EXPERIMENTAL MODEL AND MEASUREMENT STUDIES OF RISK ASSESSMENT IN HYGIENE AND EPIDEMIOLOGY

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MATHEMATICAL MODEL OF IMMUNE AND NEUROENDOCRINE SYSTEMS FUNCTIONING WITH REGARD TO EVOLUTION OF ORGAN SYNTHETIC FUNCTION VIOLATIONS

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Currently, the concept of a "three-pronged" regulatory "metasystem", which includes the immune and neuroendocrine regulation circuits, is well recognized. We are also well aware of the changes in each of the regulatory systems in response to man-made chemical factors. The paper presents the mathematical model of functioning of the immune and neuroendocrine systems on the example of the interaction of these systems in response to the introduction of bacterial pathogen. In addition, the model describes the changes in these systems in terms of exposure to chemical factors, taking into account the degree of producing body functional impairment, for example, disruption of the bone marrow. The described mathematical model of regulatory systems is the "meso" level submodel and it is developed within a multi-level model of the functional disorders' evolution, in which the individual organism is assumed to consist of a finite number of interconnected organs and systems.

Key words: *mathematical model, immune system, neuroendocrine system, chemical factors, bacterial invasion.*

Introduction. Regulation processes maintain balance in the functioning of organs, tissues, and cells. Today there is a generally acknowledged concept of a regulatory "metasystem" that includes the immune and neuro-endocrine regulatory contours [1]. Regulatory systems (immune and neuro-endocrine) have a regulatory effect on each other [2]. One of the main functions of the immune system is to fight foreign genetic material including microorganisms and, specifically, bacteria.

From literature, it is well known that starting from a certain age, the "natural ageing" processes begin; they proceed unevenly for different organs and tissues but are generally accompanied by accumulated pathophysiological disorders and fluctuating normal findings which results in poor performance of the system as a whole and the systems under study in particular [3]. Technology-related chemical factors accelerate the accumulation of those disorders and impact the effectiveness of the regulatory organs and systems [4].

These processes can be indicated as "evolution of the functional disorders of organs and systems" and have to be taken into account when studying the interaction between the immune and neuro-endocrine systems.

Purpose of Research – a mathematical description of the regulatory mechanism based on the interaction of the elements of the immune and neuro-endocrine system in response to bacterial stress with the account for the evolution of the functional disorders for the purposes of predicting the negative impact of the chemical agents entering the system from the external environment.

Materials and Methods. The functional block diagram of the model consists of several interconnected elements of the neuro-endocrine and immune systems of a human body (Figure 1) involved in bacterial invasion. Each of them can be

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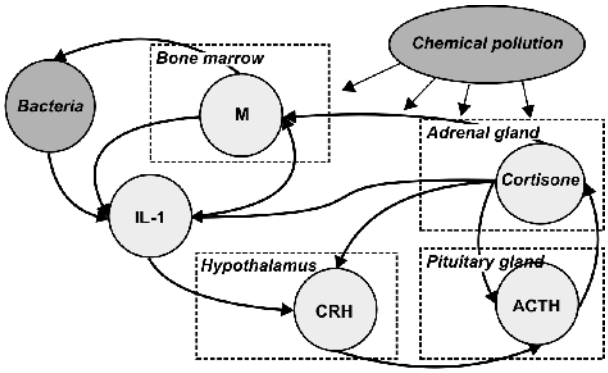

Figure 1. interaction between the elements of the immune and neuro-endocrine system (the boxes indicate the name of the producers)

impacted by chemical compounds entering the system from the external environment.

The mechanism that control bacterial invasion is based on the ability of monocytes and, to a greater extent, their mature macrophage forms to phagocytose on foreign material such as pathogenic bacteria. Since it is difficult to make a quantitative estimation of the amount of macrophages in the system, its content is then estimated by the level of monocytes in blood produced by bone marrow. The uptake of the infectious agents by the "monocyte-macrophage" (M) complex is followed by the synthesis and release of a number of cytokines including pro-inflammatory interleukine (IL-1) [5]. Conversely, an elevated level of IL-1 in blood, among other regulatory effects, stimulates the monocytes towards the inflammatory tissue, and promotes through specific the production of corticotropin-releasing hormone (CRH) which affects adenohypophysis and provokes secretion of adrenocorticotropic hormone (ACTH). Once in the blood, ACTH stimulates the adrenal gland to produce cortisone the higher level of which following the reverse feedback principle inhibits the secretion of ACTH and CRH, stimulates the "monocyte-macrophage" apoptosis, and blocks the production of IL-1.

