fact that the stimulation of a B lymphocyte, which leads to its intense proliferation, is expressed in the binding of some number of receptors on its surface with the corresponding antigen. There is reason to think that the antigen continues to provide stimulation throughout the entire process of B-cell division.

The "delivery" of antigen to immuno-competent B lymphocytes can occur both without and with the participation of other cells—macrophages (A cells) and helper T lymphocytes. Here the antigen is respectively termed T-independent and T-dependent. Helper T cells, like B cells, are descendants of bone-marrow stem cells which follow a route of differentiation to the side of the lymphoid line. However, after leaving the bone marrow these lymphocytes are "trained" in an immune organ—the thymus. In addition to helper T cells, the regulation of the humoral immune response to T-dependent antigens involves T-lymphocyte-suppressors, which inhibit the stimulation of immunocompetent cells by the antigen. The immune system is also subject to nervous, endocrinal, and mediator effects.

Antibody synthesis occurs in lymphatic organs. These are the spleen, the lymph nodes, Peyer' patches, the lungs, and the appendix. The antibodies are then transferred to the blood. The dynamics of antibody accumulation in the blood has four characteristic phases: (1) a latency period, during which antibodies are not seen (the lagphase); (2) a phase of exponentially growing antibody concentration (the log-phase); (3) a plateau, a period during which the antibody concentration remains at a high level; (4) the phase of falling antibody concentration. The latency period is due to the time needed for the production and passage to the blood of an antibody concentration which exceeds the sensitivity threshold of the method used to measure it. The other phases result from the superposition of several processes, including cell division, increase of the rate of antibody synthesis by individual cells, stimulation of new cells, natural disintegration of antibody molecules, loss of antibodies to antigen–antibody complexes, and death of mature plasma cells.

The dynamics of the accumulation of antibody-producing cells is similar to the antibody dynamics discussed above. The latency period is determined by the time needed to produce a sufficient number of cells intensively synthesizing antibodies. The growth phase is due to cell division, cell influx from other lymphatic organs, and the onset of division of new antigen-sensitive cells, and the fall phase is due to the death of antibody-producing cells.

The basic parameters of the immune response—the maximum concentrations of antibodies and antibody-producing cells and the times to reach these maxima—depend on a great many different factors. However, the antigen is decisive. The response will therefore be more intense, the larger the amount of antigen introduced. (This is true only up to a certain level of initial antigen concentra-

tion.) The intensity of the immune response is also significantly affected by whether or not the organism has previously come into contact with the antigen. If it has, the maximum antibody concentration is, as a rule, one to two orders of magnitude higher than the maximum antibody concentration in the primary response to the same quantity of antigen, and the duration of the latency period is smaller. The ability of an organism to give an enhanced and faster response in a repeat encounter with an antigen is referred to as immunological memory. In mammals this memory is preserved for a long time, sometimes the entire lifetime. It is thought that immunological memory is due to an increase of the number of cells capable of responding to the stimulus of a given antigen.

Cellular immunity is another type of specific immune reaction. The cellular forms of the immune response are related to the functioning of T-lymphocyte-effectors. These are capable of recognizing an antigen, responding to stimulation by multiplication, and then becoming "killers"—cells which annihilate foreign antigenic substances. Cellular immunity occurs in delayed hypersensitivity, in the rejection of transplants and tumors, in the antiviral immune reaction, and also in autoimmune illnesses. The latter occur when the natural insensitivity of the organism to its own components is destroyed. The autoimmunity problem will be discussed in detail in Sec. 2.

1.2. Mathematical models of immunity in mammals not exposed to radiation

During the last two and a half decades, mathematical modeling has been used to study a broad spectrum of immunological processes and phenomena. We can therefore already speak of the creation of a new area in immunology: mathematical immunology. The first studies in this area were those of Bell (USA),[17–20] the present author and Stepanova,[21–26], Jilek *et al.* (Czechoslovakia),[27–30] and Molchanov.[31,32] These were all carried out at practically the same time, in the early 1970s. Later, important contributions in this area were made by Marchuk *et al.*[33–44] and Bell *et al.*[45–57] Interesting studies have been carried out by Vol'kenshteĭn *et al.*,[58–61] Glushkov *et al.*,[62] and others.[7,63–66]

In some of these studies the phenomenon of immunity is treated at the level of individual molecules in describing the antigen–antibody reaction, or at the level of individual cells in reproducing the interaction of antigen-presenting cells and lymphocytes and T and B lymphocytes. The most interesting models are those in which immunity is studied for the organism as a whole: immunity to infections, immunity to tumors, immunity in the presence of AIDS. The models which have been constructed have been used to quantitatively check the validity of a number of immunological theories, to explain many experimental regularities and clinical observations, and to suggest treatment for some illnesses. We should note that these models have been used to study various aspects of immunity in mammals located in ecologically favorable conditions. In addition, there are models in the literature which describe the dynamics of the humoral immunity system in mammals both exposed and not exposed to radiation.[67–80] They are discussed in more detail in the following sections.

1.3. A model of the humoral immune response to a T-independent antigen in mammals not exposed to radiation

In Refs. 67 and 68 we proposed a mathematical model describing the humoral immune response to protein antigens in solution. This is the most thoroughly studied reaction in immunology. In developing this model we limited ourselves to consideration of the primary immune response to a soluble T-independent antigen, when the role of T-lymphocytes, macrophages, and immunological memory cells can be neglected.

The model is based on the clonal selection theory of Burnet,[11] according to which the mammalian organism contains only a small number of B lymphocytes capable of recognizing a certain antigen. It was assumed that these cells pass into the blood from the bone marrow, and after some time they die. It was also assumed that from the moment they leave the bone marrow, B lymphocytes can pass through all the developmental stages, including the dead end of a plasma cell, without antigenic stimulation; in this case this process is not associated with B-cell multiplication.[73] In accordance with the available data,[74,75] it was assumed that the maturation process of a B cell is accompanied by an increase of the number of antibody-like receptors on its surface, and that this number then decreases immediately before transformation into a plasma cell. It was also assumed that the binding of cell receptors with antigenic molecules can lead either to cell multiplication or to cell death, depending on the number of bound receptors on the cell. With these assumptions, the dynamics of the change of the concentrations of B cells predetermined to produce antibodies of a certain specificity in n different stages of maturity $(x_1,\ldots,x_n)$, of white blood cells (x_{n+1}), of antigenic molecules (x_{n+2}), and of antigenic determinants (x_{n+3}) is described by a system of nonlinear differential equations:

$$\frac{dx_1}{dt}=\eta-kx_1+P_1(R_1)k_Px_1, \tag{1.1}$$

$$\frac{dx_i}{dt}=k(x_{i-1}-x_i)+P_i(R_i)k_Px_i \quad (i=2,\ldots,n), \tag{1.2}$$

$$\frac{dx_{n+1}}{dt}=kx_n-k_z\,x_{n+1}, \tag{1.3}$$

$$\frac{dx_{n+2}}{dt}=hx_{n+1}-k_ax_{n+2}-\sigma k_cx_{n+2}, \tag{1.4}$$

$$\frac{dx_{n+3}}{dt}=-k_gx_{n+3}-k_cx'_{n+3}, \tag{1.5}$$

where

$$\sigma=\sum_{l=1}^{m}C_m^lr^l(1-r)^{m-l}, \tag{1.6}$$

$$x'_{n+3}=(x_{n+3}-L-r'R). \tag{1.7}$$

The block diagram of the system (1.1)–(1.5) is shown in Fig. 1.

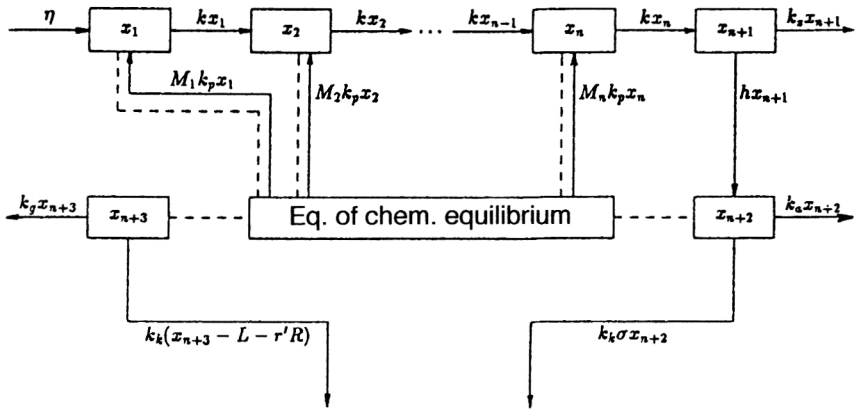

FIG. 1. Block diagram of the system (1.1)–(1.5). The arrows show the rates of change of concentrations of B lymphocytes ($x_1,\ldots x_n$), plasma cells (x_{n+1}), antibody molecules (x_{n+2}), and antigenic determinants (x_{n+3}). The directions of the arrows into and out of the boxes indicate the signs of the rates denoted by them: positive and negative, respectively. The dashed lines show the information fluxes.

In Eq. (1.1) the coefficient η is the rate of influx of predetermined cells from the bone marrow, and k is the unit rate of transition of a cell from one age group to another, equal to the number of age groups n divided by the B-cell development time. The parameters $P_i(R_i)$ in Eqs. (1.1) and (1.2) describe the outcome of interactions between cell receptors and antigenic molecules. If the number of bound receptors R_i on cells of group i is smaller than some threshold value F_1, multiplication is not stimulated, i.e., $P_i=0$. If $F_1 \leqslant R_i \leqslant F_2$, the cell multiplies at constant unit rate k_P, i.e., $P_i=1$. If $R_i>F_2$, all cells of group i die: $x_i=0$. In the model it was assumed that cells of a certain age group i have the same number of receptors ξ_i, given by a step function:

$$\xi_i=\xi_1 \exp[\alpha(i-1)] \quad (i=1,\ldots,s), \tag{1.8}$$

$$\xi_j=\xi_s \exp[\beta(s-j)] \quad (j=s+1,\ldots,n). \tag{1.9}$$

The parameter k_z in Eq. (1.3) describes the unit rate of death of plasma cells, and h in Eq. (1.4) describes the rate at which they produce antigenic molecules. In Eqs. (1.4) and (1.5), the coefficients k_a and k_g are the unit rates of natural extraction of antigenic molecules and antigen, and k_c is the unit rate of extraction of complexes of them. The parameter σ in Eq. (1.4) characterizes the fraction of antibody molecules for which at least one of the m active centers is bound to an antigen, when the fraction of occupied active centers on the antigenic molecule is equal to r [see Eq. (1.6)]. In Eq. (1.5) x'_{n+3} is the concentration of antigenic determinants bound with active antibody centers. It is given by Eq. (1.7), in which L is the concentration of free antigenic determinants, $r'R$ is the concentration of antigenic determinants bound to cell receptors, r' is the fraction of cell receptors bound to antigenic determinants, and $R=\Sigma_{i=1}^{n}\xi_i x_i$ is the total concentration of cell receptors.

The quantities r, r', and $R_i=\xi_i r'$ were calculated in the model using expressions known from immunology:[16]

$$r=\frac{KL}{1+KL}, \quad r'=\frac{K'L}{1+K'L}, \quad R_i=\xi_i\frac{K'L}{1+K'L}, \tag{1.10}$$

where K and K' are the association constants in the interaction of free antibodies and cell receptors with antigenic determinants. The concentration of free antigenic determinants L was found from the equation of chemical equilibrium between antigenic determinants, active centers of the antibodies, and cell receptors:[16]

$$x_{n+3}=L\left(1+\frac{mKx_{n+2}}{1+KL}+\frac{K'R}{1+K'L}\right). \tag{1.11}$$

For zero antigen concentration ($x_{n+3}=0$), Eqs. (1.1)–(1.4) represent a model of the dynamics of immunocompetent lymphocytes, plasma cells, and antibodies in the absence of an antigenic stimulus. Equations (1.1)–(1.4) have a single stable stationary solution:

$$\bar{x}_i=\eta/k \quad (i=1,\ldots,n),$$

$$\bar{x}_{n+1}=k\bar{x}_n/k_z=\eta/k_z,$$

$$\bar{x}_{n+2}=h\bar{x}_{n+1}/k_a=h\eta/(k_zk_a)=hk\bar{x}_i(k_ak_z). \tag{1.12}$$

The stationary concentrations $\bar{x}_i$ $(i=1,\ldots,n)$, $\bar{x}_{n+1}$, and $\bar{x}_{n+2}$ can be identified as the concentrations of immunocompetent lymphocytes of a certain specificity at n different developmental stages and of their plasma-cell and normal-antibody descendents of the same specificity in nonimmunized mammals. This result of the model agrees with the experimental observations (Refs. 15, 76, and 77), which indicate that the blood of mammals contains normal antibodies, that is, antibodies to antigens which the organism has not previously encountered, and the lymphatic organs contain cells capable of producing antibodies without the corresponding antigenic stimulus.

