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Pathogenetic aspects of retroviral infections

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Abstract

Bovine leukemia and equine infectious anemia are registered in most regions of Ukraine and in many countries worldwide. This is accompanied by economic losses and reduced quality of livestock products, which determines the relevance of the study of retroviral infections, their diagnosis, and pathogenesis. The goal of our research was to find and improve the methodological foundations of the development of the pathological process for a more in-depth study of the etiology, pathogenesis, treatment, and prevention of retroviral infections. The object of the study was blood, lymph nodes, spleen, heart, lungs, liver, and kidneys for bovine leukemia and equine infectious anemia. Hematological, anatomical, histological, histochemical, morphometric, and statistical research methods were used for their study. The research group included 304 cattle aged 4–9 years and 42 horses, of which 25 were infected with the virus, and 17 were in the control group. It has been established that bovine leukemia and infectious anemia of horses is an irreversible pathological process characterized by slow progression, the presence of a latent or persistent form, with damage to cells, organs, and systems of the body, which leads to death. Infectious anemia of horses differs from leukemia of cattle by the hidden course of the pathological process. The pathogenesis of leukemia occurs in six stages, which we have identified and conventionally named.

Keywords: bovine leukemia, equine infectious anemia, pathogenesis, morphology.

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1. Introduction

The problem of retroviral infections is quite relevant to modern veterinary medicine (Abd-Eldaim et al., 2005; Dunham & Graham, 2008; Caringella et al., 2019). This is due to their widespread distribution, especially in bovine leukemia (BL) (Juliarena et al., 2017; Ruggiero et al., 2019; Corredor-Figueroa et al., 2020) and infectious anemia of horses (INAH) (Gim & Kim, 2017; Lupulovic et al., 2021).

Bovine leukemia occupies a special place among infectious diseases since the disease is diagnosed not only in many regions of Ukraine but also in many countries of the world – the USA, several Central European countries – Denmark, Sweden, countries of the Middle East, Asia, etc. (Acaite et al., 2007; Yang et al., 2016; Bauermann et al., 2017; Pluta et al., 2017; Polat et al., 2017). The problem of leukemia is of great biological, economic and social importance (Cook & Pardee, 2013; Bartlett et al., 2013). Leukemia incidence and mortality from them, mainly in high-yielding cows, continue to increase in many countries, which to some extent is reflected in the production of livestock products and their quality (Pandey et al., 2017; LaDronka et al., 2018; Mekata et al., 2018; Moe et al., 2020).

Infectious anemia of horses is registered in most countries of the world (Malossi et al., 2020). In Ukraine, it is periodically found in the Poliska and Forest-Steppe zones. Significant economic losses are the result of high animal mortality during the initial outbreak of infection (up to 80 %), the forced slaughter of sick horses, extended quarantine, and strict veterinary and sanitary measures to eliminate the disease (Vissani et al., 2016; Radoja et al., 2017; Sharav et al., 2017; Batmagnai et al., 2018; Cursino et al., 2018; Naves et al., 2019; Staiger et al., 2019).

In animals affected by retroviruses, the infectious process proceeds differently (Gallo & Wong-Staal, 1982). In

some cases, clinical signs develop exceptionally quickly (from several weeks to several months); in others – over the years. Many animals remain virus carriers for almost their entire lives (Nahaeva et al., 2001).

Under such conditions, the effectiveness of combating these infections depends most on timely diagnosis (Brenner et al., 1989; Kisera, 2002). In the diagnostic complex for retroviral infections, an important place belongs to pathological and anatomical studies, which make it possible to identify specific changes and obtain objective criteria for their differentiation. However, in most cases, during the latent course of the disease, there are no clearly expressed and characteristic macroscopic changes in the organs, therefore, to establish the presence of pathological processes in the animal body, to differentiate the form and stage of the disease, microscopic histological studies with morphometric components are of great importance. The high efficiency of morphometric assessment of structural and functional changes in the animal body at the organ, tissue, and cellular levels has been proven (Horalskyi, 2000). Early diagnosis is possible on the 13th day after infection in laboratory conditions (Donnik et al., 2017).