The interaction between the elements of the regulatory systems is described by a set of six equations with initial data, and looks like a Cauchy problem written for the system of first-order ordinary differential equations with a retarded argument. The parameters of the model are identified from the conditions of the progress of the Streptococcus **pulmonary infections**.

To describe the age-related decrease in the functional (synthetic) activity of organs (in this case – producing cells or regulatory molecules), we used a mathematical model of the evolution of functional disorders of organs and systems caused by the environmental factors [6, 7], according to which the disorder of the synthetic ability of the j-th organ is characterized by damage D_j. $D_j \in [0;1]$. The value $D_j = 0$ indicates normal (ideal) functional condition, and $D_j = 1$ indicates that the function is completely damaged. The evolution of damage is determined by the external (in terms of the organs under study) impacts and internal disorders due to natural reasons (ageing). The impacts imply regulation of the flow of the substance that affects the condition of the organs and systems.

The set of equations that describe the evolution of damaging of the synthetic ability is presented below:

$$\frac{dD_j}{dt} = a_j D_j + \sum_{i=1}^{n} b_{ji} \left\langle \frac{p_i}{p_{ji}^N} - 1 \right\rangle,$$

where a_j – coefficient that describes the rate of damage (disorder) of the j-th organ due to natural reasons [1/year]; b_{ji} – coefficient that describes the intensity of impact of the i-th negative factor on the *j*-th organ. [1/ год]; p_i – flow of the *i*-th substance in a human body; p_{ji}^N – normal (limit) value of the flow of the i-th substance for the j-th organ; $\langle x \rangle$ – McCauley brackets: $\langle x \rangle = 0$ at $x < 0$ and $\langle x \rangle = x$ at $x \geq 0$.

The above set of equations (1) reflects the general aspect of the evolution of damage and takes into account the macro-level processes – self-destruction (natural ageing) and accumulated damages of the synthetic function as a result of abnormal flow of substances.

Results. To test the model, we set up a numerical experiment. Bone marrow was used as an example of producing organ since the monocytes-macrophages produced by this organ are the central link of all the immune responses in the described example. The solution illustrated in Figure 2 reflects the possibility of dysfunction of bone marrow due to natural ageing as well as combined impact of natural ageing and chemical factors. At the same time, the graph shows that exposure to chemical factors can significantly accelerate the accumulation of damage to the synthetic ability.

To test the adequacy of the model, we made calculations for the three scenarios which differed by the level of damage to the monocyte-production function of bone marrow associated with exposure to chemical compounds: *D*=0 (scenario 1); *D*=0.17 (scenario 2) and *D*=0,2 (scenario 3). The indicated

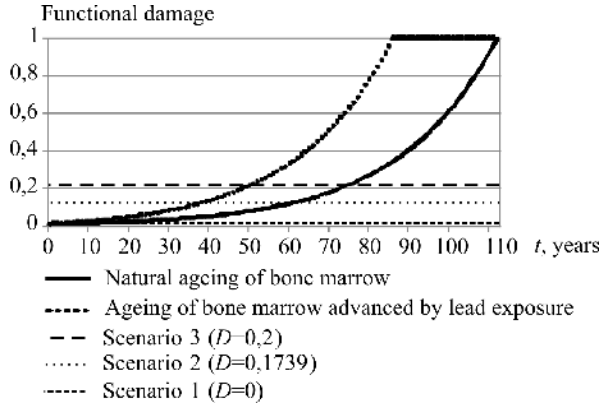

Figure 2. Evolution of damage to the monocyte-producing function performed by bone marrow

values of damage may be observed throughout different age periods depending on the level of exposure to chemical factors. Possible solutions of the system of differential equations that describe the interaction between the immune and neuroendocrine systems are shown in Figure 3.