This model has been studied numerically. Equations (1.1)–(1.5) have been solved by the Runge–Kutta method, and Eq. (1.11) by the method of Newton tangents. The model mimics the dynamics of the primary immune response of mice of the CBA line to the abdominal introduction of varying amounts of T-independent antigen—capsular antigen of the plague microbe. The initial parameter values and the initial conditions were determined from the data in the literature and from the experimental results of Levi and coworkers.[78,79] In particular, the initial conditions for the concentrations of immuno-competent lymphocytes at various developmental

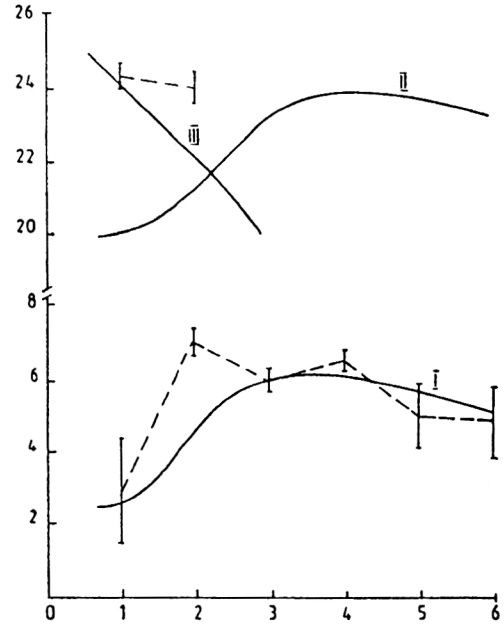

FIG. 2. Dynamics of the change of concentration of antibody-producing cells (APCs) (I), antibody molecules (ABs) (II), and antigen molecules (AGs) (III) during the immune response to 10^{12} molecules of capsular antigen of the plague virus. The dashed line is from experiment, and the solid lines are the model calculation. Along the horizontal axis is the time after immunization in days, and along the vertical axis is the natural logarithm of the numbers of APCs, ABs, and AGs.

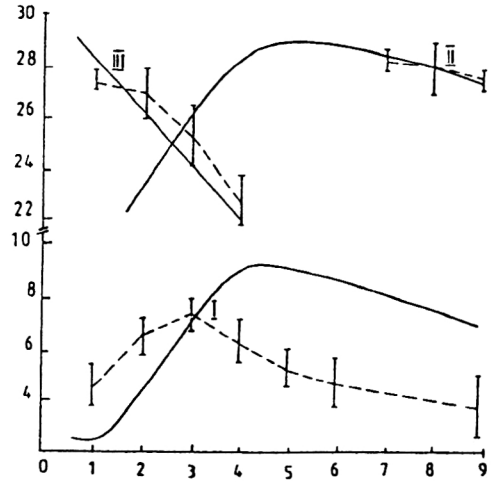

FIG. 3. Dynamics of the change of the number of antibody-producing cells (I), antibody molecules (II), and antigen molecules (III) during the immune response to 10^{13} molecules of capsular antigen of the plague virus. The notation is the same as in Fig. 2.

stages were calculated in the model starting from the concentration of normal antibodies to the plague microbe in mice ($\bar{x}_{n+2}$), which was measured using highly sensitive serological reactions. The following formulas were used

$$x_i(0)=\bar{x}_i=k_z k_a \bar{x}_{n+2}/(kh) \quad (i=1, \ldots, n), \tag{1.13}$$

$$x_{n+1}(0)=\bar{x}_{n+1}=k_a \bar{x}_{n+2}/h. \tag{1.14}$$

The value of $\bar{x}_{n+2}$ in the model was also used to determine the rate of influx of immuno-competent cells from the bone marrow:

$$\eta=k_z k_a \bar{x}_{n+2}/h. \tag{1.15}$$

The values of the parameters and the initial conditions are given in Refs. 67 and 68.

The number n of different age groups of B cells was selected to be 44. Studies showed that increase of the number n does not significantly change the model predictions, but only increases the required computer time.

In the computer study of the model the boundary values F_1 and F_2 of the number of cell receptors occupied by an antigen stimulating multiplication were varied. Better agreement with the experimental results was obtained for $F_1=10^3$ and $F_2=10^5$. These values correspond to the estimates obtained from analysis of experiments in which immunization was performed using very small and very large amounts of capsular antigen of the plague microbe.[67,68]

The system (1.1)–(1.5) was solved with various initial conditions for the antigen concentration. The results of numerical calculation of the model for two values of the initial antigen concentration are shown in Figs. 2 and 3. These reflect the dynamics of the variation of the number of antibody-producing cells (APCs), antibody molecules (ABs), and antigenic molecules (AGs). In these graphs we give the experimental data on the abdominal immunization of mice of the CBA line by the capsular antigen of the plague microbe. These are the average values and rms deviations of the number of antibody-producing cells in the spleen, and also of antigenic and antibody molecules in the animal blood, measured at various times after immunization. It should be noted that in the experiments serological reactions were used to determine the antibody and antigen concentrations in the blood. These allow measurement of only the excess of antibodies over antigens or the excess of antigens over antibodies. Therefore, experimental data on the antigen dynamics are available for the first few days of the immune response, when the level of antibodies is still low, and data are available on the antibody dynamics for the last days of the immune reaction, when the antigen concentration becomes significantly smaller than the antibody concentration.

In Figs. 2 and 3 we see that the model qualitatively reproduces all four phases of the dynamics of accumulation of antibody-producing cells in the spleen and antibodies in the blood of immunized mammals. During the 1–1.5 days after introduction of the antigen the amounts of APCs and ABs are at very low levels which cannot be reached by measurements using ordinary methods (the lagphase). Then these quantities begin to rise exponentially (the logphase). When high levels are reached the APC and AB concentrations continue to increase slowly, and then they slowly decrease (the plateau phase). Then a more rapid decrease of these quantities sets in (the fall phase). In Figs. 2 and 3 we show the initial part of this last phase.

It follows from the results shown in these figures that the model gives a good reproduction of the experimental data even at the quantitative level. There is good agreement between the model and experimental dynamics of APC accumulation (Fig. 2), the dynamics of antigen extraction (Figs. 2 and 3), and the dynamics of AB accumulation (Fig. 3). Even

the slight disagreement between the model and experimental dynamics of the APC concentration in Fig. 3 reflects the real situation. The point is that for abdominal introduction of large amounts of antigen, up to half of the antibody-producing cells can be located not in the spleen, but in other lymphatic organs. Therefore, there is a difference between the calculated curve describing the dynamics of all the plasma cells producing antibodies of a certain specificity, and the experimental data reflecting the number of APCs in the spleen, while there are no discrepancies between the model and experimental results on the dynamics of antibody molecules. The good agreement between the model and experimental results suggests the possibility of using the system (1.1)–(1.5) as the basis for modeling radiation-induced effects on humoral immunity.

1.4. The two-link model of post-radiation dynamics of the bone-marrow lymphopoietic system in nonimmunized animals

In modeling the dynamics of the humoral immune reaction of exposed mammals to T-independent antigen it is possible to limit ourselves to considering the effect of ionizing radiation on the bone-marrow lymphopoietic system, because the leading role played by the bone marrow in the formation of the B-lymphocyte pool is considered to be proved.[15] A mathematical model of the dynamics of the post-radiation bone-marrow lymphopoietic system in nonimmunized mammals has been presented in Refs. 70 and 71. The variables of the model are the concentrations of undamaged X, damaged X_d, and severely damaged X_{sd} lymphocyte predecessors in bone marrow, including the stem cells located in the corresponding microenvironment, and all the subsequent phases of differentiation of these cells in the direction of the lymphoid line, together with the concentrations of undamaged Y, damaged Y_d, and severely damaged Y_{sd} blood lymphocytes. The dynamics of the change of concentration of these cells (x, x_d, x_{sd}, y, y_d, and y_{sd}) is described by the differential equations

$$\frac{dx}{dt}=Bx-\gamma x, \tag{1.16}$$

$$\frac{dy}{dt}=\gamma x-\psi y, \tag{1.17}$$

$$\frac{dx_d}{dt}=-\mu x_d, \tag{1.18}$$

$$\frac{y_d}{dt}=-\mu y_d, \tag{1.19}$$

$$\frac{dx_{sd}}{dt}=-\nu x_{sd}, \tag{1.20}$$

$$\frac{dy_{sd}}{dt}=-\nu y_{sd}. \tag{1.21}$$

Here B is the unit rate of multiplication of lymphocyte predecessors in bone marrow, γ is the unit rate of influx of lymphoid cells from the bone marrow to the blood, ψ is the unit rate of natural death of lymphocytes or their removal from circulation, and μ and ν are the unit rates of death of cells damaged and severely damaged by radiation.

In the traditional manner of describing the cell multiplication rate in a self-supporting population with regulation by feedback, the quantity B is represented as a function of the concentrations of X and Y cells (Refs. 5 and 7):

$$B=\alpha/[1+\beta(x+\theta y)], \tag{1.22}$$

where α is the maximum unit rate of proliferation of X cells, and β and $\beta\theta$ are the feedback coefficients in the equation for the breeding of X cells by X cells and by their descendants, Y cells.

In the absence of a radiation effect the dynamics of the lymphopoietic system is described by Eqs. (1.16) and (1.17). The system (1.16), (1.17) has two singular points. The first is trivial. The coordinates of the second are

$$\bar{x}=(\alpha/\gamma-1)/[\beta(1+\theta\gamma/\psi)], \quad \bar{y}=(\gamma/\psi)\bar{x}. \tag{1.23}$$

It follows from (1.23) that the coordinates of the second singular point are positive if the parameters satisfy the condition

$$\alpha>\gamma. \tag{1.24}$$

The system (1.16) and (1.17) has been studied using the techniques of the qualitative theory of differential equations and oscillation theory. The trivial singular point is unstable (a saddle) if the inequality (1.24) holds, and stable (a node) if (1.24) is not satisfied. The second singular point, lying in the positive quadrant, is either a stable focus for

$$\left[\psi+\frac{\gamma\psi(\alpha-\gamma)}{\alpha(\psi+\theta\gamma)}\right]^2<4\frac{\psi\gamma(\alpha-\gamma)}{\alpha}, \tag{1.25}$$

or a stable node if the condition (1.25) is violated. Accordingly, the dynamics of recovery processes in the lymphopoietic system either has the nature of damped oscillations, or is aperiodic. The condition (1.25) determining the nature of the stability of the second singular point is equivalent to two other conditions on the parameters θ and ψ:

$$\theta>\frac{\psi}{\gamma}\left[1-\sqrt{\frac{\gamma}{\psi}\left(1-\frac{\gamma}{\alpha}\right)}\right]^2\left[2\sqrt{\frac{\gamma}{\psi}\left(1-\frac{\gamma}{\alpha}\right)}-1\right]^{-1}, \tag{1.26}$$

$$\psi<4\gamma\left(1-\frac{\gamma}{\alpha}\right). \tag{1.27}$$

It follows from these equations that the dynamics of recovery processes in the lymphopoietic system has the nature of damped oscillations if the feedback coefficient in the equation for the breeding of X cells by Y cells is sufficiently large, and the unit rate of death of Y cells is less than the value of some function of the unit rate of transition from X to Y cells.

The stay of the system (1.16), (1.17) at the second singular point with positive coordinates, where it is stable [i.e., when (1.24) holds], can be identified with the normal state of the bone-marrow lymphopoietic system. It is this region of parameter variation given by the inequality (1.24) which was studied in Refs. 70 and 71.