Despite the progress achieved in this direction and a large number of published works on the problems of bovine leukemia and equine infectious anemia, the epizootic features of the diseases, the role of exogenous and endogenous factors in the occurrence and spread of retroviral infections are still insufficiently studied.

Therefore, for a more in-depth study of the issues of etiology, pathogenesis, treatment, and prevention of retroviral infections, an important place is given to the search and improvement of the methodological foundations of the development of the pathological process according to BL and INAH.

2. Materials and methods

Experimental studies were conducted at the Institute of Epizootology of the Ukrainian Academy of Sciences, following the scientific program "To study morpho-functional changes in the body's immune system and to develop measures to correct immunity", state registration No. 0196U024149-02 "To study mechanisms of metabolism, morpho-functional changes in bovine leukemia and equine infectious anemia" (1994–2003) and at the Zhytomyr National Agroecological University (ZhNAEU) during (2003–2019). following the scientific research plans of ZhNAEU, which is a fragment of the research topic of the Department of Normal and Pathological Morphology, Hygiene and Expertise of the Faculty of Veterinary Medicine of ZhNAEU (currently Polissia National University) "Development, morphology, and histochemistry of animal organs in normal and pathological conditions" (state registration no. 0113U000900).

When conducting scientific research, the basic rules of good laboratory practice GLP (1981), the provisions of the "General ethical principles of animal experiments" adopted by the First National Congress of Bioethics (Kyiv, 2001), and the requirements of the "Rules for conducting work using experimental animals".

The object of research was lymph nodes, spleen, heart, lungs, liver, and kidneys for leukemia in cattle and infectious anemia in horses.

The study of histological changes in chronic lymphoid leukemia in cattle using hematological, anatomical, histological, and morphometric research methods were carried out on material from 304 cattle, of which 68 were only seropositive according to IDR, 166 were seropositive according to IDR with the presence of hematological changes and 70 – clinically healthy cows.

The research material was collected from animals slaughtered at a meat processing plant or those who died at 4–9 years old.

The study of histoarchitectonics and morphometric indicators of organs and tissues during the hidden course of infectious anemia was carried out on material from 42 horses, of which 25 were infected with the virus, and 17 were in the control group.

The work used hematological, serological, anatomical, histological, histochemical, and morphometric methods.

Hematological and serological tests for leukemia in cattle were carried out following the "Methodical guidelines for the diagnosis of bovine leukemia" for INAH horses – following the recommendations for the diagnosis of INAH.

For conducting histological and histochemical studies, generally accepted methods of fixation and preparation of sections were used (Horalskyi et al., 2019).

Staining with hematoxylin and eosin was used to study the morphology of cells and tissues, which was used to obtain examination preparations, conduct morphometric studies, and served as a control during histochemical studies (Horalskyi et al., 2019).

Morphometric studies of structural elements of tissues were carried out under light microscopy, and microstructure measurements were made using MBI – 15/2 and "Biolam-Lomo" microscopes with a constant tube length.

Measurements of the thickness of the connective tissue capsule, the size of the diameter of cells and nuclei, and the cross-section of cardiomyocytes were carried out with an eyepiece-micrometer MOV-1-15x (at least 30 measurements on a separate section, 3–4 preparations from each animal).

Counting the number of renal corpuscles and lymph nodes of the spleen was performed on a conventional unit of area equal to 5.0 mm^2, with an MBS-10 microscope, on ten preparations in 20 fields of view for each group. The number of liver lobules was determined in the same way, only on a conventional unit of area equal to 14 mm^2.

The ratio of the cortical and medullary substance of lymph nodes, red and white pulp of the spleen, its trabecular apparatus, the respiratory part, and the connective tissue base of the lungs was carried out with the help of a reticle mounted in the eyepiece of a microscope (Horalskyi et al., 2019). In all animals, at the same magnification, the number of squares occupied by the investigated histostructure was counted, and by comparing its area on the surface of the section to the total, the percentage ratio of the crucial indicator was determined. Measurements were performed on at least ten drugs.

