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ENZOOTIC BOVINE LEUKOSIS — DIAGNOSTICS, ERADICATION, AND ANTHROPOZOONOTIC POTENTIAL (BACKGROUND)

(review)

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Abstract

Of tumor diseases in the global animal husbandry industry, the greatest danger is enzootic bovine leukosis. Since the last century, this neoplastic disease has remained relevant for veterinary medicine and, in addition, more and more questions arise concerning the potential threat of the Bovine leukemia virus (BLV) for humans. The problem is being discussed (G.Yu. Kosovskiy et al., 2016) which additionally stimulates both fundamental research of the pathogen and the pathology, as well as the methods for detection to improve dairy cattle breeding and veterinary safety. A number of publications are devoted to BLV prevalence, peculiarities, the prospects for improving animal health and welfare based on selection and vaccines developed in the world (S.G. Hopkins et al., 1997; M.A. Juliarena et al., 2017). In our report, we retrospectively compare the experience of BLV eradication in the USSR, Russia and abroad, additionally focusing on the possible role of this pathogen in the occurrence of cancer in humans. In veterinary practice, serological tests, i.e., agar gel immunodiffusion assay (AGID) and enzyme-linked immunosorbent assay (ELISA) are mostly used to detect the BLV infection. G.C. Buehring et al. (2019) reported the detection of BLV proviral DNA in blood leukocytes in 38% of patients examined by PCR and DNA sequencing. IgG antibodies to BLV were detected in 32%, IgM — in 58%, and IgA — in 32% of the samples tested. Accumulated data indicate metabolic changes in the BLV-positive animals, e.g., disorder in the metabolism of tryptophan, a critical essential acid, leading to the accumulation of dangerous endogenous metabolites in the body. Particularly, free tryptophan, indole and anthranilic acid increased in level 4-8-fold are deposited in the organs of the immune and hematopoietic system (lymph nodes, spleen, liver), in the mammary gland, lungs, and kidneys. It has been established that the milk of leukemic animals differs from the milk of healthy cows in terms of physicochemical, bacteriological (lysozyme), technological parameters and mineral composition. In C57 mice fed with pasteurized milk and heat-treated meat from ID-positive cows, the blood cell profile changed. Available data drive to the unambiguous conclusion that the products derived from BLV-infected cattle pose an increased risk to humans. Despite the lack of convincing evidence of the BLV pathogenicity for humans, concerns about the etiological role of this virus in the occurance of cancer in humans additionally necessitates continuing research on the control and eradication of this common oncogenic retro-virus in livestock farms.

Keywords: leukemia, Bovine leukemia virus, proviral DNA, PCR indication, IgA, IgM, IgG, blood cells, endogenous metabolites, milk, vaccination, eradication

Enzootic bovine leukosis (EBL) is a dangerous chronic infectious disease caused by oncogenic Bovine leukemia virus (BLV) [1, 2]. Cattle and other domestic ruminants, as well as wild ruminants are BLV susceptible [3, 4]. Treatment of cattle enzootic leukemia is ineffective. By the mid-1960s, the incidence

of the disease was reported on several continents in most countries with developed cattle breeding, which, in turn, provokes even higher incidence and wider spread of the diseases which poses a threat to the industry [5, 6]. Bovine leukemia causes huge economic damage to pedigree and commercial livestock raising, and also via restrictions in live animal markets and animal product markets [7, 8]. The improvement of BLV sanitary situation is a prerequisite for increasing dairy cattle performance and ensuring the veterinary and sanitary safety of animal products [9, 10].

