# Immunology and Disease Control: A Systems Approach

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***Abstract*—The application of system theory (or more precisely, differential equations) to immunology and disease, in general, is presented here. Particular results from U.S.-Russian research collaboration depict the potential role of such systematic analysis for more effective health care and disease control. In particular, some emphasis is given to control of influenza. After a brief systematic overview of immunology, a simple infectious disease model is developed to explain four basic forms of disease: subclinical, acute, lethal and chronic. Then, disease treatment is studied.**

## NOMENCLATURE

| | |
|---|---|
| $C$ | Concentration of generalized plasma cells. |
| $C_I$ | Concentration of infection-insensitive cells due to interferon. |
| $C_v$ | Concentration of virus-infected cells. |
| $C_0$ | Concentration of all cells sensitive to the virus. |
| $F$ | Concentration of generalized antibodies. |
| $k_{C_v}$ | $C_v$ growth rate coefficient. |
| $k_v$ | $V$ growth rate coefficient from $C_v$. |
| $L_e$ | Effecter-cell concentrations. |
| $L_p$ | Lymphocyte concentration. |
| $m$ | Relative degree of damage to organ eliciting immunity. |
| $V$ | Concentration of generalized germs or viruses. |
| $\alpha$ | Combined coefficient of rate of stimulation and fission of plasma cells. |
| $\alpha_i$ | $i = 1, \ldots, 12$, convenient parameters in transformed equation. |
| $\beta$ | Germ rate of growth coefficient. |
| $\gamma$ | Germ rate of binding coefficient. |
| $\gamma_{C_v L_e}$ | $C_v$-$L_e$ binding coefficient. |
| $\gamma_{vF}$ | Viral $V$-$F$ binding coefficient. |
| $\gamma\eta$ | Antibody rate of binding coefficients. |
| $\mu_c$ | Plasma cell death rate coefficient. |
| $\mu_C$ | Natural $C_v$ death rate. |
| $\mu_f$ | Natural antibody death rate. |
| $\mu_m$ | Natural aging coefficient of organ. |
| $\mu_v$ | Natural viral death rate. |
| $\xi$ | Damage coefficient of generalized plasma cell production. |
| $\rho$ | Generalized antibody production rate coefficient. |
| $\sigma$ | Disease damage coefficient to organ health state. |
| $\sigma_f$ | Generalized antibody damage to organ health state. |
| $\tau$ | Delay time in sufficient cell stimulation. |
| $*$ | Designates normal equilibrium. |
| $0$ | Designates initial values. |

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## I. INTRODUCTION

THE OBJECT of this paper is a tutorial overview of recent results on disease dynamics and control. It is suggested that systems analysis and control theory may play an increasing role in more effective patient health care. In particular, ordinary differential equations and their dependence on certain parameters form a building-block, mathematical synthesis of the immune system which is amenable to the study of health state maintenance. Then, an antiviral immune-response model is derived, and analyses made of influenza. Statistical estimation of influenza model parameter and state is obtained from patient data.

A good base for this paper is given by a tutorial paper on immunological systems [1], which studied the dynamics of cellular fission and chemical reactions. Some emphasis was given to the humoral process and the subsequent generation of antibodies which, in turn, can lead to certain alien destruction. The disease dynamics, however, were not studied in this former paper.

Details of basic immunology and its systematic analysis are presented in [1]–[15]. While our detailed knowledge of immunology is constantly improving, the basic principles of biochemistry, upon which immunology is based, rarely change. This allows us to form a reasonable model structure upon which to add complexity according to questions addressed and data available.

The immune system is the set of lymphoid organs and cells that contains the thymus, spleen, liver, lymphatic nodes, Peyer's patches, lymphocytes of bone-marrow derivation and peripheral blood. All these represent the connected "diffuse" organ with mass about 1.5–2 kg. The total number of lymphoid cells is approximately equal to $10^{12}$.

The main aim of the immune system is the defense of the organism from agents with properties of genetically alien information (such as bacteria, viruses, proteins, tissue and transformed own cells, such as tumor cells). The immune system generates cells and molecules to bind and destroy the alien. These defenders are circulated throughout the body

organs by the bloodstream to virtually all tissue; they are appropriately processed in their migration and recirculated back through the lymphatic vessels. The generation of these defender cells and molecules is termed the *immune response*. Any alien substance which is able to induce such a response is a form of *antigen*. Antigen can occur free as well as bound, such as to immune system molecules which may be free or on the surface of cells. It should be noted here that every living cell presents antigens on its surface membrane and in its core.

A class of white blood cells called lymphocytes is dedicated to immunity. These cells of the immune system circulate in the body and are present in high concentration in certain lymphoid organs, such as spleen and lymph nodes. Since about $10^{10}$ lymphocytes circulate in the blood with a correspondingly broad diversity of antigen recognition receptors, the immune system can recognize and respond to virtually any antigen that may penetrate the organism. Any such antigen has some finite probability of meeting in the blood a lymphocyte that recognizes it automatically. With a series of stimulations of differentiations and generation of antibody molecules, such recognition leads to the development of an immune response.

During the immune response, the molecules and the cells of the immune system interact with each other as well as with other cells and molecules of the organism. Therefore, to model this process, we can use the principles of cellular and molecular kinetics.

As discussed above, cellular and molecular kinetics are the basis of the entire immune process. These processes are quite well defined from conservation equations and chemical mass-action principles. In general, the *cellular population* (or concentration), $x_i$, of the $i$th class may be described by

$$\frac{dx_i}{dt} = \begin{array}{l}\text{source rate} - \text{death rate} + \text{division rate} \\ + \text{ rate differentiation to } - \text{ rate differentiation from.}\end{array} \tag{1}$$

An $m$th class of molecular concentrations, $y_m$, may be described by

$$\frac{dy_m}{dt} = \begin{array}{l}\text{molecular rate} - \text{net death rate} \\ + \text{dissociation rate of appropriate complexes} \\ - \text{association rate of appropriate complexes.}\end{array} \tag{2}$$

## II. A Simple Model of Infectious Disease

In this section, we study a mathematical model of a disease, which was proposed by Marchuk [16]–[19], and studied by Asachenkov [20] and Belykh [21], [22]. This model is only a crude approximation and generally requires further refinement. However, even in this form, it enables us to bring various factors essential to understand the dynamics of an infectious disease. It is also possible that separate results of the theory can be used for finding effective methods of treatment.

### A. Model Development

The model is constructed on the basis of equilibrium relations for each component of the immune system. For this simplest model, we follow the general conservation equations ((1) and (2)), and assume a basic humoral response [2]. However, the so-called cellular response is similar with both involving lymphocytes and secreted molecules. Consequently, we call these molecules antibodies. This is reasonable since appropriate $T$ cells and macrophages secrete active molecules similar to the secretion of antibodies by $B$ cells of the humoral component [2]. We assume the presence of sufficient activation by cellular components, and confine ourselves to considering three components: antigen, antibody, and plasma cells for generated antibodies. We refer to the stimulators of an infectious disease (antigens) as germs (a popular form including viruses, bacteria, etc.), placing no precise biological meaning to this term. Therefore, in the model, the germ is a multiplying pathogenic antigen. It should also be noted that during illness the degree of organ damage subject to the disease (antigens) is of great significance, since it leads, in the final analysis, to lower activity of the immune system. This phenomenon should be accounted for in the mathematical models.