Counting of blasts, small, medium, and large lymphocytes, reticular cells, macrophages, and destroyed cells in the microstructures of lymph nodes and spleen was carried out based on every 100 cells at a magnification of 10 × 90 on ten preparations in 20 fields of view for each group of animals. Based on the obtained data, the average percentage of each type of cell was determined. The bioethics commission approved the research protocol of ZhNAEU.

Statistical processing of the obtained results was carried out on a PC using a licensed Microsoft Excel program.

3. Results and discussion

3.1. Results

Our histological and morphometric studies in organs and tissues of animals with a latent course of the pathological process in lymphoid leukemia showed that this process develops gradually and manifests quite ambiguously. Considering serological, morphological, and morphometric indicators, we tentatively identified six stages of the development of the infectious process in lymphoid leukemia (Fig. 1).

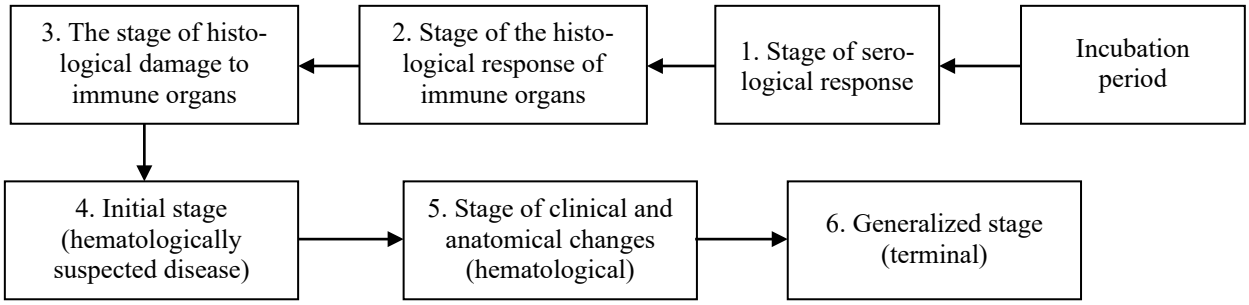

Fig. 1. Scheme of the development of the leukemic process during the spontaneous course of lymphoid leukemia

The first stage is a serological response to the presence of the virus in the body. Such animals do not yet have pathological-anatomical, pathological-histological, hematological, and morphometric indicators in the body, but they react in IDR. According to the results of our research, 10 percent of them are found in animals with a latent course of the leukemic process.

The second stage is the histological reaction of immune organs. We established this stage in 30 percent of animals with a latent disease course. Such animals are seropositive in IDR and have morphometric changes in the organs of immunogenesis.

Thus, in the lymph nodes, there is a tendency to increase the area of the cortical substance and a significant decrease (at $P > 0.95$) by almost 1.5 times the area of the brain substance. The average area of lymph nodes increased and was 0.60 ± 0.11 mm^2 in the animals of the experimental group and 0.46 ± 0.07 mm^2 in the control group. The number of blasts and large lymphocytes increased from 3.8 ± 0.78 % to 4.66 ± 1.33 % in lymph nodes and from 1.2 ± 0.2 % to 1.66±0.67% in chorda medullaris. There is a noticeable tendency to increase the number of macrophages and decrease the number of average lymphocytes.

Changes in morphometric indicators occurred in the histostructure of the spleen. In particular, the results of morphometric studies showed a tendency toward an increase in the share of white pulp from 21.93 ± 0.92 % in the control groups of animals to 23.70 ± 4.62 % in the experimental ones and the average area of lymph nodes from 0.55 ± 0.03 mm^2 to 0.63 ± 0.13 mm^2, respectively. Cytopopulation changes were expressed in a reliable (at $P > 0.999$) increase by 2.36 times in reactive centers and by 2.66 times – in the marginal zone of blasts and large lymphocytes. An increase in average lymphocytes was observed: in the reactive centers from 17.1 ± 1.8 % to 26.16 ± 2.11 %, in the marginal zone from 16.0 ± 4.6 % to 22.67±3.0 %, and as well as an increase in the relative number of reticular cells and macrophages in these zones. Thus, the above-mentioned cytological shifts, especially towards an increase in the number of macrophages, blasts, and large lymphocytes in the lymph nodes and spleen, are associated with an increase in the functional activity and reflect the dynamics of the body's adaptation mechanisms to the invasion of the leukemia virus.