B-lymphotropic bovine leukemia virus (a C-type retrovirus with single-stranded RNA) is a member of the *Retroviradae* family [11, 12]. Like hepatitis virus-derived transcripts [13], BLV transcripts are detected in malignant human tissues. BLV is phylogenetically close to human T-cell leukemia virus type 1 (HTLV-1) [12] infecting CD4+ T cells

Common patterns of neoplastic processes in the hematopoietic organs of humans and cattle arouse interest in veterinary, medical, and biological aspects of the pathology caused by BLV [14, 15]. A possible role of this pathogen in the etiology of oncological diseases in humans is being discussed [16, 17] which additionally stimulates fundamental studies of the BLV and the pathology it causes, as well as the improvement of methods for BLV detection and eradication.

This review gives a retrospect view on and prospects of bovine leukemia eradication in Russia and abroad and debates the zoonotic and anthropozoonotic potential of BLV.

Enzootic bovine leukosis — sings, diagnostics and indication aspects. CEL was first described in 1871 [18, as cited in 19], although its causative agent was first identified only in 1969 which made it possible to further study the pathogen and to develop eradication measures [1, 12, 20, 21]. It is known that BLV-induced multistep leukemogenesis is characterized by several steps. Many BLV-infected animals do not develop any clinical symptoms of viral infection while some cows develop humoral immune response to virus antigens. The next progressive stages are persistent lymphocytosis (hematological stage of the disease) and lymphosarcoma with a malignant transformation [22]. Hematological changes develop in 30 % of dairy cattle older than 3 years while lymphosarcomas of internal organs occur in 0.1-10 % of infected animals [23-25]. Transition from one stage to another, especially at the beginning of the disease progression, explains the disappearance and reappearance of clinical signs in some animals, as well as remissions in animals with persistent lymphocytosis [26].

BLV in naturally transmitted mainly horizontally (with infected lymphocytes, including through the biological secrets) [26]. Transplacental transmission occurs in 5-8 % of cows with asymptomatic infection and in 10-20 % of cows with clinical manifestations of leukemia. Close contacts between animals and improper therapeutic and prophylactic measures enhance the BLV contagiousness. Animals become infected when lymphocytes containing BLV enter the body enterally or parenterally. It was experimentally found that for a cow to become infected with the leukemia virus, it is enough to inject 2500 infected leukocytes intradermally into the skin. It has been established that 0.5 μl of blood infected with the leukemia virus is sufficient to infect an animal [27]. The transmission by flies and through mucosal surfaces or broken skin cannot be ruled out either [28, 29].

The strategy for bovine leukemia eradication is specific to a country conditions and based on data about the pathogenesis of the disease, the characteristics of the immune response in susceptible animals, and the transmission routs of the pathogen. In Europe, in the 1950s, the first successfully applied method for detecting infected animals was based on clinical, pathological and hematological

studies followed by isolation and elimination of sick cows from the herd [23].

In 1967, the World Organization for Animal Health (OIE) recommended diagnosing the disease by a hematological study using a hematological key to determine persistent lymphocytosis. Counting the ratio of lymphocytes has become the main diagnostic tool for many years in all countries, including the USSR [30, 31].

Miller and Olson [32], considering the absence of EBL clinical signs at the initial stages of the developing infection while the level of virus-specific antibodies is rather high, have proposed the anti-BLV antibody test (agar gel immunodiffusion assay, AGID) to diagnose EBL. AGID assay was advanced for its time and, being approved as a basic diagnostic approach in veterinary practice, significantly accelerated both preventive measures and the eradication of bovine leukemia [33]. Currently, the AGID assay [34] and enzyme-linked immunosorbent assay (ELISA) [35] are basic tests for the detection of antibodies to BLV in blood and milk. In Europe, in cattle farms, serological tests have been used since 1970 to detect virus-specific antibodies. By 1979, hematological studies for leukemia were completely abolished in Danish livestock herds and the mandatory use of the immunodiffusion reaction was recommended [36, 37]. Since 1988, EU legislative documents have also provided for the use of ELISA test for the diagnosis of leukemia in addition to ID test [38]. ELISA detects virus-specific antibodies with low titers in both blood and milk, which cannot be detected by AGID test [39].