Each of the scenarios is based on disturbing the balance of the system by setting up the base degree of streptococcus infection. At the initial stage (in the first 2-3 days), all the scenarios demonstrated a growing amount of "macrophages'-monocytes" and initiation of the regulatory mechanisms.

In the first scenario, the system reaches the state of stable equilibrium after 4-5 days which is associated with suppression of bacterial contamination and bringing the parameters into normal condition. In humans, such changes correspond either to the condition of no symptoms of a disease or acute inflammation resulting in prompt recovery ("sanation-recovery" scenario).

In the second scenario, the synthetic function of bone marrow is damaged insignificantly when the two processes – bacteria growth and destruction by macrophages – are in balance. At the same time, bacteria count is not increasing, and the tension of the immune system remains. In humans, examples of such conditions include acute exacerbation or remission of a chronic disease ("chronic disease" scenario).

In the third scenario, production of monocytes-macrophages by bone marrow is damaged significantly by The change to the IL-1 level does not significantly differ from the second level due to the adequate performance of the neuroendocrine system. One can observe unlimited growth in the bacteria count which is related to the reduction in monocytes-macrophages due to lower production by bone marrow as a result of exposure to external

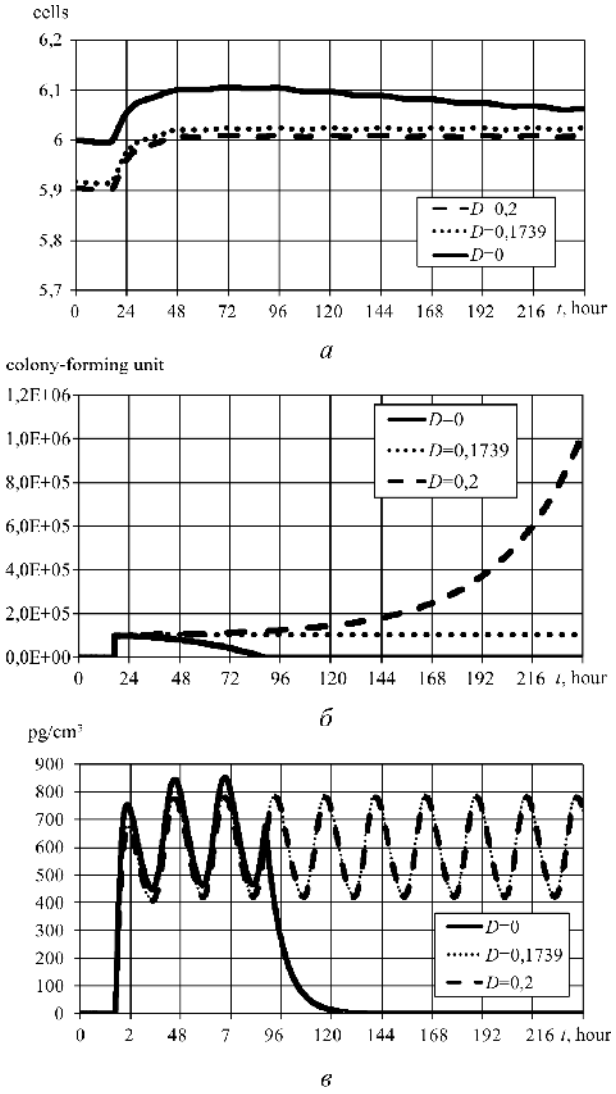

Figure 3. Graph of behavior a) monocyte/macrophage content, b) bacteria count, c) IL-1 blood level

chemical factors. This results in repression of the regulatory indicators manifested in acute conditions or acute exacerbation of a chronic infection ("severe infection" scenario) which can cause death.

Conclusion. The suggested model gives a rather adequate description of the process of development of a bacterial infection with the account for the impact of environmental chemical factors. Even though the analyzed structure of interaction between the elements of the immune and neuroendocrine systems is not complete and contains only some of the regulatory mechanisms, one can say this is a base model that reflects the multicomponent interaction between the regulatory systems on inflammatory responses of bacterial genesis; the model can be completed by adding additional parameters and connections.

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