When transformed to dimensionless variables $\xi=x/\bar{x}$, $\eta=y/\bar{y}$, $\xi_d=x_d/\bar{x}$, $\xi_{sd}=x_{sd}/\bar{x}$, $\eta_d=y_d/\bar{y}$, $\eta_{sd}=y_{sd}/\bar{y}$, Eqs. (1.18)–(1.21) take the form

$$\frac{d\xi}{dt}=\frac{\alpha\xi}{1+b[\xi+\theta(\gamma/\psi)\eta]}-\gamma\xi, \tag{1.28}$$

$$\frac{d\eta}{dt}=\psi(\xi-\eta), \tag{1.29}$$

$$\frac{d\xi_d}{dt}=-\mu\xi_d, \tag{1.30}$$

$$\frac{d\eta_d}{dt}=-\mu\eta_d, \tag{1.31}$$

$$\frac{d\xi_{sd}}{dt}=-\nu\xi_{sd}, \tag{1.32}$$

$$\frac{d\eta_{sd}}{dt}=-\nu\eta_{sd}, \tag{1.33}$$

where $b=\beta\bar{x}=(\alpha/\gamma-1)(1+\theta\gamma/\psi)$ is a dimensionless parameter. Since cells of the lymphoid line remain in the bone marrow and blood for several days, cells damaged by radiation die in 1–2 days on average, and severely damaged cells die in 4–7 hours, Eqs. (1.32) and (1.33) can be considered fast compared with Eqs. (1.28)–(1.31). Therefore, following the theorem of Tikhonov,[5] Eqs. (1.32) and (1.33) were replaced by the stationary solutions

$$\xi_{sd}(t)=\bar{\xi}_{sd}=0, \tag{1.34}$$

$$\eta_{sd}(t)=\bar{\eta}_{sd}=0. \tag{1.35}$$

The initial conditions for solving Eqs. (1.24) and (1.31) were determined in accordance with the one-target, one-hit theory of radiation damage to cells:[80]

$$\xi(0)=\exp(-D/D_1), \tag{1.36}$$

$$\eta(0)=\exp(-D/D_2), \tag{1.37}$$

$$\xi_d(0)=[1-\exp(-D/D_1)](1+\rho_1)^{-1}, \tag{1.38}$$

$$\eta_d(0)=[1-\exp(-D/D_2)](1+\rho_2)^{-1}. \tag{1.39}$$

In Eqs. (1.38) and (1.39) the quantities ρ_1 and ρ_2 are equal to the ratios of the fractions of severely damaged and damaged cells X_{sd} and X_d, and also Y_{sd} and Y_d, respectively. They were calculated using an expression derived in Ref. 81:

$$\rho_i=\frac{1-\exp(-D/D_{mi})}{\exp(-D/D_{mi})-\exp(-D/D_i)} \quad (i=1,2). \tag{1.40}$$

In Eqs. (1.36)–(1.40) the quantities D_{mi} and D_i $(i=1,2)$ are the doses traditionally measured in radiobiology. After receiving doses D_1 and D_2, the numbers of X and Y cells remaining undamaged are e=2.7... times smaller than the initial value. After receiving doses D_{m1} and D_{m2}, the numbers of X and Y cells which have not undergone interphase destruction are e=2.7... times smaller than the initial value.

The model was used to simulate processes of post-radiation damage and recovery of the bone-marrow lymphopoietic system in small laboratory animals (rats). The parameter values are given in Ref. 71. The results of the modeling were compared with the data from experiments performed at the Heavy Ion Laboratory of the Institute of Medical and Biological Problems in Dubna. The effect of various doses of acute exposure on the dynamics of nucleus-containing cells (karyocytes) of bone marrow and blood lymphocytes in rats was studied.[82] When comparing the model and experimental data, the authors took into account the fact that the dynamics of the total number of bone-marrow karyocytes can serve as an indicator of the post-radiation changes in the population of bone-marrow cells which are lymphocyte predecessors. In Fig. 4 we show the dimensionless total concentrations of blood lymphocytes undamaged and damaged by radiation, $y(t)=\eta(t)+\eta_d(t)$, and the same for their predecessors in bone marrow, $x(t)=\xi(t)+\xi_d(t)$, calculated in the model for $D=2$ Gy. We give the average values and rms deviations of the dimensionless concentrations of blood lymphocytes and bone-marrow karyocytes of rats, measured at different times after acute exposure at the same dose.[82] From this figure we see that the model describes the extinction and restoration of the populations of blood lymphocytes and bone-marrow predecessor cells. During the first two days after exposure, both the model and the experimental concentrations of cells in the X and Y pools are decreased to some minimum values x_{min} and y_{min}, then they begin to grow and reach normal levels after 8 days and 23 days, respectively. After this the restoration process has the nature of rapidly damped oscillations of the concentrations of X and Y cells about their stationary values. In the concluding stage of the restoration process the lymphocyte concentration in the blood is lower in experiment than in the model. This discrepancy is apparently related to the uncompensated enhancement of lymphocyte migration from blood to lymph, which is not taken into account in the model.

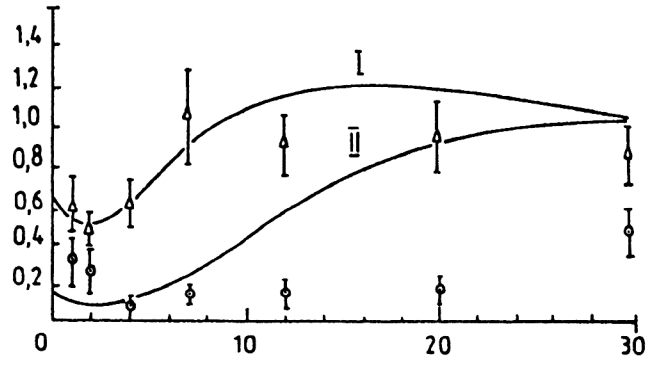

FIG. 4. Post-radiation dynamics of the bone-marrow lymphopoietic system for radiation dose $D=2$ Gy. Curves I and II are the calculated concentrations $x(t)$ and $y(t)$, and the points are the corresponding experimental values of the concentrations of blood lymphocytes (○) and bone-marrow karyocytes (△) of rats exposed to radiation.[82] Along the horizontal axis is the time after exposure in days, and along the vertical axis are the dimensionless cell concentrations.

A special study was made of the dependence of x_{min} and y_{min} on the radiation dose D in the model. The results are shown in Fig. 5. We see from this figure that the model qualitatively reproduces the experimental data.[82] Calculations showed that there is also quantitative agreement be-

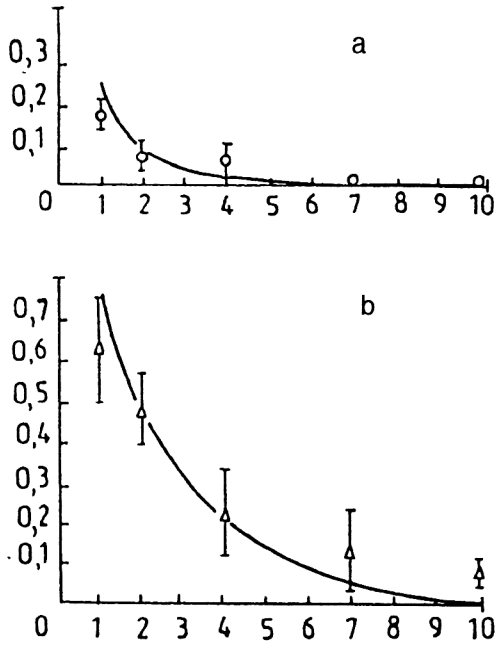

FIG. 5. Dose dependence of minimum concentrations of (a) blood lymphocytes $y_{\min}$ and (b) their predecessors in bone marrow $x_{\min}$ during post-radiation destruction. The curves are the results of the modeling, and the points are the corresponding experimental values for the concentration of blood lymphocytes (○) and bone-marrow karyocytes (△) of rats exposed to radiation.[82] Along the horizontal axes are the radiation dose D in Gy, and along the vertical axes are the dimensionless cell concentrations.

tween them. The calculated values $\chi^2=6.07$ and $\chi^2=8.84$ are less than the critical value $\chi^2_{0.05}=9.488$ (the number of degrees of freedom is $n=5-1=4$). The greater D is, the lower are $x_{\min}$ and $y_{\min}$ below the standard.

The model (1.28)–(1.31) can be used to simulate the bone-marrow lymphopoietic system of mammals in those cases where it is not necessary to predict separately the dynamics of lymphocyte predecesssors in bone marrow which are and are not capable of division, and also when the details of the dynamics of the destruction of cells severely damaged by radiation are not important. These conditions are obviously satisfied when the model is used to describe the dynamics of humoral immunity in mammals exposed to radiation.

1.5. The dynamics of humoral immunity under the combined effect of radiation and antigenic stimulation

The effect of ionizing radiation on the humoral immunity system of mammals was modeled in Refs. 69 and 72. The post-radiation damage and recovery of cells of the lymphoid line and their predecessors in bone marrow were studied. Damage to the functioning of other systems of the organism affecting the immune system was not taken into account.

The variables of the problem were the concentrations of radiation-undamaged and damaged radiation-sensitive B lymphocytes, predetermined to produce antibodies of a certain specificity and existing at n different developmental stages, x_i, x_{di} $(i=1,\ldots,n)$; the concentration of radiation-resistant plasma cells synthesizing antibodies of a certain specificity (x_{n+1}); the concentrations of antibody molecules of this specificity (x_{n+2}) and antigenic determinants of the corresponding antigen (x_{n+3}); the concentrations of blood lymphocytes undamaged and damaged by radiation which are not predetermined to produce antibodies of the specificity in question $(x_i, x_{di}, i=n+4)$; and the concentrations of lymphocyte predecessors in bone marrow undamaged and damaged by radiation $(x_i, x_{di}, i=n+5)$. In accordance with the model of the dynamics of humoral immunity to a T-independent antigen (see Sec. 1.3), the concentrations x_i $(i=1,\ldots,n+3)$ are described by the system (1.1)–(1.5). The concentrations x_i, x_{di} $(i=n+4,\ i=n+5)$ and x_{di} $(i=1,\ldots n)$ are determined, according to the model of post-radiation dynamics of the bone-marrow lymphopoietic system (see Sec. 1.4), by the equations

$$\frac{dx_{n+4}}{dt}=\eta'-\psi x_{n+4}, \tag{1.41}$$

$$\frac{dx_{n+5}}{dt}=Bx_{n+5}-\gamma x_{n+5}, \tag{1.42}$$

$$\frac{dx_{di}}{dt}=-\mu x_{di} \quad (i=1,\ldots,n,n+4,\ n+5), \tag{1.43}$$

where

$$B=\alpha\left\{1+\beta\left[x_{n+5}+\theta\left(x_{n+4}+\sum_{i=1}^{n}x_i\right)\right]\right\}^{-1}.$$

The parameters η and η' in (1.1) and (1.41) are proportional to the rate at which lymphoid cells leave the bone marrow:

$$\eta=\kappa\gamma x_{n+5}, \quad \eta'=(1-\kappa)\gamma x_{n+5}. \tag{1.44}$$

In (1.44) the coefficient κ is equal to the fraction of cells predetermined to produce antibodies of a certain specificity among all the lymphoid cells leaving the bone marrow.

In the absence of an antigenic stimulus $[x_{n+3}(0)=0]$, the dynamics of cells of the lymphoid line can be described both by the system (1.1), (1.2), (1.41)–(1.43) and by Eqs. (1.16)–(1.19), to which this system reduces. Here the variables of Eqs. (1.16)–(1.19) are expressed in terms of the variables of the system (1.1), (1.2), (1.41)–(1.43) as

$$x\equiv x_{n+5}, \quad x_d\equiv x_{dj} \quad (j=n+5),$$

$$y\equiv x_{n+4}+\sum_{i=1}^{n}x_i,$$

$$y_d=x_{dj}+\sum_{i=1}^{n}x_{di} \quad (j=n+4). \tag{1.45}$$

When the dynamics of the humoral immune response to a T-independent antigen of exposed mammals is simulated by this model, the initial conditions for solving the system (1.1)–(1.5), (1.41)–(1.43) depend on when the exposure occurs: before immunization, simultaneously with it, or after introduction of the antigen. In the first case the initial conditions are given by the expressions

$$x_i(0)=\bar{x}_i\exp(-D/D_2) \quad (i=1,\ldots,n), \tag{1.46}$$

$$x_{di}(0)=\bar{x}_i[1-\exp(-D/D_2)](1+\rho_2)^{-1}$$
$$(i=1,\ldots,n), \tag{1.47}$$
$$x_{n+1}(0)=\bar{x}_{n+1}, \tag{1.48}$$
$$x_{n+2}(0)=\bar{x}_{n+2}, \tag{1.49}$$
$$x_{n+3}(0)=0, \tag{1.50}$$
$$x_{n+4}(0)=\bar{x}_{n+4}\exp(-D/D_2), \tag{1.51}$$
$$x_{dj}(0)=\bar{x}_j[1-\exp(-d/D_2)](1+\rho_2)^{-1} \quad (j=n+4), \tag{1.52}$$
$$x_{n+5}(0)=\bar{x}_{n+5}\exp(-D/D_1), \tag{1.53}$$
$$x_{dj}(0)=\bar{x}_j[1-\exp(-D/D_1)](1+\rho_1)^{-1} \quad (j=n+5). \tag{1.54}$$

In the numerical solution of the system (1.1)–(1.5), (1.41)–(1.43) with the initial conditions (1.46)–(1.54) the concentration of antigenic determinants x_{n+3} is first zero, and then at the moment of "immunization" T_i it is set equal to $x_{n+3}(T_i)=(x_{n+3})_0$.

When the exposure and immunization occur simultaneously, the dynamics of the immune reaction is described by the system (1.1)–(1.5), (1.41)–(1.43) with the initial conditions (1.46)–(1.49), (1.51)–(1.54) and initial concentration of antigenic determinants $x_{n+3}(0)=(x_{n+3})_0$.