The next advance in CEL diagnostics was due to polymerase chain reaction (PCR) analysis and its modifications allowing detection of BLV proviral DNA in the genomic sequence of infected lymphocytes [40-42]. PCR analysis is often used for emergency detection in clinical material as early as 7 days after infecting of a macroorganism (especially calves) with a pathogen in cases of uncertain serological tests [43]. PCR analysis, due to its high accuracy, is used to detect BLV in semen samples [44] and in milk [45].

Eradication of EBL. Practical approaches to EBL eradication are represented by several strategies [46]. The first strategy called “check and remove” aims to identify infected animals hematological, serological and molecular methods, to immediately remove such animals from the herd for rapid slaughter [23, 47]. This strategy has played an important role in eradication of the disease in several European countries (in particular, in Belgium and Finland). However, the strategy's limitations are the mandatory low initial spread of infection and financial losses due to government compensation for culled animals. Countries such as the United States, Canada, Argentina and Japan where no financial compensation was applied were unable to implement this strategy [46].

The second strategy, or “check and separate”, is less costly because the infected animals are not culled but separated from the BLV-free animals. Only clinically sick animals are subject to culling [48]. This strategy has proven to be effective to significantly reduce the prevalence or even eradicate the disease in most countries [49, 50].

As for the third strategy of “check and manage”, no animals should be added to the herd instead of those BLV-infected and culled. In fact, this strategy is limited to biosafety measures, minimizing the exposure of animals to an infectious agent, thus requiring minimal financial investment [46].

Prevalence, diagnostics and measures to combat bovine leukemia in the USSR and the Russian Federation. It is believed that the spread of leukemia in our country is associated with the importation of pedigree cattle from Germany to Western Siberia, Kaliningrad, Moscow, Leningrad regions in 1940 and 1945-1947 [51]. In the USSR, the study of CEL and its causative agent began at the Kovalenko All-Union (now All-Russian) Institute of Experimental Veterinary Medicine (VIEV,

Moscow) in 1961 and at the NSC Institute of Experimental and Clinical Veterinary Medicine and Belotserkovsky State Agrarian University (the Ukrainian SSR) in the 1960s. CEL incidence was first officially reported in the Soviet Union in 1965-1966 [52]. The researchers of VIEV have developed instructive and normative materials (1965, 1969, 1984, 1989), regulating measures to combat this infectious disease.

For the last 30 years in Russia, ID assay and ELISA test have been used to detect antibodies to BLV antigens in blood and milk or colostrum to diagnose CEL. Many researchers have shown the possibility of using PCR for early diagnosis of bovine leukemia [53, 54].

In the Soviet Union, since the early 1990s, a check-and-separate strategy was used. A systemic approach was developed based on biological properties of BLV, infectious and epizootic processes. BLV is inactivated by heating to 56 °C for 15 min, to 70-74 °C for 15-17 s. In milk, BLV remains intact at 9-15 °C for in 24-48 hours. The virus remains active at a pH below 6.0, in 0.5 % sodium hydroxide solution, in 0.5 % formaldehyde and phenol solutions, and in 2 % ethyl alcohol. A 4-hour exposure to direct sunlight kills the bovine leukemia virus, ultraviolet radiation kills BLV in 30 min [10]. Importantly, there are four stages of the CEL development, namely, i) incubation period (from the inoculation until the appearance of antibodies to the pathogen); ii) serological stage (asymptomatic infection, from the appearance of antibodies until the detection of hematological changes); iii) hematological stage which corresponds to the development of persistent lymphocytosis; iv) malignant stage characterized by development of malignant tumors in the tissues of blood-forming and other organs [25, 55]. One of the main immunogenetic factors conferring cattle resistance or susceptibility to bovine leukemia are histocompatibility antigens. In particular, the resistance of animals to leukemia is determined by the alleles of the BoLA-DRB3 gene encoding class II antigens of the main cattle histocompatibility complex [56].