Note that the simplest mathematical model in this interpretation permits distinct variations which can help us to find probable explanations of some important features of the operation of the immune system: formation of subclinical, acute and chronic disease processes and their possible therapy.

The essence of the immune response to an invasion of genetically different substances (antigen), including the disease stimulants, is production of specific material substances (antibody molecules, cell-killers) which are capable of neutralizing or destroying this antigen. In these terms, an infectious disease can be interpreted as a confrontation between the population of disease stimulants and the body's immune system. In this connection, as a first step, we distinguish the following main characteristics of disease:

1) Concentration $V(t)$ of generalized germs. By germs we mean multiplying pathogenic antigens.
2) Concentration $F(t)$ of generalized antibodies. By antibodies we mean substrates of the immune system, neutralizing germs (immunoglobulins, cell receptors, interleukins, etc).
3) Concentration $C(t)$ of generalized plasma cells. This is the population of carriers and producers of antibodies (here including plasma cells, all immuno-effective molecular producers). $C^*$ designates the normal constant concentration.
4) Relative characteristic of a damaged organ $m(t)$.

The nonlinear models which are presented here are not only valid for small deviations from equilibria. As for any model, on the other hand, they are only as valid as the underlying immunological assumptions presented.

It is a simple matter to derive the disease dynamics from the conservation of matter equations ((1) and (2)) in Section I. Consequently, the model is a system of nonlinear ordinary differential equations

$$\frac{dV}{dt} = (\beta - \gamma F)V, \tag{3}$$

$$\frac{dC}{dt} = \xi(m)\alpha V(t-\tau)F(t-\tau) - \mu_c(C - C^*), \tag{4}$$

$$\frac{dF}{dt} = \rho C - (\mu_f + \eta\gamma V)F. \tag{5}$$

$\alpha, \beta, \gamma, \eta, \rho, \mu_c, \mu_f$, $C^*$, and $\tau$ are constants defined below.

Delay time, $\tau$, is introduced in (4) to approximate missing dynamic components such as resulting in plasma cell stimulation. Here, immunocompetent and memory cell dynamics are neglected, and $\tau$ is used to account for this delay in the generation of antibody-producing plasma cells. Usually, for equations with delay, the initial conditions are given on an interval $[t^0 - \tau, t^0]$. However, in the biological sense of the described processes, until the moment of infection $t = t^0$, there were no germs in the organism: $V(t) \equiv 0$ for $t < t^0$; and therefore, the initial conditions can be given at the point $t^0$. In what follows, when we speak of initial conditions for equations of this kind, we mean $V(t) \equiv 0$ for $t < t^0$. We have

$$\begin{aligned} &V(t) = 0 \text{ for } t \in [-\tau, 0] \\ &V(t^0) = V^0 > 0, \quad C(t^0) = C^0 > 0, \\ &F(t^0) = F^0 > 0. \end{aligned} \tag{6}$$

Equation (3) describes the change in the number of germs in the organism. We assume the exponential growth of viruses with coefficient $\beta$. The term $\gamma FV$ in (3) and (5) designates the number of antigens neutralized by the antibodies $F$; $\gamma$ is the coefficient connected with the probability of neutralization of the germs by the antibodies upon an encounter. No delay is introduced in (3) and (5) since it is negligible in these cases due to more direct reactions.

Equation (4) describes the growth of plasma cells. To this end, we take advantage of the simplest hypothesis on the formation of a cascaded population of plasma cells. The immunocompetent $B$ lymphocyte is stimulated by an antigen coupled with receptors of the $T$ cell, and initiates the cascade process of forming cells which synthesize the antibodies neutralizing antigens of this kind. Since, in our model, by antibodies we mean the substrates capable of binding with germs (including possibly $T$ cell receptors), the number of lymphocytes stimulated in this way are assumed proportional to $VF$. Therefore, we arrive at the relation describing the increment of plasma cells over a normal level $C^*$ which is the constant level of plasma cells in a normal organism. The first term on the right side of (4) describes the generation of plasma cells; $\tau$ denotes the time during which a cascade of plasma cells is formed; $\alpha$ denotes the coefficient allowing for: the probability of an encounter of "antigen-antibody," the stimulation of the cascade reaction, and the number of newly generated cells. The second term describes the decline in the number of plasma cells due to aging; $\mu_c$ is the coefficient equal to the inverse of the plasma cell's lifetime.

To obtain (5), let us calculate the balance of the number of antibodies reacting with antigens. The first term, $\rho C$, on the right describes the generation of antibodies by plasma cells; $\rho$ denotes the rate of production of antibodies by one plasma cell. The second term, $\mu_f F$, describes the decrease in the antibody population due to aging, where $\mu_f$ is the coefficient inversely proportional to the time of decay of an antibody. The third term, $\eta\gamma FV$, describes the decrease in the number of antibodies due to binding with antigens; $\eta$ denotes the number of antibodies needed to neutralize a single antigen.

Equations (1)–(5) do not account for the weakening of the vital activity of the organism during illness, which is caused by the fall in the activity of organs responsible for providing immunologic material: leukocytes, lymphocytes, antibodies, etc., needed for the struggle with the multiplying viruses. Let us adopt the hypothesis that the productivity of such organs depends on the amount of damage to the target organ. To this end, we consider an equation for the relative characteristic of damage to the target organ. Let $M$ be the characteristic of a normal organ (mass or volume), and let $M_0$ be the corresponding characteristic of a normal part of the damaged organ. Then $m = 1 - (M/M_0)$ designates the relative characteristic of damage to the target organ. For the intact organ m is zero, and for the completely damaged organ $m$ is one. For this characteristic, we consider the conservation equation

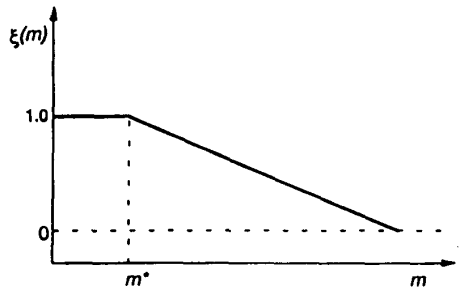


Fig. 1. Decrease of antibody production for severely damaged organs. $m$ is relative damage to organ; $m^*$ is its critical value.

$$\frac{dm}{dt} = \sigma V - \mu_m + \sigma_f F \tag{7}$$

where $m(t^0) = 0$, and the first and last terms on the right represent the degree of damage to the organ from the germs and the antibodies, respectively. The latter is caused by antibody's nonspecific attack on organ tissue. $\sigma$ and $\sigma_f$ are special constants for each particular disease. A decrease, in this characteristic, is due to the recuperative capacity of the organism. This term depends on $m$ with a proportionality coefficient $\mu_m$, characterizing the inverse of the recuperation period of the organ by $e$ times (i.e., the organ-damage time constant). It is clear that for severely damaged vital organs, the productivity of antibody production drops. This drop can be fatal for the organism. In many cases, fatality is caused exactly by this factor. In our model, the damage factor of vital organs can be accounted by product $\alpha\xi(m)$. A typical graph for the function $\xi(m)$ is presented in Fig. 1, where $\xi(m)$ on the interval $0 \leq m \leq m^*$ is equal to one. This means that the efficiency of the immunologic organs in this interval does not depend on the severity of the illness. But for $m^* \leq m \leq 1$, their productivity sharply falls, which corresponds to the linear segment of the curve in this interval. The slope of this segment of the curve as well as the quantity $m^*$ will be different for different diseases. The qualitative nature of this damage factor agrees with observed patient response in a crude sense.