If the model is used to simulate the dynamics of the humoral immune response in the case where immunization precedes exposure, the initial conditions for solving the system of equations (1.1)–(1.5), (1.41)–(1.43) are

$$x_i(0)=\bar{x}_i \quad (i=1,\ldots,n), \tag{1.55}$$
$$x_{n+1}(0)=\bar{x}_{n+1}, \tag{1.56}$$
$$x_{n+2}(0)=\bar{x}_{n+2}, \tag{1.57}$$
$$x_{n+3}(0)=(x_{n+3})_0, \tag{1.58}$$
$$x_{n+4}(0)=\bar{x}_{n+4}, \tag{1.59}$$
$$x_{n+5}(0)=\bar{x}_{n+5}, \tag{1.60}$$
$$x_{di}(0)=0 \quad (i=1,\ldots,n,n+4,n+5). \tag{1.61}$$

In the computer calculation of the model, at the time T_0 corresponding to the time of exposure the concentrations of radiation-sensitive cells change abruptly:

$$x_i=x_i(T_0)\exp(-D/D_2) \quad (i=1,\ldots,n,n+4), \tag{1.62}$$
$$x_{di}=x_i(T_0)[1-\exp(-D/D_2)](1+\rho_2)^{-1}$$
$$(i=1,\ldots,n,n+4), \tag{1.63}$$
$$x_{n+5}=x_{n+5}(T_0)\exp(-D/D_1), \tag{1.64}$$
$$x_{dj}=x_j(T_0)[1-\exp(-D/D_1)](1+\rho_1)^{-1}$$
$$(j=n+5). \tag{1.65}$$

In (1.49) and (1.57), $\bar{x}_{n+2}$ is the stationary concentration of antibody molecules of a certain specificity. It is found from the experimental data.[67,68] In (1.46), (1.47), and (1.55), $\bar{x}_i$ are the stationary concentrations of B lymphocytes predetermined to produce antibodies of the given specificity and belonging to the ith age group ($i=1,\ldots,n$), and $\bar{x}_{n+1}$ in (1.48) and (1.56) are the stationary concentrations of the corresponding plasma cells. The quantities $\bar{x}_i$ ($i=1,\ldots,n+1$) are calculated using Eqs. (1.13) and (1.14) and $\bar{x}_{n+2}$ (see Sec. 1.2). In (1.51)–(1.54), (1.59), and (1.60), $\bar{x}_{n+5}$ and $\bar{x}_{n+4}$ are the stationary values of the concentrations of lymphocyte predecessors in bone marrow and of blood lymphocytes not predetermined to produce antibodies of the given specificity. They are also calculated using $\bar{x}_{n+2}$ and the equations obtained from (1.15), (1.41), and (1.44):

$$\bar{x}_{n+4}=\frac{1-\kappa}{\kappa}\frac{k_z k_a}{\psi}\bar{x}_{n+2}, \tag{1.66}$$
$$\bar{x}_{n+5}=\frac{1}{\kappa}\frac{k_z k_a}{h\gamma}\bar{x}_{n+2}. \tag{1.67}$$

The values of the coefficients k_z, k_a, h, γ, and ψ are given in Refs. 67, 68, 70, and 71. The parameter κ is set equal to 10^{-5}, in accordance with the estimates obtained in immunology.[11]

The model was used to study the dynamics of the primary humoral immune reaction to a T-independent antigen (the capsular antigen of the plague microbe) for mice of the line CBA. The cases where the immunization was done before the radiation exposure, simultaneously with it, and after it were studied.

In Fig. 6 we show the dynamics of antibody-producing cells (APCs) and antibody molecules (ABs) obtained in modeling the immune reaction to the introduction of 10^{12} molecules of capsular antigen of the plague virus in unexposed mice, mice exposed at a dose $D=2$ Gy two days before immunization, and mice immunized one and three days before exposure at the same dose. Comparison of the curves shows that exposure both before and after immunization leads to a decrease of the intensity of the immune response: the maximum amounts of APCs and ABs in exposed mammals is lower than in unexposed ones. This model result agrees qualitatively with the experimental observations.[83,84]

The four versions of the immune response to the same quantity of antigen shown in Fig. 6 have certain features. As already noted in Sec. 1.2, for unexposed mice in the first 1–1.5 days after immunization the numbers of APCs and ABs increase very slowly, followed by exponential growth, attainment of the maximum values, and then falloff to the normal level. In this case, when exposure precedes immunization, the initial and final stages of the APC and AB dynamics differ from those studied above. After exposure the numbers of APCs and ABs decrease as a result of post-radiation death of APC predecessors in the blood and bone marrow. After immunization this falloff continues as long as the rate of replenishing the pool of plasma cells remains smaller than their natural death rate. Then, after certain minimum levels are reached, the numbers of APCs and ABs begin to increase to the maximum levels, which are lower than in unexposed animals. After this the numbers of APCs and ABs again decrease to lower than normal levels, and then return to the initial values. This feature of the final stage of the immune response of exposed mammals is due to the superposition of two processes: decrease of the intensity of APC and AB ac-

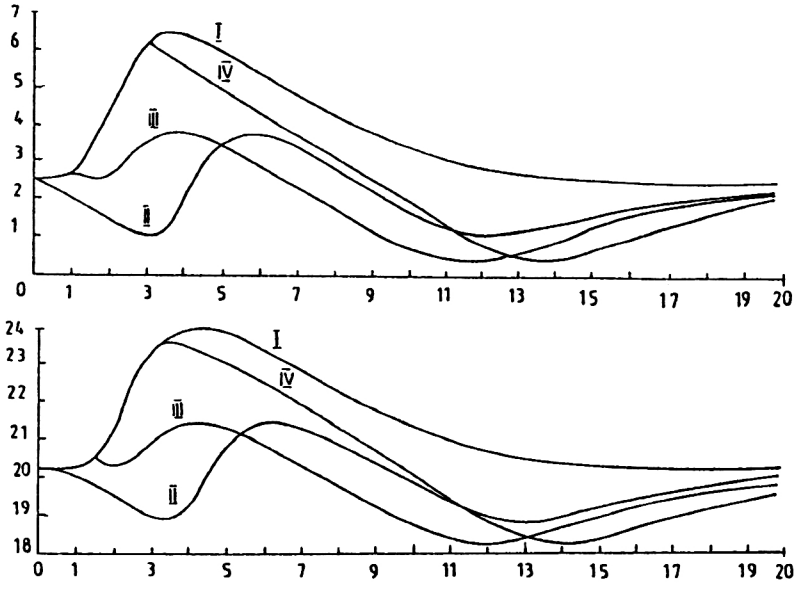

FIG. 6. Model dynamics of the number of (a) antibody-producing cells and (b) antibody molecules during the humoral immune response to the abdominal introduction of 10^{12} molecules of capsular antigen of the plague virus in unexposed mice (curve I) and mice exposed to a dose $D=2$ Gy (curve II is for exposure 2 days before immunization, and curves III and IV are for immunization 1 and 3 days before exposure). Along the horizontal axes are the time after immunization (for I, III, and IV) or after exposure (for II) in days. Along the vertical axes is the natural logarithm of the number of APCs (a) and ABs (b).

cumulation due to decrease of the concentration in the blood of antigen stimulating the division of immuno-competent B lymphocytes, and increase of the numbers of APCs and ABs to the normal level in the ongoing process of regeneration of the bone-marrow lymphopoietic system. Calculations have shown that increasing the time Δt between exposure and immunization leads to shortening and then to complete disappearance of the phase in which the amounts of APCs and ABs decrease right after immunization, and also to a "smoothing" of the final phase of the dynamics of the immune response. However, it should be noted that the values of Δt and D have practically no effect on the duration of the time intervals between immunization and the times to reach the maximum numbers of APCs and ABs. They are the same as in unexposed animals.

In cases where immunization precedes exposure ($\Delta t<0$) the nature of the dynamics of the immune reaction depends significantly on $|\Delta t|$. If the time between the introduction of antigen and exposure to radiation is small and the immune reaction does not succeed in developing fully by the time of exposure, the kinetic curves reflecting the dynamics of antibody-producing cells and antibodies have a doubly peaked shape. The numbers of APCs and ABs grow slowly during the time between immunization and exposure. After exposure the numbers of APCs and ABs decrease, owing to post-radiation death of B lymphocytes predetermined to produce antibodies of a given specificity and their predecessors in bone marrow. Then the antigen-stimulated division of predetermined B lymphocytes undamaged by radiation, together with the increase of the influx of B lymphocytes from bone marrow, leads to an increase of the numbers of APCs and ABs. They reach maximum values which are lower than in unexposed animals. The final stage of the APC and AB dynamics is the same as that in animals which are first exposed and then immunized. The immune response develops in the same way if $|\Delta t|<2$ days. For $|\Delta t|>2$ days the dynamical curves are different: they have a single peak. This happens because a large number of antibody molecules have been accumulated by the time of exposure, and these bind to the antigen circulating in the blood and hasten its removal from the organism. Then after exposure the numbers of APCs and ABs decrease both as a result of post-radiation death of B lymphocytes predetermined to produce antibodies of a given specificity and their predecessors in bone marrow, and as a result of cessation of the division of immuno-competent B lymphocytes in the absence of antigenic stimulation. The concluding part of the APC and AB dynamics (the rise phase) is due to the regeneration of the bone-marrow lymphopoietic system damaged by radiation. The calculations showed that if immunization precedes exposure, the time intervals between introduction of the antigen and the times to reach the maximum numbers of APCs and ABs are nearly independent of the radiation dose D. For example, for 2 days $\leqslant|\Delta t|<3.5$ days, the maximum number of APCs occurs at the time of exposure, and the maximum number of ABs occurs 0.5 or 1 day later. For other values of Δt the time intervals between immunization and the times to reach the maximum numbers of APCs and ABs in exposed animals are the same as in unexposed animals.

The dependence of the maximum concentrations of antibodies and antibody-producing cells on the radiation dose D for fixed amount of introduced antigen and fixed Δt was studied in the model. In Fig. 7 we show the results of the calculations for cases where the exposure occurs 2 days before and 2 days after immunization. The amount of antigen introduced was 10^{12} molecules. We see from this figure that the larger the radiation dose D, the smaller are these values compared to those corresponding to the immune response of unexposed mammals. However, the D dependence of the maximum numbers of APCs and ABs is expressed more

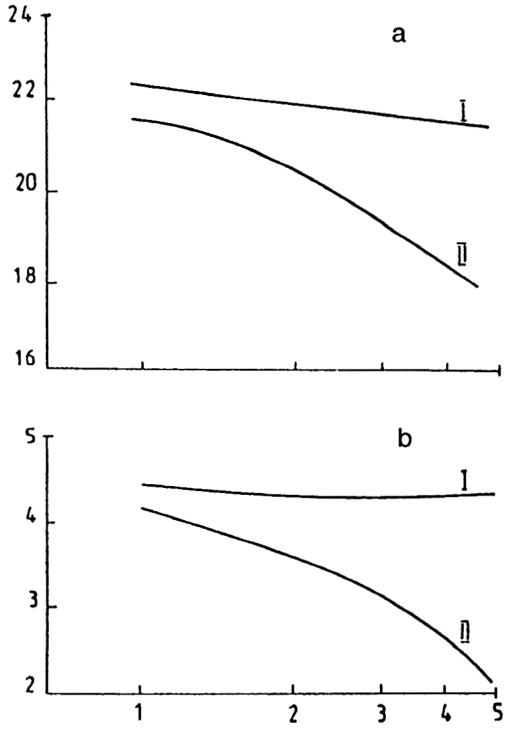

FIG. 7. Model dependence of the maximum values of the number of (a) antibody molecules AB_{max} and (b) antibody-producing cells APC_{max} on the radiation dose D for mice immunized by 10^{12} molecules of capsular antigen of the plague virus. The immunization was done 2 days before (I) and after (II) exposure. Along the horizontal axes is the dose D in Gy. Along the vertical axes is the natural logarithm of the maximum numbers of ABs and APCs.

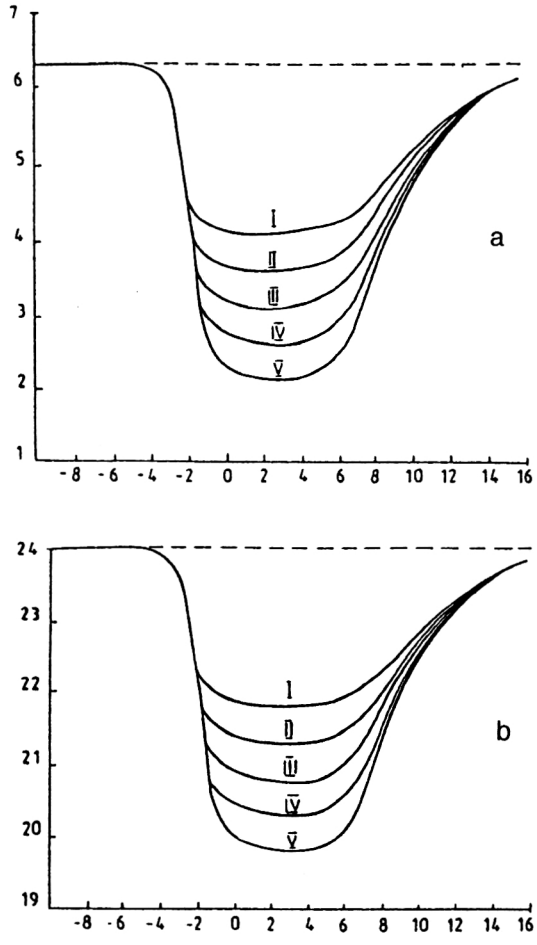

FIG. 8. Dependence of the maximum values of the number of (a) antibody molecules AB and (b) antibody-producing cells APC on the time interval Δt (in days) between exposure at doses $D=1,2,3,4,5$ Gy (curves I–V) and immunization by 10^{12} antigen molecules. The dashed lines are the levels of the maximum numbers of ABs and APCs in unexposed animals.

weakly when the immunization precedes exposure by 2 days than when the exposure precedes immunization by 2 days.