Since 1997, bovine leukemia has ranked first among infectious diseases in the Russian Federation [5, 11]. As of January 1, 2014, up to 10 % of herd infection was observed in 53 constituent entities of the Russian Federation, and in the Nizhny Novgorod region this figure exceeded 30 % [57]. In 2016, new outbreaks of bovine leukemia were registered in more than 27 regions of Russia. In 2016, bovine leukemia was registered in 68 constituent entities of the Russian Federation (58 thousand cows in total). Only a few constituent entities of the Russian Federation are free from CEL [10]. A decrease in average annual milk production in BLV-infected herds is 218 kg per cow as compared to BLV-free herds [57, 58].

A retrospective analysis of the incidence of leukemia for 2005-2015 in the Ural region (statistical reporting data of the Department of Veterinary Medicine of the Sverdlovsk Region) revealed a high epizootic intensity for cows in most dairy farms located in the zone with combined technogenic pollution characteristic of this region. It was also found that in farms located in the most contaminated areas of the East-Ural Radioactive Trace (EURT), the seropositive cows accounted for 56-76 % and 8-14 % had hematological pathology, with the average seropositivity across farms of 20 % and 5.7 % of characteristic hematological abnormalities [59]. In areas not exposed to technogenic pollution, BLV infection was about 1 %, and animals with hematological disorders were practically absent. Hematological studies revealed that 12 % of cows were positive in ID test throughout the region with combined radioactive contamination. At dairy farms located along the EURT axis, the number of animals with persistent lymphocytosis was 1.5-2.0 times more as in the region [5]. Disorder for bovine leukemia

in areas of technogenic and radioactive contamination is associated with immune disorders, leading to the rapid clinical development of leukemia [60].

The histomorphological analysis of malignant tumors in cows, carried out for the first time in the Soviet Union, showed that 85.0 % of the 5243 intravitally diagnosed CEL are leukemia (of which 82.70 % are lymphocytic leukemia, 2.07 % are hemocytoblastosis, 0.23 % are myeloid leukemia); reticulosis accounted for 14.7 % (7.20 % for reticulosarcoma, 3.40 % for lymphosarcoma, 2.10 % for systemic reticulosis, 1.52 % for lymphoreticulosis, and 0.48 % for lymphogranulomatosis)/ The remaining types of tumors accounted for 0.3 % [61].

Foreign experience in the CEL eradication. Ukraine. After 1990, in Ukraine, measures to detect and control bovine leukemia are regulated by the relevant legislation. Since 2007, the use of serological and genomic methods in research and diagnostics has been regulated. In general, since 1990, there has been a significant decrease in the incidence of leukemia in livestock [62, 63].

The annual detection of new sites of bovine leukemia indicated the presence of factors contributing to the maintenance of a tense epizootic situation. These were ignoring the incubation period of leukemic infection; errors and untimely diagnostics; the presence in healed farms of few BLV-infected cows which, when overexposed in the herd, become the main sources of the pathogen; favorable conditions for the transmission of the pathogen; human factor (improper execution of veterinary, zootechnical and organizational and economic measures, in particular, untimely isolation and delivery of animals infected with leukemia virus for slaughter). Based on the analysis of the epizootic situation, by the beginning of the 2000s, a clear set of anti-leukemic measures was proposed, including constant monitoring of each dairy farm; identification of sources of the causative agent using highly specific diagnostic tests to detect early infection; immediate (just once detected) isolation of sources of the causative agent and its elimination within 10 days; reliable zootechnical recording of animals; adaptation of technological systems for livestock moving, keeping, feeding, and raising calves in accordance with the requirements of health-improving veterinary and sanitary measures; veterinary and zootechnical measures; large-scale step-be-step program for CEL eradication in herds, which ultimately led to positive results [20, 63, 64].