The third stage is histological damage to immune organs. According to the results of our research, 60 percent of animals with a latent leukemic process were at this stage. Such animals reacted seropositively in IDR and showed small lymph nodes and spleen lesions. At the same time, no changes in the blood characteristic of leukemia were noted.

Leukemic lesions of the lymph nodes began with reactive centers and pulmonic cords. A small number of lymph nodes were infiltrated by lymphoid cells, and their light centers were expanded. Microscopic studies of the spleen showed an increase in lymph nodes and the number of lymphoblasts in them, mainly in expanded reactive centers. In individual nodules, reactive centers disappeared and were infiltrated by lymphoid cells.

Morphometric changes were observed in immune and non-hematopoietic organs. In particular, morphometric studies of the histostructures of lymph nodes showed a significant increase by 37.3 % of the cortical and a significant decrease by 22.3 % (at $P > 0.999$) of the brain substance compared to the control group of animals. The average area of lymph nodes increased to 0.76 ± 0.17 mm^2 from the initial 0.46 ± 0.07 mm2 in the control group. An increase in the relative number of blasts and large lymphocytes (11.6 ± 2.38 % and 3.8 ± 0.87 %) in lymph nodes was also observed; (2.2 ± 0.49 % and 1.1 ± 0.2 %) in pulp fibers ($P > 0.999$) and macrophages (3.5 ± 0.4 % and 1.4 ± 0.3 % and 1.7 ± 0.3 % and 1.1 ± 0.31 %) (at $P > 0.999$), respectively. The volume fraction of average lymphocytes decreased: from 31.7 ± 1.8 % to 20.6 ± 2.16 % in lymph nodes and from 31.0 ± 2.4 8% to 22.5 ± 1.45 % in pulverized fibers (at $P > 0.999$).

In the spleen, there is a noticeable trend towards an increase in the percentage of white pulp and a decrease in red pulp. At the same time, a change in the spleen's immunopoietic activity was established compared to the control. This is evidenced by an increase in reactive centers and the marginal zone of lymph nodes, blasts, and large lymphocytes (from 1.2 ± 0.33% to 4.1 ± 0.31 % and from 1.0 ± 0.26 to $3.1 \pm$

0.28 %), respectively (at P > 0.999) and a significant increase of 4.1 and 5.7 times, respectively, in the number of macrophages, the cytoplasm of which was often vacuolated and filled with various fragments of destroyed cells. The percentage of reticular cells in the reactive center of lymph nodes decreased from 19.5 ± 1.6 % to 17.6 ± 1.7 %, and in the marginal zone, it increased from 14.9 ± 2.0 % to 17.1 ± 1.8 %.

Morphometric studies of the histostructure of the myocardium, lungs, liver, and kidneys in cattle at the stage of histological damage to immune organs in lymphoid leukemia showed no significant changes compared to the control. Other scientists also noted such changes, in particular, the infiltration of all kidney structures by lymphoid cells, mainly in the cortical substance, which was polygonal in shape with a large homogeneous nucleus and a narrow strip of cytoplasm.

During the study of 166 heads of cattle with the presence of hematological and clinical changes in the body, 52.4 % of them had the initial stage (9–20 g/l leukocytes in the blood), 42.8 % – the stage of clinical and anatomical changes (up to 50 G/l leukocytes) and 4.8 % – generalized (50 or more G/l leukocytes in the blood) stage of development of the pathological process, according to the classification of G. V. Snoza (1986). The frequency of lesions and the nature of pathomorphological changes in organs and tissues depend on the stage of the disease (Table 1).