The effect of the value of Δt on the maximum levels of concentration of antibody-producing cells and antibodies for fixed amount of introduced antigen (10^{12} molecules) and for various D was also determined. The results are shown in Fig. 8. We see from this figure that when the exposure and immunization occur simultaneously ($\Delta t=0$), the larger the dose D, the smaller are the maximum amounts of APCs and ATs compared to the corresponding values in an unexposed animal. For cases where immunization precedes exposure ($\Delta t<0$), the same D dependence occurs for $0<|\Delta t|<2$ days, while for $|\Delta t|>2$ days the maximum amounts of APCs and ABs are practically the same for doses in the range $D=1-5$ Gy. If exposure precedes immunization ($\Delta t>0$), the maximum amounts of APCs and ABs are smaller than these values for unexposed animals, the larger the dose D. This is true for all values of Δt satisfying the condition $0<\Delta t<16$ days. For $\Delta t>16$ days these values are identical for the range $D=1-5$ Gy.

Regarding the dependence of the maximum numbers of APCs and ABs on the value of Δt for fixed radiation dose D (Fig. 8), we should note the following. If immunization occurs no more than 3.5 days before exposure, the maximum numbers of APCs and ABs will be smaller than the values in unexposed animals, the smaller $|\Delta t|$ is. For $|\Delta t|>3.5$ days these numbers coincide for exposed and unexposed animals, because exposure occurs after the immune response has reached its maximum level. If exposure precedes immunization, the dependence of the maximum numbers of APCs and ABs on Δt is quite different. For $0<\Delta t<6$ days these values change very little. When Δt increases from 0 to 2 days, they decrease slightly, and when Δt increases from 2 to 6 days, they increase slightly. Further increase of the time Δt between exposure and immunization leads to rapid growth of the maximum numbers of APCs and ABs. For $\Delta t\sim 23$ days these quantities approach the levels corresponding to the immune response of unexposed animals. This is caused by the post-radiation dynamics of damage and regeneration of the lymphocyte population of the blood (see Fig. 4). For 6 days after exposure the concentration of these cells is significantly lower than normal. During the first 2 days it decreases, then it begins to increase, first slowly and then, after 6 days, rapidly, until after 23 days it reaches the original level. These changes of the number of lymphocytes and, consequently, of B cells predetermined to produce antibodies of a certain specificity and of their descendents, plasma cells, by the time of immunization predetermine the decrease, and then growth

and complete restoration of the strength of the immune response when the time interval between exposure and immunization is increased.

These results agree qualitatively with the experimental data on the dynamics of the humoral immune response in mammals exposed to sublethal doses of radiation at various times before or after immunization.[84–90] In particular, it has been found experimentally that during the time of active biosynthesis of antibodies, exposure to radiation does not lead to a decrease of the maximum levels of antibodies in exposed mammals.[86–90] For example, for exposure of rabbits at a dose $D=8$ Gy three days after immunization by bovine gamma-globulin, the maximum number of antibodies in animals exposed to radiation is about 95% of the level of the antibody maximum in unexposed animals.[90] This value is 70% in the model. Meanwhile, during the initial stages of the immune response the humoral immunity system is sensitive to radiation.[90] The maximum level of antibodies in exposed mammals is significantly lower than the level for unexposed animals. For the same radiation dose and the same amount of introduced antigen this level is lower, the smaller the time interval between immunization and exposure.[90] It has also been shown experimentally that the immune response is suppressed if exposure occurs from 0 to 21 days before immunization.[89]

The model results and the experimental data are in quantitative agreement. For example, in Ref. 91 mice of the line CBA were exposed to a radiation dose of 4 Gy. Seven days after the exposure, 50 μg of T-independent antigen, *E. coli* lipopolysaccharide, strain 0111:B4, was introduced abdominally. It was found that the maximum amount of APCs in the spleen of the exposed mice was 15 times less than in unexposed ones. The model mimics the dynamics of the immune response of mice to the abdominal introduction of 10^{14} molecules of capsular antigen of the plague virus when exposure at a dose $D=4$ Gy precedes immunization by 7 days. It was found that the maximum number of APCs in exposed mice is 17.8 times smaller than in unexposed ones. Thus, the model and experimental results are close.

In Ref. 92 mice of the line CBA were exposed at a dose of 4 Gy. The same antigen, *E. coli* lipopolysaccharide, strain 0111:B4, was introduced abdominally (amount equal to 50μg) after 30 days. The number of APCs was determined 5 days after immunization. It was found that the numbers of APCs in the spleens of exposed and unexposed mice were practically the same. This implies that 30 days after exposure at a dose of 4 Gy the strength of the humoral response to a T-independent antigen is fully restored in the animals. These experimental data are consistent with the result obtained in the model: the maximum numbers of APCs in exposed and unexposed mice are equal if the time interval between exposure and immunization is greater than 23 days. This result is also consistent with the experimental observations, where the population of B lymphocytes in the spleen of mice exposed at a dose $D=4$ Gy is seen to be fully restored 20 days after exposure.[93] Restoration of the humoral immunity system 3 weeks after exposure to radiation was also noticed in Ref. 89.

Thus, this model reflects the basic regularities in the dynamics of humoral immunity in mammals exposed to radiation.

2. THE MODELING OF AUTOIMMUNE DISEASES

2.1. Current ideas about autoimmunity

Ionizing radiation can affect the immune system of mammals not only by lowering the defenses of the organism, but also by causing the development of autoimmune reactions, in the course of which the organism's own organs and tissues are damaged (Refs. 83, 94, and 95). Clinical observations indicate that autoimmunization plays an important role in the pathogenesis of acute radiation sickness arising after acute exposure to sublethal and lethal doses. Autoimmune reactions are one of the possible consequences of chronic exposure to low doses of radiation. In some cases autoimmune reactions also develop in unexposed mammals.

Normally, the immune system of an organism is in a state of tolerance (insensitivity) to the components of its own cells and tissues (autoantigens).[11–16] The organism of a healthy mammal contains only small concentrations of antibodies against the various antigenic substances of its organs and tissues. It is thought that the production of small quantities of these autoantibodies is a normal process which ensures the transport of macromolecules coming from naturally destroyed cellular and subcellular structures. Loss of tolerance leads to the development of autoimmunity, a pathological immune reaction. Large amounts of autoantibodies and aggressive T-lymphocytes (killers) appear in the organism and attack the antigens of the organism itself. Autoimmune reactions play the leading pathogenetic role in autoimmune diseases. Examples of such diseases are autoimmune haemolytic anemia, systemic lupus erythematosus, rheumatoid arthritis, dermatomyositis, autoimmune atrophic gastritis, Hashimoto's thyroid disease, and others.[15,96]

At the present time there is no single viewpoint on how autoimmune diseases develop. Some researchers support the hypothesis of Burnet,[11] according to which autoimmunity is a pathological process due to the appearance of a "forbidden" clone of lymphocytes specifically interacting with cells and proteins of the self. According to another hypothesis, autoimmunity is an ordinary immune reaction against those components of an organism which normally are inaccessible to immuno-competent lymphocytes.[12] "Accessibility" can arise as a result of various types of damage to cells and tissues. The primary injury leads to the appearance of antigen in the blood. This provokes an immune response, which leads to new damage of the tissues, and so on.

One of the recent theories of autoimmunity is a development of Burnet's hypothesis.[97–100] According to this theory, the tolerance of an organism to antigens of its own tissues is ensured by an organ of the immune system, the thymus. If its functioning is impaired owing to illness (for example, thymitus), use of cortisone, or exposure to radiation, the result can be the appearance of a forbidden clone of autoreactive lymphocytes.

Let us dwell in more detail on the mechanisms for the development of cellular autoimmune processes in mammals exposed to radiation. First, ionizing radiation directly dam-

ages part of the cells of radiation-sensitive tissues, resulting in the release of autoantigens. Second, radiation destroys the proper functioning of the thymus. This is thought to occur as follows. Among the population of medullary cells of the thymus which are resistent to radiation, there are immunocompetent predecessor cells which can recognize certain tissue-specific antigens. These cells can turn into aggressive T lymphocytes (killers) which destroy the cells of the corresponding tissues. Certain lymphocytes of the cortical layer of the thymus, T suppressors sensitive to radiation, hinder this transformation. In a healthy organism T suppressors completely suppress the production of killers directed against the self tissues. Exposure to radiation leads to a deficit of T suppressors and damages the immuno-suppression function of the thymus. This, in turn, leads to the formation of immuno-competent predecessor cells, relatively insensitive to radiation, of pools of aggressive T lymphocytes which attack the cells of the organism's own tissues. After their maturation and release from the thymus, these lymphocytes interact with cells of the corresponding tissue and damage them. This damage can be expressed both as a loss of the cell's functions and as death of the cell. The tissue-specific antigen released in the destruction of the cells will stimulate an immune response, which leads to further damage of the self tissue and the development of an autoimmune disease.

2.2. The modeling of autoimmunity in mammals not exposed to radiation

After the work of the present author with Stepanova,[101] in which the dynamics of autoimmunity in unexposed mammals was modeled, several isolated publications on this topic appeared in the literature.[102–104] In particular, the authors of Refs. 103 and 104 proposed an interesting approach to the modeling of humoral autoimmune processes. However, the model constructed in those studies[103,104] contains a large number of variables and parameters. This not only complicates its analysis, but also makes it difficult to modify the model for describing an even more complicated process: post-radiation autoimmunity. Therefore, in this section we shall dwell in more detail on Ref. 101, which later served as the basis for modeling autoimmune processes in mammals exposed to radiation.

Autoimmune illnesses are extremely diverse. However, they are similar in that they have as their basis a self-sustaining autoimmune reaction directed against some component of the organism, and the course of this reaction is practically independent of the cause of the loss of tolerance to the corresponding antigen. The authors of Ref. 101 studied a mathematical model of the final stage of the autoimmune process. Only cellular autoimmunity was considered, because it plays the leading role in long-term autoimmune diseases.[97,98] The variables of the model are the concentration x of target cells of the organism's own tissue, undamaged and having identical antigen specificity, the concentration y of effector T lymphocytes (killers) which attack these cells, and the concentration z of tissue-specific antigen produced in the destruction of target cells. The concentrations x, y, and z are expressed in moles per liter of blood.

The dynamics of the growth of healthy tissue are described by the Ferhulst equation[7]

$$\frac{dx}{dt}=\mu x-\nu x^2, \tag{2.1}$$

where μ is the unit rate of multiplication of tissue cells and νx^2 is the rate of death of these cells, which increases as the tissue grows. Equation (2.1) has a stable equilibrium state $\bar{x}=\mu/\nu$, which is identified as the "normal" concentration of tissue cells.

In constructing the model it was assumed that the interaction of tissue cells with killers leads to their mutual annihilation at rate βxy. It was assumed that the rate of production of tissue-specific autoantigen is proportional to the rate of destruction of tissue cells by killers, and that the unit rate of multiplication of aggressive T lymphocytes is proportional to the antigen concentration. In addition, the natural release of antigen from the organism (at unit rate γ) and the death of aggressive lymphocytes (at unit rate α) were taken into account in the model. The following system of equations was obtained:[101]

$$\frac{dx}{dt}=\mu x-\nu x^2-\beta xy, \tag{2.2}$$

$$\frac{dz}{dt}=\sigma\beta xy-\gamma z, \tag{2.3}$$

$$\frac{dy}{dt}=\psi zy-\beta xy-\alpha y, \tag{2.4}$$

where σ and ψ are constants.

