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# ADVANCES IN BOVINE LEUKEMIA[1, 2]

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*Bovine leukemia is a worldwide disease affecting cattle of all breeds. This article provides a timely review of the disease, the virus implicated as its causative agent, and the possible public health significance involved.*

## Introduction

Bovine leukemia (lymphosarcoma) is a malignant neoplastic disease of the lymphoreticular system which affects cattle of both sexes and all breeds. The adult form, which occurs predominantly in animals over five years of age, is by far the most frequent in most countries (*1,2*).

Lack of suitable statistics makes it very difficult to determine the incidence of the disease in the United States and the countries of Latin America. However, data published by the United States Department of Agriculture show that leukemia is responsible for the condemnation of 19 out of 100,000 whole carcasses in federally inspected plants (*3*). This information is based only on the observation of gross lesions and probably does not reflect the real incidence of the disease. According to statistics of the U.S. Federal Meat Inspection Service (*4,5*), there has been a steady increase in the frequency of bovine leukemia.

The adult form of the disease has a strong tendency to aggregate in certain areas and herds, and it is therefore also known as "leukemia (or leukosis) enzootica bovis" or "endemic leukosis." In many of the areas and herds with a high incidence of the disease it is also commonly observed that a high percentage of the cattle which are not sick have a persistent elevation in the peripheral blood lymphocytes (*6–8*). Several "hematological keys" have been developed for diagnosis of this condition. Such persistent lymphocytosis is often confused with the disease, even when it is benign and seldom evolves toward leukemia (*6,7,9,10*).

## Bovine Leukemia Virus

Recently, a leukemogenic virus which is closely associated with bovine leukemia was discovered and characterized. This virus, known as the bovine leukemia virus (BLV) belongs to the C-type oncornavirus (oncogenic RNA virus) group, which also includes the leukemia viruses of other species.

The existence of BLV was suggested initially by the observation of structures resembling mature C-type particles in bovine lymphoid cultures (*11–13*). The viral nature of these particles was first demonstrated by ultrastructural studies carried out in our laboratory (*12–14*). Subsequent immunological investigations (*15,16*) permitted us to establish the identity of BLV, demonstrating

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[1] Also appearing in Spanish in the *Boletín de la Oficina Sanitaria Panamericana*, 1978.

[2] Paper presented at the X Inter-American Meeting, at the Ministerial Level, on Foot-and-Mouth Disease and Zoonoses Control (14-17 March 1977) and published in *Animal Health Programs and Trends in the Americas, 1977* (PAHO Scientific Publication No. 358, 1978).

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that it is an indigenous bovine virus and not a contaminant originating in another species.

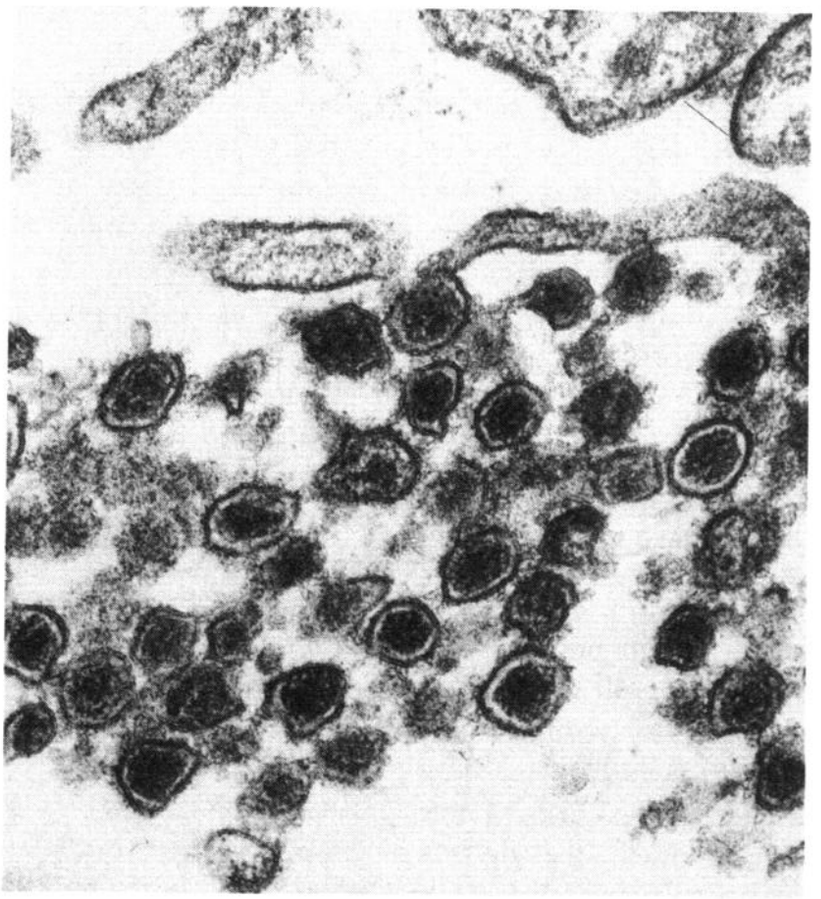
BLV has many of the structural (*11–13*) and physicochemical (*17, 18*) characteristics of the C-type leukemia viruses of other species (Figs. 1, 2). However, BLV differs serologically from all these viruses, as well as from other common bovine viruses (*16, 19, 20, 22*).