Table 1

Pathological and morphological changes in organs and tissues of cattle (n = 166) at different stages of lymphoid leukemia (%)

Organs	Stages of the disease						Total	
	Initial		Clinical and anatomical changes		Generalized			
	1^X	2^X	1	2	1	2	1	2
Lymph nodes	-	94	46	100	100	100	25	97
Spleen	-	93	51	100	100	100	27	96
Heart	-	41	8	47	62	87	7	46
Lungs	-	5	4	38	25	50	3	21
Liver	-	45	12	80	63	100	8	63
Kidneys	-	32	6	46	50	87	6	43

Note: 1^X – pathological and anatomical changes; 2^X – pathological and histological changes

The fourth stage is initial (hematologically suspected disease). It is characterized by histological changes in immune and non-hematopoietic organs and the appearance of changes in the blood characteristic of leukemia.

The fifth stage is clinical and anatomical changes. At this stage, in addition to histological, macroscopic changes in some organs and changes in the blood characteristic of leukemia are detected.

The sixth stage is generalized or terminal. At this stage of the disease, the animals showed clinical, macroscopic, and hematological changes characteristic of leukemia.

Thus, based on the results of complex studies conducted in cattle during the spontaneous course of lymphoid leukemia, we identified six stages of the development of the leukemic process. The frequency of lesions and the nature of pathomorphological changes in organs and tissues depend on the stage of the disease.

INAH of horses is currently characterized by a hidden course of the pathological process. The disease proceeds in latent or chronic forms. There are almost no cases of its clinical manifestation. With the appearance of clinical signs of the disease, it turns into a chronic form. At the same time, the development of the pathological process is restrained by the body's protective forces, and the INAH virus persists throughout the life of horses in equilibrium stages, as in animals during the latent course of leukemia.

Taking into account the retroviral nature of INAH in horses, and some differences in the manifestation of the pathological process, in comparison with bovine leukemia, we conducted pathomorphological studies in the organs and tissues of horses with infectious anemia.

The main characteristic morphological changes in INAH are a slight lymphoid proliferation of organs and tissues, violation of the characteristic structure of organs with deposition of hemosiderin in the reticuloendothelial cells of the liver. These changes are found in all forms of the disease.

However, when analyzing the morphofunctional indicators and the results of serological diagnostics, we established some features of the latent course of the disease. In particular, no histological changes in organs and tissues were detected in horses with titers of specific antibodies to RDP (native – 1 : 2) in blood serum. These animals accounted for 60% of the total number of horses with a latent disease course. Only in the presence of titers of specific antibodies in the RDP at the level of 1 : 8 – 1 : 16 during histological studies weakly expressed changes in organs and tissues were observed. At the titers of specific antibodies (1 : 32 – 1 : 64) in RDP, in addition to histological, pathological-anatomical changes, characteristics of INAH and changes in hematological parameters were also detected. The number of such horses was 12 percent.

Taking into account that the highest percentage of animals suffering from infectious anemia was horses, in which no clearly expressed histological changes in organs and tissues were detected, in order to detect immediate changes at the early stage of the disease during the latent course of INAH, we conducted appropriate morphometric studies. Their results indicate that during the latent course of infectious anemia in horses, similar to lymphoid leukemia in cattle, the development of the infectious process begins with damage to the lymph nodes and spleen. This is indicated by changes in morphometric indicators at the tissue level, in particular, an increase by 18.4 % of the cortical substance of lymph nodes and the average area of lymph nodes (from 0.0832 ± 0.0082 mm^2 in control animals to 0.1081 ± 0.0423 mm^2 in experimental animals). This is connected with the active migration of cellular elements from the brain substance into the lymph and subsequently into the blood.