The problem was simplified by taking into account the difference of the time constants of autoimmune processes (months), tissue growth (months), and establishment of equilibrium concentrations of the antigen (days). This made it possible, using the theorem of Tikhonov,[5] to replace the "fast" equation (2.3) by the algebraic equation $z=\sigma\beta xy/\gamma$. As a result, Eq. (2.4) took the form

$$\frac{dy}{dt}=\frac{\psi\sigma\beta}{\gamma}xy^2-\beta xy-\alpha y. \tag{2.5}$$

In Ref. 101, Eqs. (2.2) and (2.5) were put into dimensionless form:

$$\frac{d\xi}{d\tau}=\xi-\xi^2-\xi\eta, \tag{2.6}$$

$$\frac{d\eta}{d\tau}=a(\xi\eta^2-b\xi\eta-c\eta). \tag{2.7}$$

Here the following dimensionless variables and dimensionless parameters were introduced:

$$\xi=\nu x/\mu,\quad \eta=\beta y/\mu,\quad \tau=\mu t;$$
$$a=\psi\sigma\mu/(\gamma\nu),\quad b=\beta\gamma/(\psi\sigma\mu),\quad c=\alpha\gamma\nu/(\mu^2\psi\sigma). \tag{2.8}$$

The system (2.6), (2.7) was studied using the techniques of the qualitative theory of differential equations and oscillation theory. In Fig. 9 we show the principal isoclines of the system (2.6), (2.7): the isoclines of the horizontal tangents

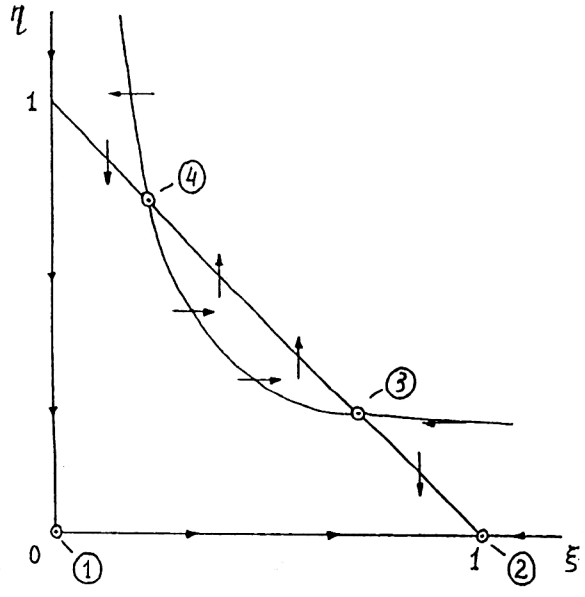

FIG. 9. Location of the principal isoclines and singular points of the system (2.6), (2.7) on the $\{\xi, \eta\}$ phase plane.

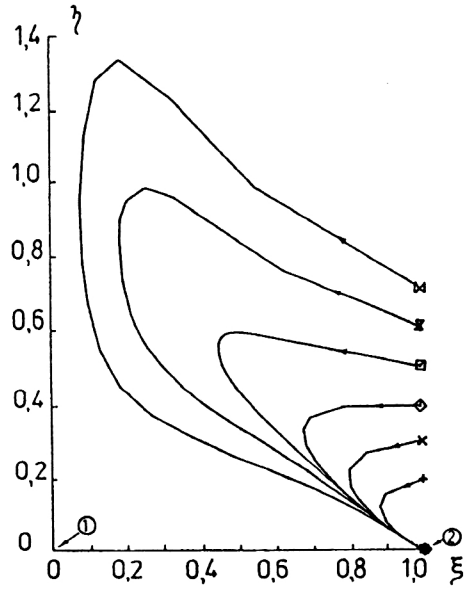

FIG. 11. Phase portrait of the system (2.6), (2.7). Results of computer calculation for $a=1.2$, $b=0.17$, $c=0.21$. The initial ($\tau=0$) and final ($\tau=100$) points of the integrated curves are marked. The singular points are labeled by numbers. The horizontal axis is the dimensionless concentration of target-tissue cells $\xi(\tau)$, and the vertical axis is the dimensionless concentration of aggressive T lymphocytes $\eta(\tau)$.

$\eta=0$, $\eta=b+c/\xi$, and the isoclines of the vertical tangents $\xi=0$ and $\eta=1-\xi$. The singular points located at the intersection of the principal isoclines are shown by the circles in Fig. 9. The trivial singular point $\xi_1=0$, $\eta_1=0$ is always unstable (a saddle). The point labeled 2 with coordinates $\xi_2=1$, $\eta_2=0$ is a stable node. It corresponds to the state of the healthy organism in which the tissue has normal size and is not damaged. The appearance of points 3 and 4 in the positive quadrant (a saddle bifurcation) is due to the intersection of the boundary $c=c^*=(1-b)^2/4$ (for $b<1$). In the bifurcation diagram (Fig. 10) the singular points 3 and 4 lie below the heavy line $c=c^*$. Study of the stability shows that the point 3 is always a saddle, and the point 4 is a node or a focus. When the boundary $c=c^{**}=(1/a-b)(1-1/a)$ is intersected (below the corresponding lines in Fig. 10), the point 4 becomes unstable, and bifurcation of the creation of a stable limit cycle occurs.

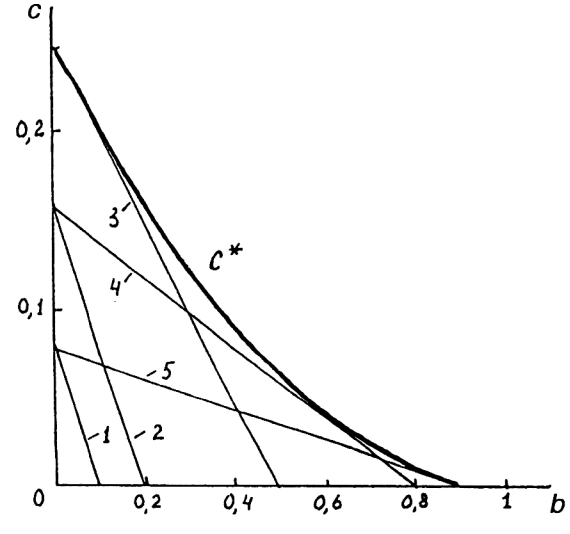

FIG. 10. Bifurcation diagram of the system (2.6), (2.7). The heavy line is the c^* saddle bifurcation line. Lines 1–5 are the c^{**} bifurcation lines of the loss of stability of singular point 4. Values of the parameter a^{-1}: 0.1 (curve *1*), 0.2 (curve *2*), 0.5 (curve *3*), 0.8 (curve *4*), and 0.9 (curve *5*).

The results of computer study of the system (2.6), (2.7) are shown in Figs. 11–13. In Fig. 11 we give the phase portrait of the system when the third and fourth singular points do not exist. All the integrated curves converge to the stable point 2. Such solutions describe the dynamics of autoimmunity in mammals possessing the potential ability to regenerate tissue or organs, no matter what the original damage was. However, in actual cases this possibility is often not realized, because death occurs owing to weakness of the damaged tissue or organ.

In Fig. 12 we show a typical phase portrait of the system when it has all four singular points, where the fourth is a stable focus. We see that the phase plane can be divided into regions I–IV according to the behavior of the integrated curves. The regions are separated by separatrices passing through the third singular point. One of the branches of the emerging separatrix ends at the second singular point, and the other circles the fourth point. The integrated curves in region I converge at the stable node 2. These solutions correspond to cases where there are small amounts of initial damage to the tissues and low concentrations of aggressive lymphocytes. Here the organism does not need to switch on additional mechanisms to arrive at the normal state.

The solutions of the system in region II can be regarded as the process of tissue regeneration in the presence of aggressive lymphocytes attacking the cells of this tissue. The time t_c during which the dimensionless concentration of tissue cells $\xi(\tau)$ changes from 0.1 to 0.9 with the condition that the concentration of aggressive lymphocytes is equal to zero

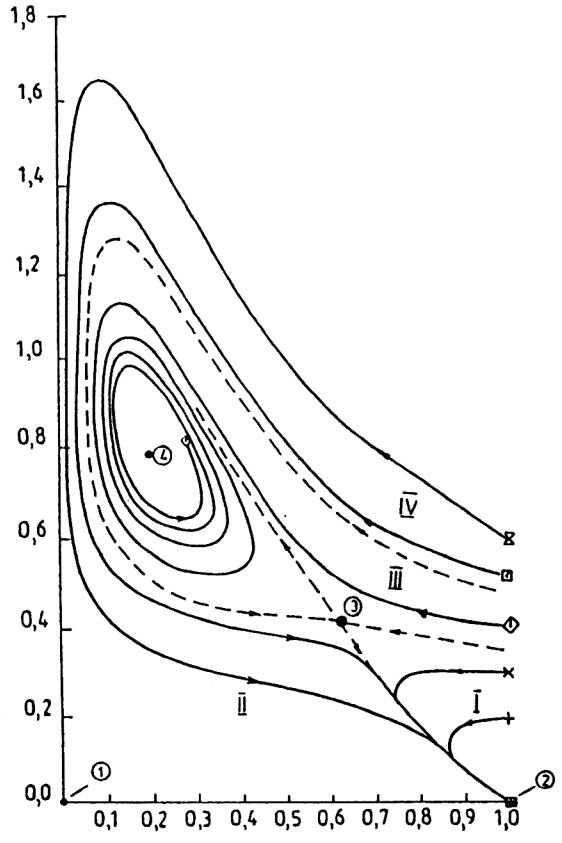

FIG. 12. Phase portrait of the system (2.6), (2.7). Results of computer calculation for $a=1.2$, $b=0.17$, $c=0.1.25$. The dashed lines are separatrices dividing the region into different dynamical domains. The other notation is the same as in Fig. 11.

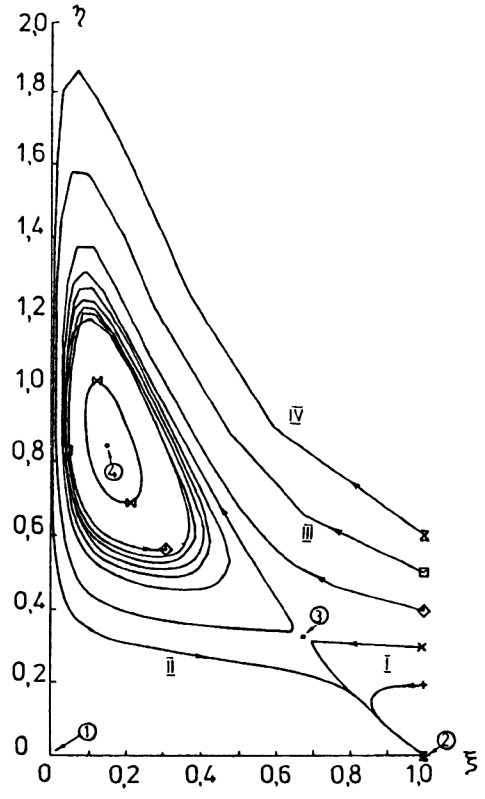

FIG. 13. Phase portrait of the system (2.6), (2.7). Results of computer calculation for $a=1.2$, $b=0.17$, $c=0.1$. The notation is the same as in Figs. 11 and 12.

$[\eta(\tau)=0]$ can be defined as the formation time of the corresponding tissue in the embryonic development of the organism.

Region III lies between the branches of the separatrix going to the third singular point. In this region the integrated curves have the form of spirals winding around the fourth singular point. The corresponding dynamical curves are damped oscillations. Such solutions describe the dynamics of progressive autoimmune diseases with periodic aggravation. The solutions in region IV are first characterized by rapid growth of the concentration of aggressive T lymphocytes and decrease of the concentration of undamaged tissue cells. Then the integrated curves go into region II. These solutions apparently are meaningful only in a restricted region of the phase plane, because in living organisms death occurs long before the complete destruction of a vitally important organ or tissue.

Of particular interest are the solutions of the system (2.6), (2.7) when the fourth singular point becomes unstable. In these cases another stable special solution appears: a limit cycle (stable oscillations of the values of the variables ξ and η about the values ξ_4 and η_4). All the integrated curves from region III converge to the limit cycle (Fig. 13). Such solutions are the analog of chronic autoimmune diseases. For a selected parameter ratio the period of oscillation of the concentrations ξ and η is approximately $2t_c$. If it is remembered that the time for the formation of organs and tissues in human embryonic development is 3/4 year, the periodicity of the aggravations is of order one to two years according to the model. This result agrees with the clinical observations.[96]

By qualitatively studying the model (2.6), (2.7) we can explain experiments on artificial autoimmunity induced in laboratory animals by the introduction together with Freund's adjuvant of extracts of self tissues or killed microbes (staphilococcus, streptococcus) having the same antigenic specificity as several tissues of the organism. The laboratory animals developed autoimmune diseases which either were cured "spontaneously" or ended in death. In the model the introduction of these components is equivalent to an abrupt increase in the autoantigen concentration and, consequently, to an increase of the concentration of aggressive lymphocytes. If here the system remains in region I in the phase plane (Fig. 13), over time it will return to the initial state. Such solutions of the model are equivalent to spontaneous recovery. If the system is in region IV, the concentration of undamaged tissue cells will decrease so greatly over time that such solutions are equivalent to acute progression of the autoimmune process and death.

The model (2.6), (2.7) was used to simulate the dynamics of the autoimmune process in the case where the disease is cured by means of immunodepressants (cortico-steroidal hormones). An excess of the latter in the blood leads to lymphocyte destruction. Therefore, the introduction of cortico-steroidal hormones into the organism can be viewed in the model as an abrupt decrease of the concentration of aggres-

sive lymphocytes. This can cause the representative point on the phase plane to move from the region of chronic illness (III) to the regions of recovery (I, II) (Fig. 13). Analysis of the model showed that the most favorable time for the introduction of medicine is a remission period, when the concentration of aggressive lymphocytes is minimal.