In 1988-1990, within the framework of a large-scale veterinary and zootechnical prophylaxis and rehabilitation, a diagnostic kit for the early detection of bovine leukemia was produced by NPS Orion (Kharkov, Ukraine) [65]. In 1991-1997, an integral assessment of the CEL incidence was performed using ID test to determine the active BLV sources. A through zootechnical survey was carried out and conditions were created for the immediate isolation of identified sick animals and their slaughter no later than in 15 days. To maintain herd size, the reproduction was intensified. Since 1998, using relevant methods of intravital diagnostics, preventive and recreational measures have been actually implemented with regards to epizootology, etiopathogenesis, and epizootic aspects [33, 63, 66, 67].

In bovine leukemia, the effectiveness of a zootechnical and veterinary system is assessed by the epizootic indicators, prevalence of the virus, incidence and the number of sites unfavorable for CEL. According to veterinary statistics, over a 17-year period (1997-2014), the prevalence of CEL in Ukraine decreased 369-fold, the incidence rate 376-fold, and the frequency of detection of unfavorable site 745-fold. As a result, by 2013-2014, the transition of the epizootic to the state of sporadic cases was recorded [63]. The developed zootechnical and veterinary system of anti-CEL measures is generally recognized as effective [63, 68]. Some researchers believe that the complete eradication of cattle is possible only through

identifying infected animals without specific prophylaxis. However, this is rather difficult, since to date the developed diagnostic tests fail to identify all animals which just began to replicate the virus [15].

Republic of Belarus. In the Republic of Belarus, in the 1990s, epizootic BLV infection was registered in 97.8 % of farms [68]. Active anti-CEL measures [69, 70] reduced the proportion of ID-positive animals from 19.6 to 2.4 % in a dairy herd and from 7.4 to 3.2 % among young animals and made it possible to improve the health of herds at 397 dairy farms. By 2011, the proportion of seropositive animals decreased to 0.1 % [68].

The Republic of Kazakhstan. In Kazakhstan in 2002-2011, from 2.3 to 43.7 % of the livestock were immunologically surveyed for CEL using ID and ELISA tests, and 3.3 % were found to be infected, ranging from 2.2 in 2009 to 11.0 % in 2005 [71]. Measures to combat this disease are given constant attention [72-74], taking into account the importance of the problem for cattle breeding in Kazakhstan [71].

Countries of Western and Eastern Europe, Asia, Africa, and America. UK is an example of successful national programs for control and eradication of CEL based on serological testing of blood and milk samples. The first outbreak of the disease was reported here in 1978, the last case in 1996, and since 1999 the UK has been officially recognized as BLV-free [68, 75-77]. The disease control strategy adopted in the UK presupposes maintaining the existing status on the basis of continuous serological monitoring of blood and milk samples and the import of livestock exclusively from Nordic countries free of bovine leukemia [68].

As per the OIE reports, the countries free of BLV are also Andorra (since 1994), Cyprus (since 1995), Czech Republic (since 2010), Denmark (since 1990), Egypt (since 1997), Estonia (since 2013), Finland (since 2008), Georgia (since 1996), Ireland (since 1999), Kyrgyzstan (since 2008), New Zealand (since 2008), Norway (since 2002), Slovenia (since 2006), South Africa (since 2012), Spain (since 1994), Sweden (since 2007), Switzerland (since 2005), Tunisia (since 2005), and Poland (since 2017 years) (the years of eradication of the disease are indicated). In Italy, Portugal, Latvia, Greece, Romania, and Bulgaria, BLV either persists with minor manifestations or the disease occurs sporadically [68]. In the countries of North and South America, Africa and Asia, as well as in Australia, in spite of the anti-CEL measures carried out there, the level of the BLV infection in dairy cattle remains high [68].