Histological studies of the spleen of horses infected with the INAH virus showed no remarkable changes at the tissue level compared to the control. At the same time, there is a tendency to increase the percentage of white pulp and the

average area of lymph nodes and to decrease the red pulp and trabecular apparatus. At the same time, an increase in the immunopoietic activity of the spleen was established, as evidenced by a significant increase in the number of blasts and large lymphocytes by 2.8 times (P > 0.999) in the reactive centers and by 2.75 in the marginal zone, macrophages by 2.9 and 2.9, respectively. 3.4 times, destroyed cells – 2.4 and 2 times. A decrease in medium and small lymphocytes and an increase in reticular cells are observed in these structures.

In the myocardium, lungs, liver, and kidneys of the horses of the research group, no significant morphometric changes were found compared to the control.

Thus, in horses with a latent course of INAH, in the presence of low titers of specific antibodies in RDP (native – 1 : 2), no histological changes in organs and tissues were detected. At the same time, the results of morphometric studies made it possible to establish changes in the lymph nodes and spleen at the tissue and cellular levels. Minor histological changes in organs and tissues (lymphoid proliferation of organs and tissues and disruption of the characteristic structure of organs with the deposition of hemosiderin in the reticuloendothelial cells of the liver) occur only in the presence of specific antibodies in RDP at the level of 1 : 8 – 1 : 16, and with an increase in the level of antibodies to 1 : 32 – 1 : 64 hematological, pathological-anatomical and histological changes characteristic of INAH are observed in RDP.

3.2. Discussion

The epizootic situation in Ukraine and the region is characterized by the presence of various infectious diseases (Fèvre et al., 2006; Merianos, 2007; Ducrot et al., 2016; Câmara et al., 2020), including those familiar to humans and animals and those (Tomley & Shirley, 2009; Buehring et al., 2019), that are subject to mandatory registration according to the list of the International Epizootic Bureau, – leukemia, infectious anemia of horses, etc. (Holovko et al., 2016; Kryvoshyia & Rud, 2018). Today, diseases of retroviral origin deserve special attention since it is practically impossible to eliminate the development of the pathological process in sick animals.

The causative agents of retroviral infections are fundamentally different from other viruses (the RNA virus replication passes through the DNA provirus stage, which integrates with the cellular genome). In addition, viruses of this group have a unique ecological characteristic that allows them to exist in the host cell's genome not only infectiously but also, like cellular genes, in a vertical genetic way. Such viruses can reside in healthy organisms, participate in normal cellular processes, and multiply in cells without destroying their vital activity. Genetic information comes not from DNA, RNA, or protein, but from RNA, DNA, and – RNA protein. This is where the name of this family comes from (in reverse). According to the morphological structure, these viruses are similar to the viruses of AIDS and human T-cell leukemia. The study of etiopathogenesis, the nature of the manifestation of the pathological process in farm animals, is not only of theoretical importance but also makes it possible to determine the boundary between the norm and pathology, make a timely diagnosis and outline the ways of prevention and recovery.

The concepts of “normal” and “pathology” are inseparable and are objective phenomena. They interact with each other, ensuring the evolution of living systems and relationships between macro-and microorganisms, and largely depend on the influence of biotic and abiotic factors on the animal body.

Thus, the development of the pathological process in non-infectious pathology is carried out as follows. Under certain circumstances, the norm can turn into pathology and vice versa (Fig. 2). At the same time, with the development of the pathological process, clinical signs of diseases with pathomorphological changes in the body may appear, and only some animals develop irreversible destructive changes that lead to the death of animals.

Fig. 2. Scheme of the development of the pathological process in non-infectious pathology

With retroviral infections, the reverse process (pathology – norm) practically does not occur, and it depends on the stage and form of the disease, species, age, and individual characteristics of the organism.

The development of the pathological process in diseases of retroviral origin proceeds in different ways and has its specific manifestation. It is practically impossible to eliminate the development of the pathological process in sick animals.

Bovine leukemia and equine infectious anemia have their peculiarities in their development (Fig. 3).