We bear in mind that, in our model, we have a joint population of immunocompetent and antibody-producing cells $C(t)$. In the absence of viruses in the organism, $C(t) = C^* > 0$; i.e., $C^*$ is, in fact, the normal level of immunocompetent

cells in a normal organism. If such cells are absent, i.e., $C^* = 0$, the organism is tolerant to a given antigen. However, it may turn out that the organism has no receptor specific for a given antigen, and consequently has no immunocompetent cells to oppose it. In such cases, it still is possible that the reaction involves immunocompetent cells with specifically similar receptors capable of awakening some immune response to this antigen. We assume that the organism has a nonzero level of cells $C^*$ with their own receptors of population $F^*$ capable of causing immune reaction. We shall identify this case with the one mentioned above. More refined trigger mechanisms of immune reaction can be traced only on more complex mathematical models.

So, according to the model, the disease process is described as follows. At the moment of infection $t^0 = 0$, a small population of germs $V^0$ penetrate into the body and begin to multiply and injure cells of the target organ. Some portion of the germs bind with the receptors of the immunocompetent cells (with antibodies), and this leads to immune system stimulation resulting in the formation of a large population of plasma cells during the period of time $\tau$. These plasma cells begin to produce antibodies which neutralize the germ population. An outcome of the disease is determined by the outcome of this competition. If the germs can damage the organ severely during the formation of the immune response, the general condition of the organism deteriorates and, as a result, the immune response becomes less efficient. The antibody production declines, and so does the probability of recovery.

Since germs are composed of competing species, $V$ from one species actually destroys that of another and does indeed improve the organ's health state. Such cross-linking of germ species is neglected here. Also, it is assumed that the effect of antibody damage is included in that of the virus (i.e., $\sigma_f = 0$).

The following conclusions, which are mathematically and biologically significant, have been rigorously proven from the above assumptions [6], [22].

1) For all $t \geq 0$, there exists the unique non-negative solution of (3)–(5) and (7) with initial conditions (6).
2) The stationary solution, *healthy state*

$$V_1 = 0, F_1 = \rho C^*/\mu_f = F^*, C_1 = C, m_1 = 0, \quad (8)$$

is asymptotically stable if $\beta < \gamma F^*$; in this case, at $F^0 = F^*, C^0 = C^*, m^0 = m^*$ if the inequality (infected zone of attraction to healthy state)

$$0 < V^0 < V^* = \frac{\mu) f(\gamma F^* - \beta)}{\beta \eta \gamma}$$

is valid, then $V(t) < V^0 e^{-at}$ where $a = \gamma p C^*/(\mu_f - \eta\gamma V^0) - \beta > 0$.

This estimate $V^*$ has been called the immunological barrier against given types of germs. If germs cannot get over it ($V^0 < V^*$), no disease occurs since the germ population is removed from the body in the course of time. The model (6) has another stationary solution which may be interpreted as a chronic form of disease.

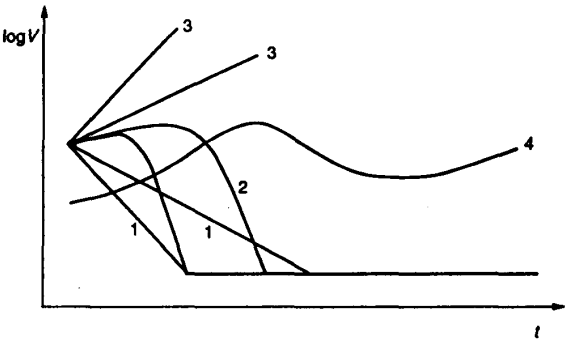


Fig. 2. The possible form of disease: 1-subclinical; 2-acute; 3-lethal; 4-chronic. $V$ is germ concentration.

3) The stationary solution (chronic disease state)

$$V_2 = \frac{\mu_c(\mu_f \beta - \gamma p C^*)}{\beta(\alpha p - \mu_c \eta\gamma)} > 0, \quad F_2 = \beta/\gamma,$$
$$C_2 = \frac{\alpha\mu_f\beta - \eta\mu_c\gamma^2 C^*}{\gamma(\alpha p - \mu_c\eta\gamma)}, \quad m_2 = \sigma V_2/\mu_m < m^*, \quad (9)$$

is asymptotically stable if

$$\mu_c \tau \leq 1, \qquad 0 < \frac{f-d}{a-g\tau} < b - g - f\tau, \qquad (10)$$

where

$$\alpha = \mu_c + \mu_f + \eta\gamma V_2,$$
$$b = \mu_c(\eta\gamma V_2 + \mu_f) - \eta\gamma\beta V_2,$$
$$d = \mu_c \eta\gamma\beta V_2,$$
$$g = \alpha\rho V_2,$$
$$f = \beta\alpha\rho V_2.$$

In the case $\alpha \to \infty$, the second condition from (10) can be reduced to the inequality

$$0 < \beta - \gamma F^* < \left[\tau + \frac{1}{\mu_c + \mu_f}\right]^{-1}. \qquad (11)$$

It is proven that, even in the case of a highly sensitive immune response $\alpha \to \infty$, a stable chronic form of disease is possible. Therefore, from the mathematical model, we can establish the conditions for the development of the different forms of disease course. This can be useful for disease treatment.

### *B. Disease Simulations*

The infection of the healthy body by a small dose of germs is simulated with appropriate initial conditions: $V(0) = V^0 > 0, F(0) = F^*, C(0) = C^*, m(0) = 0$. This simulation shows that there exist four qualitatively different types of solutions, which were interpreted as disease forms: subclinical, acute with recovery, chronic, and lethal outcome. They are diagrammed in Fig. 2.