Note, however, that each country has its own plan to combat CEL. For instance, in the United States, there are no federal lows to limit the BLV spreading in herds, and there is no mandatory recording of BLV infection which causes great difficulties in assessing the problem [6]. In 2007, seropositivity for BLV was detected by ELISA test on average in 83.9 % of the surveyed herds where pooled samples were collected, and in large herds of more than 500 cows the infection rate reached 100 % [68]. Seroprevalence for BLV was also found at 38.0 % of meat farms [68]. According to data for 2018, when examining milk samples by ELISA test, BLV-specific antibodies were detected on average in 46.5 % of samples [78]. The figures increased from 29. 7% in cows of the 1st lactation to 58.9 % in cows of ≥ the 4th lactations [78].

Since 2000 in Canada, up to 37.2 % of cows and 89.0 % of herds have been reported to be BLV-positive [79, 80-82]. Leukemia infection is also widespread in China and Japan with seroprevalence, reaching in some herds of dairy cattle 49.1 and 40.9 %, respectively [82]. Less than 6 % of cattle were infected in Mongolia (3.9 %) and Cambodia (5.3 %) [82].

It should be noted that the status of zones (states) and herds free of BLV

is determined by the sanitary requirements for international animal and livestock product trade set forth in the "Sanitary Code of Terrestrial Animals" approved by the OIE [83]. These are territories where, within 3 years, 99.8 % of herds are BLV-free, and control of pathological material from animals with suspicion for lymphosarcoma is carried out. To maintain the status of a BLV-free territory, annual serological monitoring is performed, covering up to 99 % of the livestock/ All requirements for imported livestock and genetic resources are also mandatory.

Zoonotic and possible anthropozoonotic potential of BLV. Functional and structural similarity of BLV with causative agents of human T-cell leukemia (HTLV-I, HTLV-II) and T-lymphotropic viruses of monkeys, which tend to overcome the species barrier and, under experimental conditions, provoke an infectious process in sheep [84, 85], rabbits, pigs, and monkeys [29, 86, 87], is the reason for social significance of CEL [88]. One of the earliest and most cited works of McClure et al. [87] described the development of erythroleukemia and pneumonia (*Pneumocystis carinii*) in two out of six chimpanzee infants who, from birth, ate unpasteurized milk from cows naturally infected by BLV. Chimpanzees died at 34 and 45 weeks of age after an illness that lasted 5 to 6 weeks and was characterized by lethargy, anorexia, leukocytosis, anemia, and progressive pneumonia. Blast and immature myeloid cells were found in the bone marrow and peripheral blood of the dead animals [87].

Noteworthy are the findings of Soviet scientists reported in the early 1970s on the development of a neoplastic process in calves experimentally infected with the blood of a person with leukemia. The presence of common antigenic determinants in the organs of people and animals with leukemia has been proven [26].

In 1981, summarizing the accumulated data, Burridge [38] concludes that there are no epidemiological or serological findings that indicate that BLV can infect humans.

The studies were continued, as the presence of BLV-infected cells in the milk of most naturally infected cows indicates that humans are often exposed to this pathogen when ingested orally. The interspecies BLV transmission to rabbits by direct injection into the bloodstream or through the gastrointestinal tract has been proven [29], which confirms the infectious properties of milk from cows with CEL and indicates the potential danger of deinking row milk consumption for humans. Molecular methods revealed the BLV *gag* gene in 49 % of the samples of raw milk and beef [15]. This was the first study to highlight the presence of *gag* gene in food and confirm the presence of viral DNA in raw milk. Since milk pasteurization completely inactivates BLV, the possibility of human infection through milk should be studied, first of all, among livestock breeders working with BLV-infected cows and consuming unpasteurized milk [38, 89, 90].

Extensive epidemiological studies carried out in the late 20th and early 21st centuries in the USA, Denmark and Sweden failed to demonstrate a link between human leukemia and bovine leukemia. Serological studies also did not detect antibodies to BLV in people with various possible exposure to the pathogen [38].