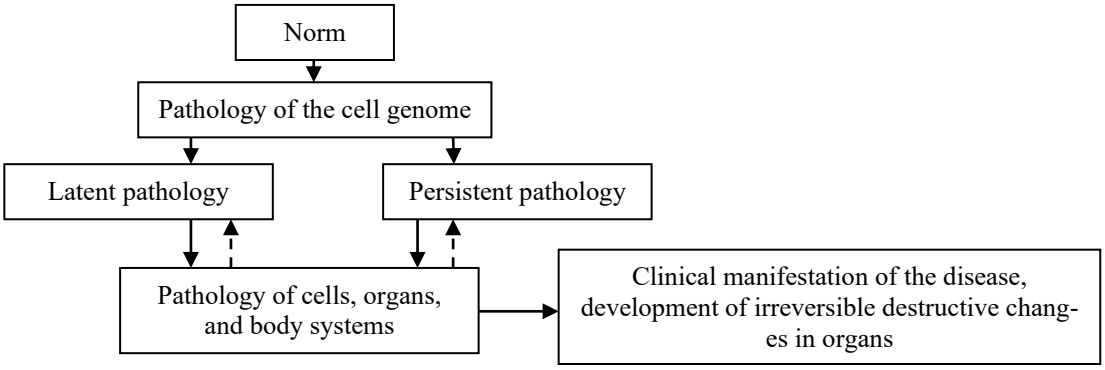

Fig. 3. Scheme of the development of the pathological process in retroviral infections

If, during the development of non-contagious pathology, we observed the reversibility of the pathological process (norm pathology), then during the development of bovine leukemia and INAN in horses, the pathology is irreversible. The pathological process, progressing slowly, can manifest itself both in a latent and persistent form, with subsequent damage to cells, organs, and systems and the organism's death.

Thus, chronic lymphoid leukemia, which is the primary type of pathology in cattle leukemias, is characterized by the progression of the neoplastic process, with the hematological manifestation of the disease in 5–10 % of animals, which is also indicated by other researchers (Kryvoshyia et al., 2017; Akagami et al., 2019). The hematological stage of the disease continues for years, and 10–20 % of such animals have a clinical manifestation of the disease (enlargement of superficial lymph nodes, exophthalmia, cachexia). In 90–95 % of animals with a chronic and latent form of the disease (seropositive in the immune diffusion-reaction (IDR) with the absence of hematological changes in the blood), there are no significant pathomorphological changes. However, the leukemia virus persists in the body of these animals. They are a potential source of infection in the herd and contribute to the infection of other animals. In these animals, the pathological process is at the stages of equilibrium and dynamic transition from latent pathology to persistent pathology.

With INAH, there are differences in the manifestation of the pathological process compared to bovine leukemia. Currently, INAH horses are characterized by a hidden course of the pathological process. The disease proceeds in latent or chronic forms. There are almost no cases of its clinical manifestation. With the appearance of clinical signs of the disease, it turns into a chronic form. At the same time, the development of the pathological process is restrained by the body's protective forces, and the virus persists throughout the life of horses in equilibrium stages, as in cattle during the latent course of leukemia.

4. Conclusions

1. With the development of bovine leukemia and infectious anemia in horses, the pathology is irreversible: the pathological process, slowly progressing, can manifest itself both in a latent and persistent form with subsequent damage to cells, organs, and systems the death of the organism.

2. The development of the pathological process in lymphoid leukemia occurs gradually and manifests quite ambiguously. Taking into account serological, morphological, and morphometric indicators, we conditionally identified six stages of the development of the infectious process in lymphoid leukemia: the stage of serological response; stage of the histological response of immune organs; the stage of histological damage to immune organs; initial stage (hematologically suspected disease); the stage of clinical and anatomical changes (hematological); generalized stage (terminal).

3. Infectious anemia of horses is characterized by a hidden course of the pathological process: it manifests itself in latent or chronic forms, and there are no clinical signs. The appearance of clinical signs makes the disease a chronic form. At the same time, the development of the pathological process is restrained by the body's protective forces, and the virus persists throughout the life of horses in equilibrium stages, as in cattle during the latent course of leukemia.

Conflict of interest.
The authors state that there is no conflict of interest.

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