A subclinical form of disease develops under the conditions of Statement 2 above; it is characterized by a stable removal

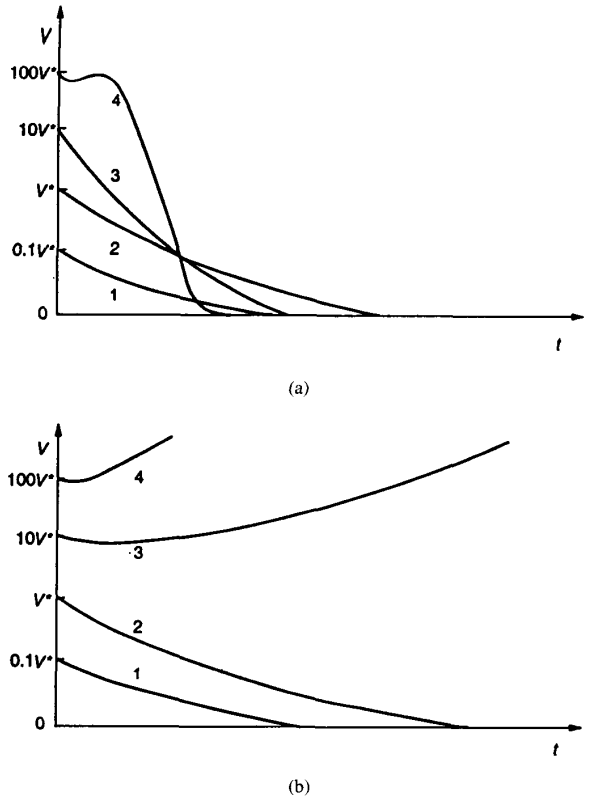


Fig. 3. Subclinical form of disease: (a) normal immune system $\alpha\rho > \mu_c\eta\gamma$; (b) immunodeficiency $\alpha\rho < \mu_c\eta\gamma$. $V^*$ is an immunological barrier for germ concentration.

of the germs from the body (curve 1). The characteristic of the acute form with recovery is a particular dynamic behavior of germs: first, a fast proliferation of germs or viruses during several days and then, a drastic contraction, practically to zero, due to a powerful immune response (curve 2). The chronic form of the disease is characterized by a persistent presence of germs in the body (curve 4); it arises especially under the conditions of Statement 3 above. The unlimited growth of germs in the body and the entire damage of the organ are characteristic of lethal outcome (curves 3).

We now go on to a more detailed description of numerical experiments simulated for a particular form of the disease and also discuss their biological implications.

*Subclinical Form of Disease:* The simulation results for the case when $\beta < \gamma F^*$ are represented in Fig. 3. Here, two situations are distinguished:

a) $\alpha\rho > \mu_c\eta\gamma$ that corresponds to normal functioning of immune response, and

b) $\alpha\rho < \mu_c\eta\gamma$ that corresponds to immunodeficiency state.

For infection doses smaller than the immunological barrier ($V^0 \leq V^*$), the character of germ or virus removal from the body depends neither on the infection nor the power of the immune response (Fig. 3, curves 1 and 2). This elimination of germs is possible due to the constant level of antibodies $F^*$. This situation seems to correspond to daily contact of the body with small doses of antigen which penetrate into the body by respiration or with food.

With an essentially higher dose of infection relative to the immunological barrier, the power of the immune response begins to play a major role. The efficient (normal) immune response is able to prevent an infectious disease (Fig. 3(a), curve 4). With a weak immune response, the germs penetrate through the immunological barrier ($V^0 > V^*$), which leads to death (Fig. 3(b), curve 3). Thus, the immune resistance of persons with normal immune system ($\alpha\rho > \mu_c\eta\gamma$) is much higher than in immunodeficient patients, who, naturally, are more susceptible to infection.

The case, $\beta < \gamma F^*$, can be interpreted as a vaccination of a healthy body by weakened living antigens. The vaccination is meant to provoke a powerful immune response with the purpose of an essential accumulation of memory cells. According to our model, it is equivalent to an increasing level of immunocompetent cells $C^*$ constantly present in the healthy body (as memory cells), and thereby to a rising immunological barrier $V^*$. The effect of vaccination is determined by the injected doses of antigen, as well as by the condition of the immune system. The simulation shows that injections of doses smaller than the immunological barrier have only negligible effect because, in this case, the antigen is removed from the body stimulating no immune response at all, or only a weak response. In neither situation is there an essential accumulation of memory cells. On the other hand, injections of larger doses ($V^0 > V^*$) into the organism with normal immune system ($\alpha\rho > \mu_c\eta\gamma$) stimulate a strong immune response and lead to desirable results in treatment, whereas the vaccination of immunodeficient patients by high doses can cause a serious form of the disease (Fig. 3(b), curve 3).

*Acute Form of Disease:* Simulation results of an acute form of disease with recovery in the case of a normal immune system ($\alpha\rho < \mu_c\eta\gamma$) are presented in Fig. 4(a). This form of disease occurs when $\beta > \gamma F^*$, and hence there is no immunological barrier to the stimulant of disease. As we noted earlier, the characteristics of this course of illness are: rapid (during several days) growth of germs and viruses in the body until their number substantially exceeds the value of the infective dose, and rapid elimination of antigens from the body. The reason is twofold: 1) a high rate of germ multiplication leading to fast accumulation of them in the body, and 2) the effective immune response caused by the accumulated antigenic mass.

Fig. 4(a) illustrates the course of an acute form of disease depending on the rate of germ multiplication $\beta$ and infective dose $V^0$. The higher the multiplication rate at a given infective dose, the higher the maximum quantity of germs, the faster they reach it and the faster the process terminates. This is explained by the fact that high infective dose or high rate of multiplication enable the germs to reach the amounts which effectively stimulate the immune system in a short period of time, and as a result, the powerful immune system becomes capable of resisting the infection.

It appears that under other circumstances, the maximum level of germs depends very little (practically independent) on infective dose (see Fig. 4(b)). We obtained the estimate of

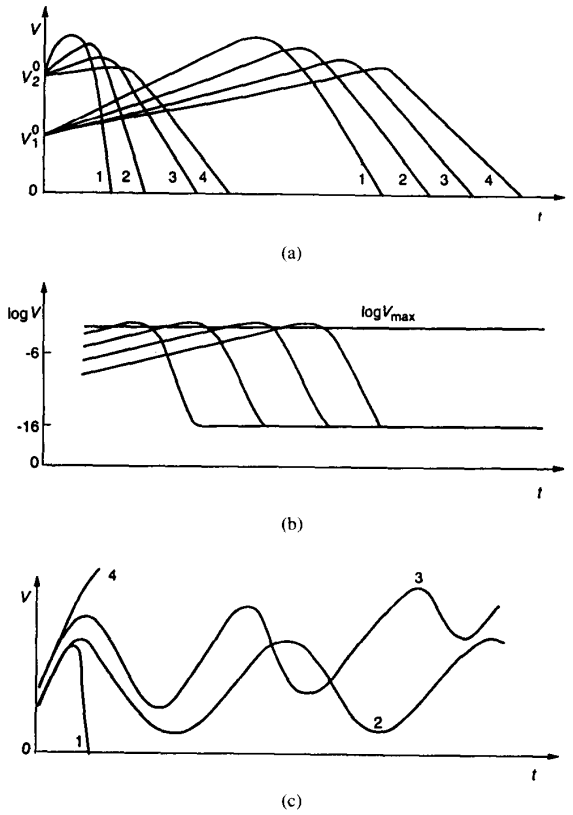


Fig. 4. Acute form of disease: (a) dependent on $V^0$ and reproduction rate $\beta$; (b) independent of maximal infection dose; (c) dependent on the organ damage $\sigma$. $V^0$ is infective germ dose with levels $V_1^0$ and $V_2^0$.