Thus, the model developed in Ref. 101 reproduces the main features of the autoimmune process and can be used as a basis for constructing models of the dynamics of autoimmunity in mammals exposed to radiation.

2.3. Autoimmune reactions induced by acute radiation exposure

The autoimmune process developing in a healthy organism after acute radiation exposure was modeled in Ref. 105. The ionizing radiation causes some of the cells of radiation-sensitive tissue to die. According to the one-target, one-hit model of cellular radiation damage,[80] the concentrations of tissue cells undamaged (x) and damaged (x_d) by radiation are

$$x=\bar{x}\exp(-D/D_k), \tag{2.9}$$

$$x_d=\bar{x}[1-\exp(-D/D_k)], \tag{2.10}$$

Here $\bar{x}$ is the concentration of tissue cells before exposure, and D_k is the dose D_0 characterizing the radiation sensitivity of these cells.

The cells of the self tissue damaged by radiation release tissue-specific autoantigen. Its concentration z is proportional to x_d:

$$z=\sigma x_d=\sigma x[1-\exp(-D/D_k)], \tag{2.11}$$

where σ is a constant.

The radiation also leads to death of part of the population of T suppressors. Their concentration S_d is given by an expression analogous to (2.10):

$$S_d=\bar{S}[1-\exp(-D/D_s)]. \tag{2.12}$$

In (2.12), $\bar{S}$ is the initial concentration of T suppressors, and D_s is the dose D_0 characterizing their radiation sensitivity.

In turn, the death of T suppressors leads to loss of tolerance of a part of the population of immuno-competent cell-predecessors proportional to the concentration of dead T suppressors S_d. Accordingly, the concentration of aggressive T lymphocytes y is given by

$$y(t_t)=\kappa S_d=\kappa\bar{S}[1-\exp(-D/D_s)], \tag{2.13}$$

where κ is a constant, and t_t is the time needed for aggressive T lymphocytes to mature in the thymus.

The natural death of antigen molecules at unit rate γ also occurs during this process:

$$\frac{dz}{dt}=-\gamma z. \tag{2.14}$$

At the instant (t_t) when aggressive T lymphocytes are released from the thymus, according to (2.11) and (2.14) the concentration of tissue-specific antigen becomes

$$z(t_t)=\sigma\bar{x}[1-\exp(-D/D_k)]\exp(-\gamma t_t). \tag{2.15}$$

The time for the initial concentration of tissue-specific antigen to be exhausted and, accordingly, the time for the multiplication of the aggressive T lymphocytes stimulated by this antigen (several days) are much smaller than the time for autoimmune processes to develop (months). Therefore, the first case studied in the model was this "fast" process described by (2.14) and by the equation

$$\frac{dy}{dt}=\psi z y. \tag{2.16}$$

In turn, the solutions of the system (2.14), (2.16) with the initial conditions (2.15), (2.13) were taken as the initial conditions for Eqs. (2.3) and (2.4). These initial conditions are

$$z(0)=0, \tag{2.17}$$

$$y(0)=\kappa\bar{S}[1-\exp(-D/D_s)]\exp\{(\psi\sigma\bar{x}/\gamma)\times\exp(-\gamma t_t)[1-\exp(-D/D_k)]\}. \tag{2.18}$$

The initial condition for solving (2.2) is expressed as (2.9) if the time to exhaust the initial concentration of tissue-specific antigen is smaller than the characteristic time for recovery processes in the target-cell population. It is precisely these situations which were studied in Ref. 105.

The system (2.2)–(2.4) reduces to (2.2), (2.5) if we use the fact that the "fast" equation (2.3) can, as before, be replaced by the stationary solution. In dimensionless variables Eqs. (2.2) and (2.5) take the form (2.6), (2.7), and the initial conditions (2.9) and (2.18) are written as

$$\xi(0)=\exp(-D/D_k), \tag{2.19}$$

$$\eta(0)=l[1-\exp(-D/D_s)]\exp\{m[1-\exp(-D/D_k)]\}. \tag{2.20}$$

Here $l=\kappa\bar{S}\beta/\mu$ and $m=(\psi\sigma\bar{x}/\gamma)\exp(-\gamma t_t)$ are new dimensionless parameters.

Studies of the model carried out in Ref. 105 show that the suggested description of the effect of radiation on the dynamics of autoimmune processes ensures that the main situations observed experimentally will be reproduced by the model.[83,94] For example, the dynamics of the autoimmune process in mammals exposed to various doses of ionizing radiation was studied (Fig. 14). The three integrated curves of the phase portrait correspond to three different radiation doses D. We see from this figure that small doses [$D\ll\min(D_k, D_s)$] do not induce development of an autoimmune disease. The concentration of aggressive T lymphocytes decreases to zero, and the population of cells of the self tissue is completely restored. Doses $D<\min(D_k, D_s)$ lead to the establishment in the system of stable oscillations of the concentrations of undamaged target-tissue cells and aggressive T lymphocytes which attack these cells, i.e., to the development of a chronic autoimmune disease. Doses $D\sim\min(D_k, D_s)$ induce an abrupt increase of the concentration of killers and decrease of the concentration of undamaged target cells. Such solutions can be viewed as mimicking "acute" autoimmune processes. They can terminate either in death of the organism if the tissue in question performs vitally important functions, or in spontaneous recovery.

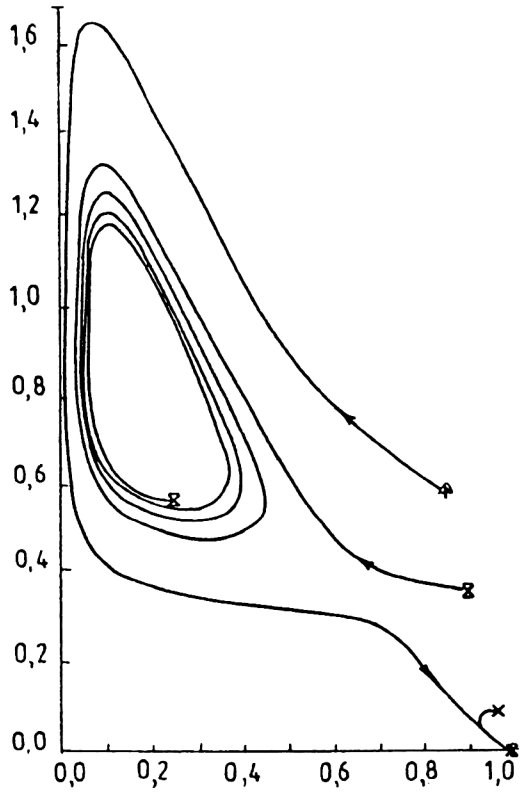

FIG. 14. Change of concentrations of target-tissue cells ξ and aggressive T lymphocytes η after various radiation doses D. The results of computer calculation for the system (2.6), (2.7) with the initial conditions (2.19), (2.20) and the parameters $a=1.2$, $b=0.17$, $c=0.1$, $l=m=1$, $D_s=1$ Gy, $D_k=4$ Gy are shown as integrated curves on the phase plane [the horizontal axis is $\xi(\tau)$, and the vertical axis is $\eta(\tau)$]. The curves labeled $\times$, $\underline{\times}$, and $+$ at the initial ($\tau=0$) and final ($\tau=100$) points correspond to doses $D=0.1$, 0.4, and 0.7 Gy.

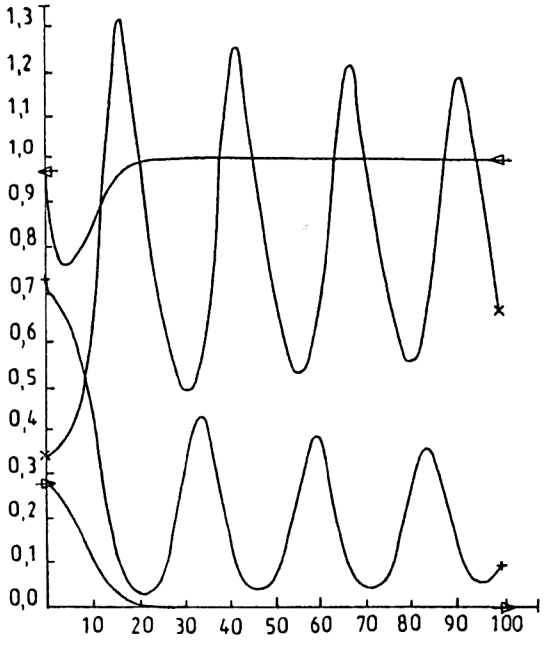

FIG. 15. Dynamics of the change of concentrations of cells of radiation-resistant ($\leftarrow$) and radiation-sensitive ($+$) tissues (ξ) and of aggressive T lymphocytes attacking these cells (η) ($\rightarrow$ and $\times$, respectively) after acute exposure at a dose $D=0.3$ Gy. Results of the computer calculation of the system (2.6), (2.7) with the initial conditions (2.19), (2.20) and parameter values $D_k=1$ Gy and $D_k=10$ Gy. The values of the coefficients a, b, c, l, m, and D_s are given in the caption to Fig. 14. Along the horizontal axis is the dimensionless time τ, and along the vertical axis are the dimensionless concentrations ξ and η.

The model also reflects the experimentally observed fact that post-radiation autoimmunity is directed against the tissues most sensitive to radiation. In Fig. 15 we show the dynamics of the autoimmune processes developing after two tissues of an organism differing in their radiation sensitivity were exposed to equal doses of radiation. We see that the population of cells of the radiation-resistant tissue is completely restored, and the concentration of the corresponding aggressive T lymphocytes falls to zero. The population of cells of the radiation-sensitive tissue is damaged by a chronic autoimmune disease: the concentrations of tissue cells undamaged by killers and of the corresponding aggressive T lymphocytes oscillate about new stationary values.

Thus, the proposed model reproduces the main regularities of autoimmune processes developing in mammals after acute radiation exposure.

2.4. Autoimmunity in chronic radiation exposure

A model of the autoimmune process developing in mammals chronically exposed to radiation was developed and studied in Ref. 106. The variables of the model are the concentration of T suppressors of the cortical layer of the thymus S, and, as in Refs. 101 and 105, the concentrations of cells of the self tissue x, of aggressive T lymphocytes y, and of the specific antigen z. The dynamics of cells subjected to prolonged radiation exposure were described, as in Ref. 105, by the one-target, one-hit model, according to which the rate of cellular radiation damage is proportional to the dose rate N (Ref. 80). According to this model and the model (2.2)–(2.4), the dynamics of autoimmune processes in mammals for chronic exposure is described by the following system of equations:

$$\frac{dx}{dt}=\mu x-\nu x^2-\beta xy-\frac{N}{D_k}x, \tag{2.21}$$

$$\frac{dy}{dt}=\psi zy-\beta xy-\alpha y+\varepsilon, \tag{2.22}$$

$$\frac{dz}{dt}=\sigma\beta xy-\gamma z+\frac{\sigma N}{D_k}x, \tag{2.23}$$

$$\frac{dS}{dt}=\omega S-\varphi S^2-\frac{N}{D_s}S. \tag{2.24}$$

For $N=0$ and $\varepsilon=0$ the system (2.21)–(2.23) is equivalent to (2.2)–(2.4).

Equation (2.24) for $N=0$ is the Ferhulst equation: the terms ωS and φS^2 describe the rates of multiplication and natural death of T suppressors. The stationary solution of this equation is $\bar{S}=\omega/\varphi$, representing the concentration of T suppressors of the cortical layer of the thymus in a healthy, unexposed mammal. The terms proportional to the dose rate N in (2.21) and (2.24) are the specific rates at which

radiation-sensitive cells of the target tissue and T suppressors are killed by the effects of radiation. The coefficients D_k and D_s have the same meaning as in (2.9)–(2.12). The term $\sigma(N/D_k)x$ in (2.23) is the rate of formation of tissue-specific antigen in the post-radiation destruction of tissue cells. The quantity ε is the rate at which killers arrive from the thymus. As in Ref. 105, it was assumed that the destruction of a certain number of T suppressors of the cortical layer of the thymus leads to loss of tolerance of a proportionate number of immuno-competent cell-predecessors from the medullary region. Therefore, ε is given by the piecewise-linear function

$$\varepsilon=\begin{cases}0 & \text{for } S\geqslant\bar{S},\\ \chi\kappa(\bar{S}-S) & \text{for } S<\bar{S},\end{cases} \tag{2.25}$$

where κ is the coefficient of proportionality and χ is the unit rate at which aggressive T lymphocytes mature in the thymus.