The absence of BLV-specific sequences in 157 cases of acute lymphoblastic leukemia in children with lymphoma (USA) [91] and in 517 cases of human leukemia and 162 patients with lung cancer (Korea) [92] provided additional evidence that BLV was not an etiological factor in human hemoblastosis.

Concerns about human infection with BLV have re-emerged from the findings of Buehring et al. [93] who found reactivity to the BLV p24 protein in 74 % of the examined human sera. The authors argued that the serological methods used in the original studies were not sensitive enough to detect BLV-specific antibodies in humans. Although less than 10 % of people with specific antibodies

report direct contact with cows or their biological products, the authors conclude that antibodies in humans could be a response to oral exposure to heat-denatured virus in food or resulted from direct human infection with this pathogen [93]. It was also found that sera from people infected with HTLV-1 and HTLV-2 cross-react with p24 BLV due to a common epitope [37].

Another evidence of the possible transmission of the BLV from cattle to humans was the PCR detection of virus sequences in 44 % of breast tissue samples. The most striking discovery was the immunohistochemical detection of BLV protein p24 expression in the secretory epithelium of the mammary gland [89]. The analysis showed that the number of BLV sequences in samples from patients with breast cancer is twice as in sections of normal breast tissue. The authors concluded that the presence of BLV in breast tissue was associated with breast cancer [89]. Retro-transcribed BLV DNA was found in 40 out of 50 women (80 %) with breast cancer. When comparing paired breast tissue samples collected with an interval of 3-10 years from patients in whom the first sample was diagnosed as benign and the second as malignant, BLV was found at the first examination in 74 % of women in benign breast tissue [89]. This is consistent with the assumption of a causal relationship between BLV infection and cancer development. It is also noted that the women with BLV proviral DNA in the mammary gland and no history of cancer accounted for 41 % [89].

Buehring and colleagues reported on the detection of BLV proviral DNA in 38 % of human leukocytes detected by PCR analysis and sequencing of genomic proviral DNA. IgG antibodies to BLV were detected in 32 %, IgM in 58 %, and IgA in 32 % of the examined persons [90]. However, there are also reports that antibodies to BLV and its genomic sequences are not detected in healthy women and women with breast cancer [16, 94]. Studies of more than 3700 human malignant tumors, including 810 breast adenocarcinomas, using RNA sequences did not confirm previous data on BLV expression in breast tissue [13].

Products from BLV-infected animals. A large body of data has been accumulated on metabolic changes in animals infected with BLV. During infection, the metabolism of tryptophan, the critical essential acid is disrupted, which leads to the accumulation of dangerous endogenous metabolites. E.g., free tryptophan, indole and anthranilic acid increase 4-8-fold in amount and are deposited in the organs of the immune and hematopoietic system (lymph nodes, spleen, liver), mammary gland, lungs, and kidneys [68, 95]. It has been established that milk from leukemic animals differs from the milk of healthy animals in terms of physicochemical, bacteriological (lysozyme), technological parameters and mineral composition. In C57 mice, drinking pasteurized milk and heat-treated meat from ID-positive cows led to changes in the blood cell composition [96]. Veterinary and sanitary examinations classify meat and slaughter products from BLV-infected animals as conditionally suitable raw materials, which requires special processing and veterinary control to ensure the biosafety of livestock products [27, 68, 97, 98].

Thus, bovine leukemia (cattle enzootic leukemia), a dangerous chronic oncogenic infectious disease, is caused by the bovine leukemia virus (BLV), a member of the *Retroviradae* family. Many countries are officially recognized as free of BLV, nevertheless, its eradication is still a problem. Analysis of the available data allows us to make an unambiguous conclusion about the increased risk of products from BLV-infected cattle for human health. Despite the lack of convincing evidence of BLV pathogenicity for humans, concerns about the etiological role of this virus in the onset of human cancer requires further in-depth research and improved control over this common infectious retroviral proliferative disease

common in livestock farms.

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