this maximum $V_{\max}$, which is independent of $V^0$

$$V_{\max} = \frac{(\beta - \gamma F^*)(\mu_f + \alpha)}{\gamma(\rho g - \eta\gamma f)},$$

where

$$f \in (F^*, \beta/\gamma), \alpha = \beta - \gamma f, \quad g = \alpha f e^{-\alpha\tau}(\mu_c + \alpha)^{-1}.$$

In Fig. 4(b), we choose $f = (F^* + \beta/\gamma)/2$. Hence, in the case of acute form of disease, the value of the "peak of the disease" is independent of infective dose but determined by the immune characteristics of the organism, with respect to germs of a given type (the set of model parameters). The infective dose influences the moment of reaching the peak: the smaller the $V^0$, the later the peak is reached.

Fig. 4(c) demonstrates possible changes in the acute form with increasing coefficient of organ damage $\sigma$. As a result of the organ damage, Fig. 4 demonstrates that the acute form can turn into a chronic one (curve 2), into a chronic form with unpredictable outcome (curve 3), or chronic form with lethal outcome (curve 4). The possibility of such transition is due to the fact that, because of damage, the general condition of the body deteriorates, which makes the efficiency of the immune response decrease and the antibody production fall. Therefore, to prevent transition of the acute form into the more serious

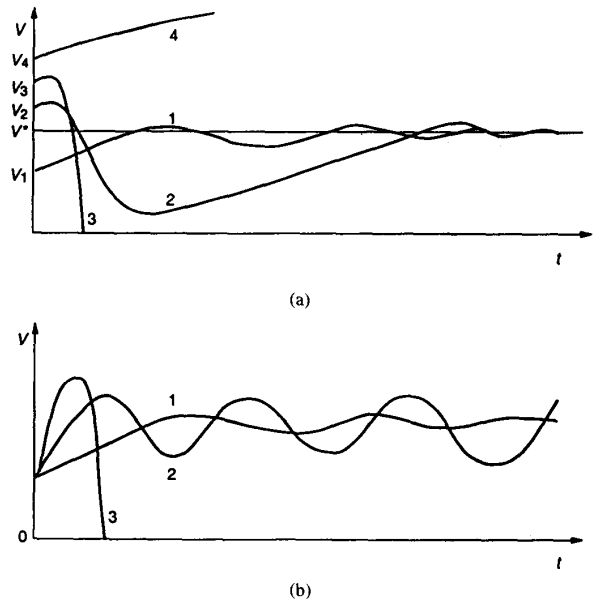


Fig. 5. Chronic form of disease: (a) dependence on infection dose $V^0$; (b) dependence on virus reproduction rate $\beta$:$\beta_1 < \beta_2 < \beta_3$. $V_i, i = 1, \ldots, 4$, represent different infection doses.

form, the treatment is to be aimed at either lowering the germ pathogenicity or to protecting the organ against damage.

*Chronic Form of Disease:* We have already noted the possibility of the occurrence of chronic form from acute infection, with serious organ damage (Fig. 4(c), curve 2). Now, we deal with other kinds of stable chronic forms occurring especially under the conditions of Statement 3 above. Characteristic of such typical chronic form is the flaccid dynamics of germs relative to the acute form. In this case, the passive germ dynamics lead in time to equilibrium between amounts of newborn germs and those neutralized by disease stimulants. Their concentration tends to a stationary level $V_2$. With an increase of infective dose above $V_2$, the dynamics of disease stimulants are more pronounced and the transition into the acute form with recovery becomes possible (Fig. 5(a), curve 3). The efficiency of the immune response can be enhanced by injecting higher infective doses. An analysis of the dependence between the course of the chronic form of disease and the infective dose of weakly pathogenic germs has brought us to the following conclusions: 1) It is possible to treat a chronic form of disease by exacerbation (essentially increasing the number of germs in the body). 2) It is not reasonable for the immune system to react to small doses of germs in order to prevent a chronic form of disease. A study of dependence of the course of chronic form on a germ multiplication rate (see Fig. 5(b)) proves the existence of a stable periodic solution (curve 2) and establishes that the treatment of the acute form using drugs, to decrease the multiplication rate, promotes chronicity of the disease process.

*The Origin of Chronic Forms and Their Possible Treatment:* A hypothesis on the immunological origin of forms has been proposed by Marchuk and Belykh [19]: *chronic forms of*

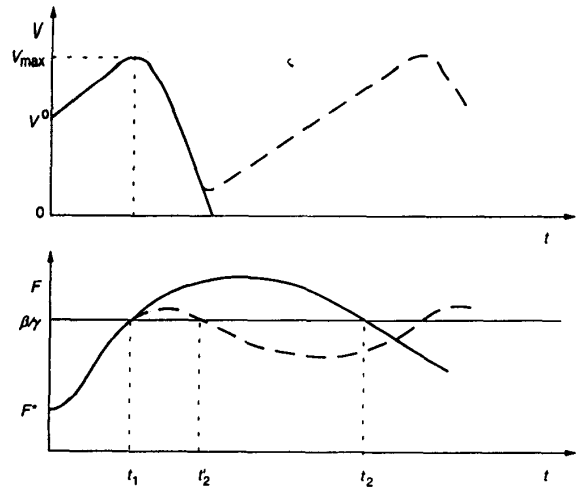


Fig. 6. The rise of chronic form from acute. Dynamics of infectious process are depicted by a solid line. Biostimulators have been injected during 23 days at an interval $\Delta t = 1$ day. $V$ is germ concentration and $F$ is antibody concentration.

*disease are due to weak stimulation of the immune response.* This hypothesis is based on the following premises. In the framework of the model, the disease outcome (chronization or recovery) depends on the width of an interval $(t_1, t_2)$ at which the concentration of viruses is decreasing, and consequently $dV/dt < 0$. If this interval is sufficiently wide (see Fig. 6, solid line), then the number of germs decreases until the values close to zero are taken as the recovery. Otherwise, i.e., in a sufficiently narrow interval $(t_1, t_2)$, the amount of germs fails to approach zero, but for $t = t_2$ it reaches the minimum and begins to grow again for $t > t_2$. Then, the process is repeated. This is the way the chronic form develops. Since $dV/dt < 0$ means $F(t) > \beta/\gamma$, the width of the interval $(t_1, t_2)$ is determined by how long the latter inequality holds. Apparently, the more antibodies produced and the higher their maximum, the wider the interval $(t_1, t_2)$. If we allow for the fact that antibody production is essentially determined by the efficiency of immune system stimulation, then the competence of the suggested hypothesis is obvious.