The system (2.21)–(2.23) was simplified by using the difference in the time constants for the development of autoimmune processes (months) and the establishment of stationary antigen concentrations (days). According to the Tikhonov theorem,[5] the "fast" equation (2.23) is replaced by the stationary solution $z=(\sigma/\gamma)[\beta xy+(\nu/D_k)x]$, so that (2.22) takes the form

$$\frac{dy}{dt}=\frac{\psi\sigma\beta}{\gamma}xy^2-\left[\beta-\frac{\sigma\psi}{\gamma}\frac{N}{D_k}\right]xy-\alpha y+\varepsilon. \tag{2.26}$$

After changing to dimensionless variables $\xi=\nu x/\mu$, $\eta=\beta y/\mu$, $\zeta=\varphi S/\omega$, and $\tau=\mu t$ and the dimensionless parameters $a=\psi\sigma\mu/(\gamma\nu)$, $b=\beta\gamma/(\psi\sigma\mu)$, $q=\omega/\mu$, $c=\alpha\gamma\nu/(\mu^2\varphi\sigma)$, and $h=\gamma\nu\beta\kappa\chi\omega/(\psi\sigma\mu^3\varphi)$, the following system of equations was obtained in Ref. 106:

$$\frac{d\xi}{d\tau}=\xi\left\{\left(1-\frac{N}{\mu D_k}\right)-\xi-\eta\right\}, \tag{2.27}$$

$$\frac{d\eta}{d\tau}=a\left\{\xi\eta^2-\left[b-\frac{N}{\mu D_k}\right]\xi\eta-c\eta+\varepsilon'\right\}, \tag{2.28}$$

$$\frac{d\zeta}{d\tau}=q\zeta\left\{\left[1-\frac{N}{\omega D_s}\right]-\zeta\right\}, \tag{2.29}$$

where

$$\varepsilon'=\begin{cases}0 & \text{for } \zeta\geqslant 1,\\ h(1-\zeta) & \text{for } \zeta<1.\end{cases} \tag{2.30}$$

The system (2.27)–(2.29) has been studied by the methods of the qualitative theory of differential equations and oscillation theory. Using analytic expressions, it was possible to find the position and stability of its five singular points, and also to obtain relations between the dose rate N and other coefficients of the model, which give in parameter space the conditions for saddle bifurcation and bifurcation of the creation of the limit cycle. From this analysis expressions were obtained which can be used to calculate the critical values of the dose rate of chronic exposure N_c, which when received or exceeded lead to irreversible destruction of all the target-tissue cells. Depending on the relations between the parameters, these expressions take the form

$$N_c=\frac{\mu D_k}{1+h\mu D_k/c\omega D_s} \quad \text{for } \mu D_k\left(1-\frac{h}{c}\right)<\omega D_s; \tag{2.31}$$

$$N_c=\mu D_k\left(1-\frac{h}{c}\right) \quad \text{for } \mu D_k\left(1-\frac{h}{c}\right)>\omega D_s. \tag{2.32}$$

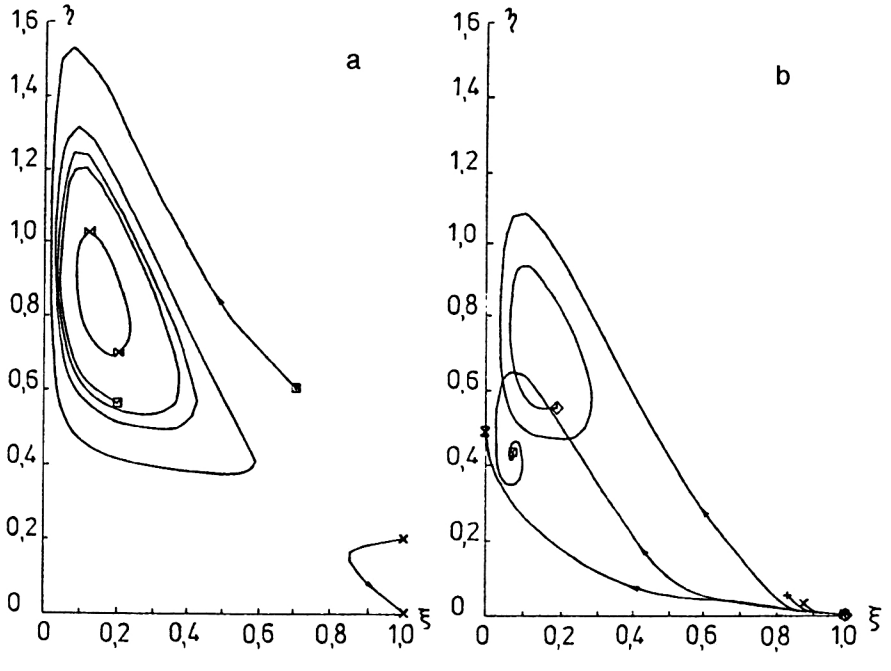

FIG. 16. Projections on the plane of states $\{\xi,\eta\}$ of integrated curves of the system (2.27)–(2.29) for $D_s=1$ Gy and $D_k=4$ Gy: (a) for fixed dose rate $N_1=0.001$ Gy/day and initial conditions $\xi(0)=1$, $\eta(0)=0.2$, $\zeta(0)=1$ (×); $\xi(0)=0.7$, $\eta(0)=0.6$, $\zeta(0)=1$ (□); $\xi(0)=0.2$, $\eta(0)=0.7$, $\zeta(0)=1$ (⋈); (b) for fixed initial conditions $\xi(0)=1$, $\eta(0)=0$, $\zeta(0)=1$ and dose rate $N_2=0.04$ (×); $N_3=0.049$ (+); $N_4=0.063$ (◇); $N_5=0.2$ (□); $N_6=0.5$ Gy/day (⧖). Markers label the initial ($\tau=0$) and final ($\tau=100$) points of the integrated curves.

The analysis made it possible to perform a goal-directed computer study of the model. The initial values of the coefficients were set to $a=1.2$, $b=0.17$, $c=0.1$, $h=0.1$, $\omega=1\,\text{day}^{-1}$, and $\mu=0.1\ \text{day}^{-1}$. For this choice of parameters the system (2.27)–(2.29) at $N=0$ most completely describes the experimentally observed dynamical regimes of autoimmune diseases in unexposed mammals (Fig. 13).

The dependence of autoimmune processes on the dose rate of chronic exposure N was studied in a numerical experiment. For the smallest dose rate considered, N_1 (Fig. 16a), the system (2.27)–(2.29) has a special solution: a stable limit cycle, the analog of the chronic autoimmune process. However, calculations show that it is possible to reach this dynamical regime only if before the exposure starts the concentration of aggressive lymphocytes is sufficiently large and target cells are damaged. In cases where before exposure at low dose rates (N_1,N_2,N_3) the concentration of aggressive lymphocytes is small or zero and the tissue is not damaged, the integrated curves terminate at a singular point. Remaining at this point can be viewed as a "stable" autoimmune process characterized by slight damage to the target tissue and low killer concentrations (Figs. 16a and 16b). This result suggests that long-term exposure to radiation even at low doses can, in some cases, lead to enhancement of autoimmune processes occurring before exposure. When the dose rate is increased (N_4,N_5), the autoimmune process develops, even if a healthy organism is subjected to prolonged radiation exposure [$\xi(0)=1$, $\eta(0)=0$, $\zeta(0)=1$]. Therefore, the larger N is, the larger the number of target-tissue cells that will be damaged as a result of autoaggression (Fig. 16b). In those cases where N becomes equal to or greater than some critical value (N_6), the concentration of tissue cells undamaged by radiation decreases to zero. Such solutions can be viewed as the analog of death of the organism if the tissue in question performs vitally important functions.

The dependence of the autoimmunity dynamics on the

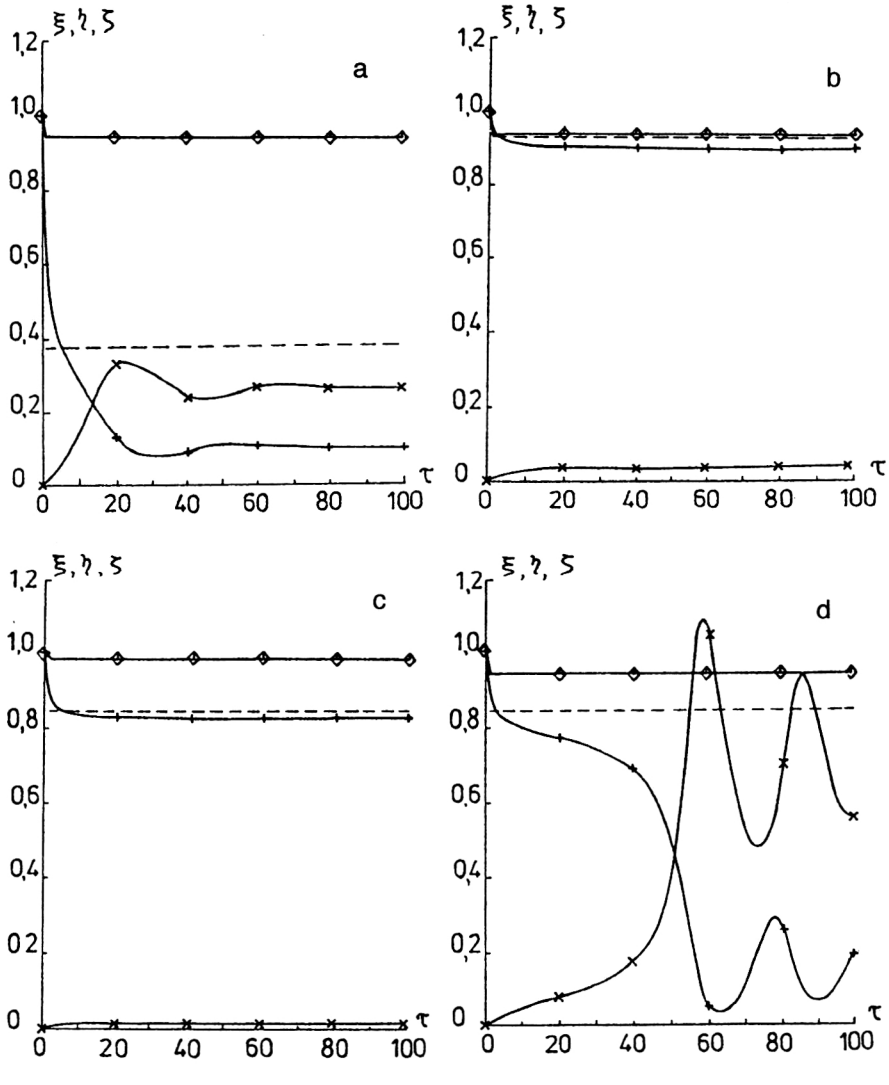

FIG. 17. Effect of radiation shielding on the dynamics of autoimmune processes. (a) No radiation shielding ($N_{\text{eff}}=N$); (b) target-tissue screening ($N_{\text{eff}}=0.1N$); (c) screening of tissue and thymus ($N_{\text{eff}}=0.25N$); (d) screening of target tissue ($N_{\text{eff}}=0.25N$). The curves $\xi(\tau)$, $\eta(\tau)$, and $\zeta(\tau)$ are marked ($+$, $\times$, $\diamond$). The dashed lines show the levels of decrease of the concentration of target-tissue cells as a result of direct radiation damage to cells for dose rate N_{eff} and without autoaggression $\bar{\xi}_R$.

radiation sensitivity of tissue cells and T suppressors of the cortical layer of the thymus was also studied. The parameters D_k and D_s were varied in a wide range. It was found that chronic exposure at the same dose rate N leads to the development of autoimmune processes in which the higher the radiation sensitivity of the cells of this tissue and the T suppressors, the larger the number of target-tissue cells that are damaged.

The model (2.27)–(2.29) was also used to simulate the effect of shielding of the target tissue and the thymus on the autoimmunity dynamics. Here the different degrees of radiation protection were specified by varying the effective rate of the radiation dose (N_{eff}) acting on the shielded organ or tissue. In Figs. 17a–17d we show the results of the calculations using the model (2.27)–(2.29) for $N=0.063$ Gy/day and $D_k=D_s=1$ Gy. We indicate the stationary levels of concentration of target-tissue cells $\bar{\xi}_R=1-N_{\text{eff}}/(\mu D_k)$ to which the value of ξ would be decreased as a result of direct radiation damage to the tissue at dose rate N_{eff} and neglecting autoaggression. Fig. 17a corresponds to the case where neither the thymus nor the target tissue are screened ($N_{\text{eff}}=N$). We see from this figure that the combined action of radiation and autoaggression leads to damage of a significant number of target-tissue cells, which in some cases can terminate in death of the mammal. Screening of the target tissue which decreases the effective dose rate by a factor of 10 (Fig. 17b) almost completely prevents the development of the autoimmune reaction. The same results are obtained for the simultaneous screening of the tissue and the thymus decreasing the effective dose rate by a factor of 4 altogether (Fig. 17c). As in Fig. 17b, the tissue is slightly damaged, mainly by the effect of ionizing radiation. It should be noted that radiation shielding of only the target tissue which also decreases the effective dose rate by a factor of 4 does not stop the development of the autoimmune process, although it does lessen the damage to the shielded organ (Fig. 17d). These results show that screening of the thymus plays an important role in preventing remote consequences of prolonged exposure to radiation, namely, the development of autoimmune processes which damage radiation-sensitive organs and tissues.

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