This hypothesis explains the simulation results obtained, namely the transition of the acute form to the chronic one with serious organ damage, and transition of chronic form to acute with high infective dose. In the first case, organ damage reduces the efficiency of immune system stimulation that leads to a narrower interval $(t_1, t_2)$, and thus to a chronic process. In the second case, there is an inverse effect: high dose of infection enhances the stimulation, thus leading to a wider interval $(t_1, t_2)$.

It becomes obvious that theoretically the treatment of chronic form should promote a widening of the interval $(t_1, t_2)$. In practice, the stimulation of antibody production (SAP) and disease exacerbation (biostimulation) can be demonstrated.

The action of SAP factor is demonstrated by an approximately threefold increase in the quantity of antibodies when the SAP factor has been injected at the peak of immune response. This apparently makes the interval $(t_1, t_2)$ wider. The simulation of SAP-factor action shows its possible successful application to treating chronic forms of disease in Fig. 6. In the case of exacerbation, so-called biostimulation theory was studied for (6) with several additional state equations. The basic notion of this theory is the following. In the body subject to a stable chronic form of disease, a new nonpathogenic, nonmultiplying antigen (biostimulator) is injected, beginning from some instant of time. The injections are repeated over some discrete interval of time, and the dose of injection grows with time. This leads to the situation that, due to the concurrence of macrophages between the two antigens (biostimulators and disease stimulants), the immune response to germs is blocked. So, the immune system "forgets" the disease stimulants and this enables the germs to increase their antigenic mass. Some time later, the biostimulator injections are terminated and then removed quickly from the body. The organism is again face-to-face with the disease stimulants. But the situation has essentially changed. During the interval when biostimulators were in the body, the amount of germs in the body reached the values which stimulate effectively the immune system. As a result, a powerful immune response is formed and this leads to elimination of germs from the body and recovery follows.

The above basic results are presented to explain the immune response to infectious disease in a qualitative rather than precise quantitative form. However, typical responses here are normalized to a germ level of $10^{16}$, $\tau = 0.5$ day, and for a subclinical form of disease $\beta = 8$, $\alpha = 10^4$, $\mu_f = 0.17$, $\mu_c = 0.5$, and $\mu_m = 8$ with more detailed parameter values given in [6]. The next section provides more precise model parameter estimates based on a particular influenza model.

## III. An Experimental Influenza Investigation

The increasing study of realistic mathematical models in medicine is a reflection of their use in helping to understand a disease and practical health service. One of the main problems in this area is drug action. It is very important to have clear ideas about strategy and tactics of drug use. Here, we consider a mathematical model for the analysis of drug action on influenza. A short discussion about the mechanisms of antiviral effects of chemical preparations and its prophylactic or therapeutic effects are presented.

The first step in this problem is the construction of a mathematical model for a subsequent investigation of the possibility of a directed action in the viral process (using an influenza virus as an example). The model consists of a system of ordinary differential equations. Its state variables describe the dynamics of the virus and of the cell populations of an animal, while the coefficients are interpreted as parameters of the corresponding interactions. Therefore, by determining the coefficients of the model from the results of experiments using chemical preparations possessing antiviral action, it appears possible to judge how a drug affects the parameters of the process under study.

Of course, the construction of a mathematical model represents an idealization of the real scheme of the interaction of a virus with the host organism. However, the following main

characteristics of the system must be considered: the number of viruses in the infected organism, the influence of the interferon system on the process and the cellular and humoral aspects of immunity [23], [24].

All interactions between cellular and humoral components are considered as homogeneous reactions. Such factors as interferon $(\alpha, \beta, \gamma)$, and immunoglobulin $(M, G, A)$, specific lymphocyte-effectors are represented in a generalized sense. The variable "interferon" is used as a factor under action of which a cell acquires an insensitivity to viral infection. "Antibodies" supply the specific neutralization of free viruses. "Specific lymphocyte-effectors" are understood to be the population of lymphocyte-effectors (again, without division into $T$ and $B$ and subpopulations) with which the processes of antibody production and elimination of cells infected by viruses are connected. Let $C_v(t)$ be the concentration of cells infected by viruses of particle concentration $V(t)\,t$ days after infection; $F(t)$ is the concentration of antibodies; $C(t)$ is the concentration of plasma cells (including, in general, $B, T$ and killer equivalents) and $L_p(t)$ is concentration of lymphocytes having corresponding specificity towards the viral antigen proliferating and differentiating under antigenic stimulus.

Suppose that a common number of sensitive cells in the lungs is approximately constant and $C_I \approx \alpha C_v$, where $C_I$ is the concentration of cells that have become insensitive to infection under the action of interferon, and $\alpha \approx 0.1$ is typical of an acute, sublethal lung infection. The conservation equations for $C_v$ and $V$ have a form

$$\begin{aligned} \frac{d}{dt}C_v &= \underset{\text{I}}{k_{c_v} V(C_0 - C_I - C_v)} - \underset{\text{II}}{\gamma_{C_v L_e} C_v l_e} - \underset{\text{III}}{\mu_{C_v} C_v} \\ \frac{d}{dt}V &= \underset{\text{IV}}{k_v C_v} - \underset{\text{V}}{\gamma_{vF} V F} - \underset{\text{VI}}{\mu_v V} \end{aligned} \tag{12}$$

where (I) corresponds to the appearance of new infected cells as the result of the interaction of the infected particles $V$ and intact susceptible cells $C_0 - C_I - C_V, C_0$ is a value characterizing all cells potentially sensitive to the virus (e.g., pulmonary epithelium); (II) is the decrease in the $C_v$ due to specific effector-lymphocytes of concentation $L_e$ (integral effect); (III) corresponds to the destruction of $C_v$ cells due to the effect of the breakdown by the virus of the cell in which it is being synthesized, a "background" cytotoxic effect not connected with specific effector lymphocytes, etc.; (IV) describes the synthesis of new viral particles solely from infected cells; (V) represents the neutralization of extracellular infective particles by immunoglobulins; and (VI) represents the process of elimination of viral particles from the intracellular space not caused by specific humoral factors; this includes the absorption and penetration of the virus into the cells, the loss of infectiveness by the virus under the action of various types of "background" factors (temperature, inhibitors, acidity, etc.). It should be noted that infective virus is, in fact, an effective stimulator of the immune system.

In processes described above, one can clearly distinguish both space and time hierarchy. Viral particle size of an animal cell is about $10^{-5}$ m [25] and of immunoglobulin about 30–40 Å. One viral particle is capable of infecting a cell [26] after which it can produce about $10^3$ viral particles during the generation cycle of about eight hours (after this cell dies) [27]. The time of absorption and penetration of virus into the cell is about 10–20 min. The free virus disappears very fast.

The molecular reaction in study (binding of virus by immunoglobulin, absorption and penetration of viruses into new cells) has the characteristic time of the order of several minutes, while the complex of cellular reactions leading to the destruction of the infected cells is characterized by longer times. So, neglecting the fast events with small characteristic times of the order of ten minutes to one hour and using the chemical equilibrium law, we can write the approximation

$$V = \frac{k_v C_v}{\mu_v + \gamma_{vF} F}. \tag{13}$$

After this, (12) acquires the form

$$\frac{d}{dt}C_v = \frac{k_{C_v} k_v C_v [C_0 - (1+\nu)C_v]}{\mu_v + \gamma_{vF} F} - \gamma_{C_v L_e} C_v L_e - \mu_{c_v} C_v. \tag{14}$$

At this point, we determine $C_v(0) = C_v^0$ as an initial condition. Here, $C_v^0$ is some effective number of infected cells from which infection begins (after 1–2 h the transition processes cease and the dynamical equilibrium (14) becomes valid). For the description of the dynamics of immune system cells, we adopt the following model scheme. The resting precursor-cells (cellular phase $G_0$) specific for a given virus are activated by antigenic stimulus and transformed to proliferating cells $L_p$ which, in turn, differentiate into terminal effector cells $C$.

We distinguish these variables because there exists the hypothesis that the specific lymphocyte system plays a key role in organism recovery. A number of various mechanisms of virus neutralization and infected cell destruction are either directly determined by the lymphocyte effectors (specific cytotoxins, immunoglobulins) or controlled and induced by them ($NK$ cells, macrophages, $K$ cells) [28]. In the model, variables $L_p$ and $C$ are the main ones that reflect in the whole the defensive mechanism. We write the following conservation relation for $L_p$, $C$

$$\begin{aligned} \frac{d}{dt}L_p &= L_{p_0}\delta(t - t^*) + U(C_v)(\alpha_{L_p} L_p - \beta_{L_p} L_p) \\ \frac{d}{dt}L_e &= U(C_v)\beta_{L_p} L_p - \mu_{L_e} L_e \\ U(C_v) &= [1 - \exp(C_v/q)]. \end{aligned} \tag{15}$$

In explanation of these equations, $L_{\rho_0}\delta(t - t^*)$ corresponds to resting precursors' activation; $L_p$ is their common number, and $t^*$ is the activation time. Here, $\delta(t)$ is the unit delta-function. It is supposed that proliferation and differentiation processes have a threshold character to account for neglected fast dynamics. They have the maximal rate at $C_v \gg q$ but cease when $C_v \ll q$.

Expression $-\mu_{L_e} L_e$ in (15) reflects the processes of activity loss and/or natural death of effectors cells. The corresponding term in the first expression of (15) is absent since variable $L_p$ must correspond to forming a clone of memory cells the lifetime of which is 1–2 years. This is a very long time interval in comparison with one needed for the acute process

development. For antibodies $F$, similar to (6)

$$\frac{d}{dt}F = \rho L_e - \gamma_{FV} FV - \mu_F F.$$

But considering (12)

$$\frac{d}{dt}F = \rho L_e - \frac{\gamma_{Fv} k_v F C_v}{\mu_v + \gamma_{vF} F} - \mu_F F, \tag{16}$$

it is seen that approximately

$$V = \frac{k_v}{\mu_v} C_v. \tag{17}$$

Here, dependence on $F$ is presented in the right-hand sides of (14) and (16).

For practical convenience in using experimental data for parameter estimation, rewrite the model equations in the following form

$$\begin{aligned}
\frac{d}{dt}V &= \frac{\alpha_1 + \alpha_{10}}{1 + \alpha_9 F} V - \alpha_2 V^2 - \alpha_3 V L_e - \alpha_{10} V \\
\frac{d}{dt}L_p &= L_{p^0} \delta(t - t^*) + \alpha_{11} L_p [1 - \exp(-\alpha_{12} V)] \\
\frac{d}{dt}L_e &= \alpha_4 L_p [1 - \exp(-\alpha_{12} V] - \alpha_5 L_e \\
\frac{d}{dt}F &= \alpha_6 L_e - \frac{\alpha_7 V F}{1 + \alpha_9 F} - \alpha_8 F \\
V(0) &= V^0, \qquad L_p(0) = L_e(0) = 0, \qquad F(0) = 0.
\end{aligned} \tag{18}$$

The acute, uncomplicated viral infection, which is studied here, clearly demonstates immune defense. Simulation shows the structure of the model solutions corresponding to the process in study is such that the interferon system ($\alpha_2 V^2$) and generalized cytotoxic action of effectors are the mechanisms that supply saturation in virus dynamics (during 4–5 days), which is followed by a sharp decrease in the number of virus infections in the lungs (5–8 days). The influence of antibody $F$ on the solution is practically absent. It begins to manifest itself later (8–14 days) when $F$ reaches large values. Until this moment, the number of viruses is quite small in comparison with the maximum. So the term $\alpha_2 V^2$ is negligibly small for this interval. It is likely that such structure of solution reflects the real picture of the defense mechanism over time. The model derived matches the experimental data quite well, as shown in Fig. 7, and next it is used to study treatment. Here, F1 mice were infected intranasally with influenza virus A/PR8/34 at the Institute of Experimental Medicine, St. Petersburg, Russia.

In Fig. 7, the model (15) solutions are shown by solid lines. The solution corresponds to coefficients calculated from data for an animal group that had not been given the drug. The observed results are shown by pluses. In Fig. 8(a) and (b), the analogous results are presented. These were derived from experimental data with animals that were treated by ionol and $\epsilon$-aminocaproic acid, respectively. From these data, conventional maximum likelihood estimates of coefficients are computed and used for the model simulation as given in Table I. The application of a verification criterion of statistical hypothesis shows that changes in the coefficient vector under treatment action are significant with high levels of statistical validity.

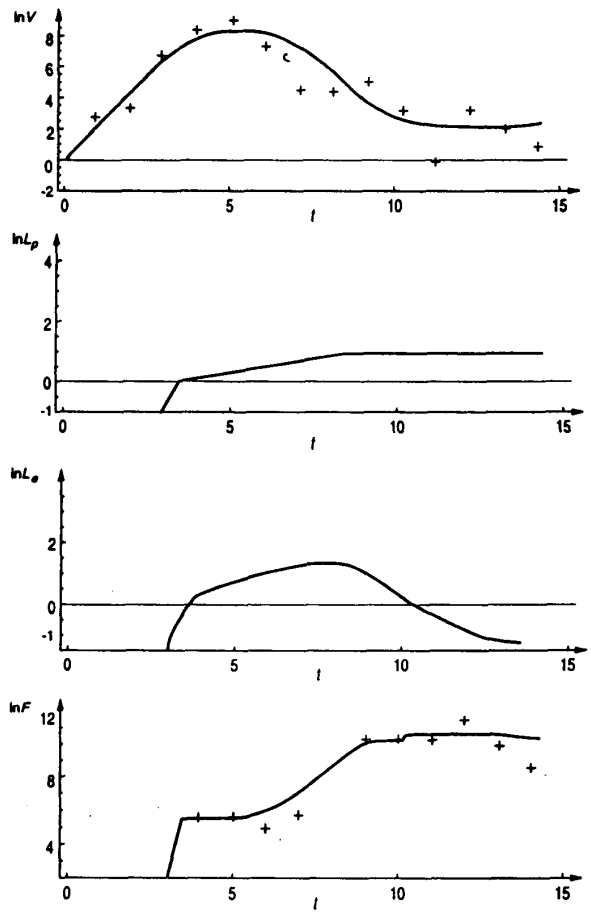


Fig. 7. Control animals group (sublethal influenza without treatment). Solution of model (solid line), + experimental data, virus-log of 50% embryonal infections doses for animal lungs, Ab-log (IgM + IgG) in serum. $L_p$ is lymphocyte concentrations and $L_e$ is effector cell concentration.

The conclusions below are, to some extent, hypotheses and serve for illustrations of the methodology for such solutions.

It is interesting that for the third group (with $\epsilon$-aminocaproic acid), $\alpha_6$, which characterizes the rate of antibody production, is one order smaller in comparison with the control group. For the same group, we derived $\alpha_8 = \alpha_9 = 0$. We can conclude from here that the influence of immunoglobulin on the studied process is weak in comparison with other defense mechanisms. In the case of the third group, $\alpha_2 \neq 0$, while in the cases of the second and the first groups $\alpha_2 = 0$. This can be interpreted as the fact that, in the case of the first and second groups, the maximum of the virus curve and its decrease is mainly explained by the cytotoxic mechanism mediated by lymphocyte-effectors. In the third group, added to this is the saturating mechanism which is due to interferon action. Except for this, the initial value $V_0$ is decreased for those groups which were treated. In the model, the value $V_0$ is the number of viruses which reach the lung cells after intranasal infection. This fact allows us to formulate a hypothesis about the prophylactic effect of these drugs.

As we can see from Table I, in the three groups of animals, the coefficients ( $\alpha_1, \alpha_3, \alpha_5$) are practically unchanged. It can

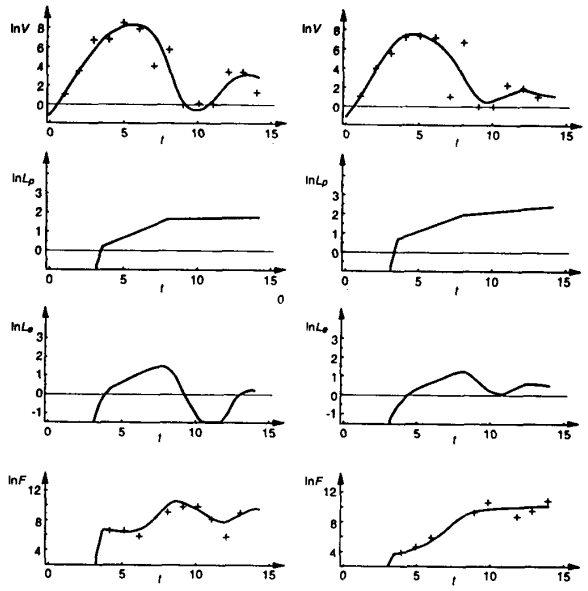


Fig. 8. (a) The group of sublethally infected animals which were treated by ionol. (b) The group of sublethally infected animals which were treated by $\varepsilon$-aminocaproic acid. Denotations are the same as Fig. 7.

TABLE I
MAXIMUM-LIKELIHOOD ESTIMATES OF COEFFICIENTS

| Coefficients | Fig. 7. | Fig. 8a | Fig. 8b |
|---|---|---|---|
| $\alpha_1$ | 2.0 | 2.328 | 2.581 |
| $\alpha_2$ | 0.0 | 0.0 | $4.316\times10^{-4}$ |
| $\alpha_3$ | 0.958 | 0.972 | 0.950 |
| $\alpha_4^*$ | 1.8 | 1.8 | 1.8 |
| $\alpha_5$ | 0.891 | 1.51 | 1.0 |
| $\alpha_6$ | $1.530\times10^{4}$ | $2.178\times10^{4}$ | $1.411\times10^{3}$ |
| $\alpha_7^*$ | $2.190\times10^{-2}$ | $2.190\times10^{-2}$ | $2.190\times10^{-2}$ |
| $\alpha_8$ | 0.0 | 1.834 | 0.0 |
| $\alpha_9$ | $4.730\times10^{-6}$ | $2.226\times10^{-5}$ | 0.0 |
| $\alpha_{10}^*$ | 7.0 | 7.0 | 7.0 |
| $\alpha_{11}$ | 0.201 | 0.331 | 0.294 |
| $\alpha_{12}$ | $3.870\times10^{-3}$ | $1.115\times10^{-2}$ | $7.664\times10^{-2}$ |
| $t^*$ | 3 days | 3 days | 3 days |
| $\ln V^0$ | $5.037\times10^{-2}$ | -1.139 | -1.394 |
| $L_{p0}$ | 1 | 1 | 1 |

be seen that such process parameters as generalized cytotoxic effect of effectors, rate of virus multiplication, the rate of removal (and inactivation) of cells-effectors were not changed. For animal groups treated by preparations, $\alpha_{12}$ is several times smaller than in the control group. This might reflect the increase of threshold for the virus population beginning from which the proliferation and differentiation process possess the maximal rate. The studies show that these changes are very essential. Except for this, the coefficient $\alpha_{11}$ is 1.5 times increased for more intensive processes of proliferation and of immune memory.

The results suggest the effectiveness of the application of systems theory to treat acute infectious process. Beyond this, the mathematical model enables us to obtain quantitative characteristics of the internal process using *in vivo* data. A larger experimental data base should enable us to create and test a new scenario of infectious disease development and treatment.

## IV. Future Directions and Conclusion

The results presented here suggest that system theory may play an important role in understanding immunology, disease, and its treatment. While the immune system is an exceedingly complex controller, it does appear that appropriate stimulation (i.e., immunotherapy) can play a crucial role in effective disease treatment. Here, this is demonstrated by treatment of influenza which was analyzed by computer simulation of carefully derived mathematical models based on first principles of biochemistry. In the case of influenza, the simulated immune response compares favorably with *in vivo* experimental data. Medication is shown actually to manipulate system parameters which results in effective multiplicative (state or output multiplied) control. Similar control arises quite naturally in the immune system when operating as required, and indeed the tumor control problem demonstrates this nicely. For example, interleukin 2 and interferon are generated quite naturally to stimulate an appropriate immune response to control tumor size in some cases [29]. A promising approach in the very early stage at the National Cancer Institute is to affect the basic cell cycle kinetics by altering the cellular DNA to increase interleukin 2 production if it is necessary [30]. Undoubtedly, the interface of genetics and control theory holds great promise for future interdisciplinary research.

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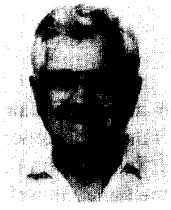

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