**Diagnosis of BLV Infection**

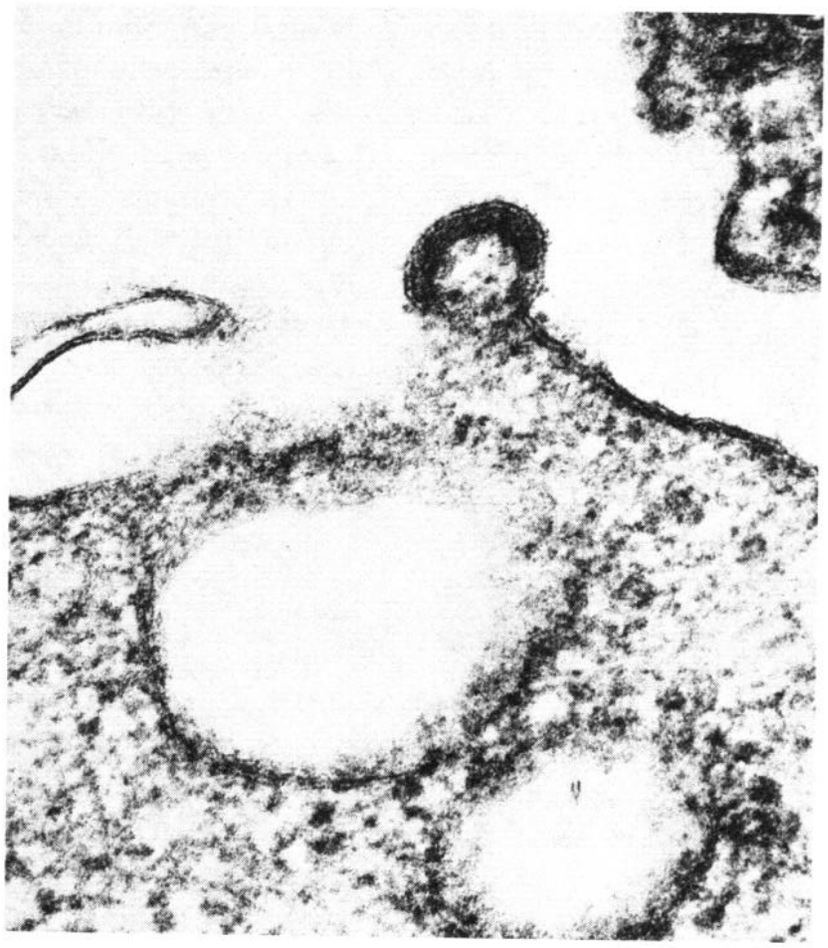
Recently, we have developed a highly sensitive and specific in vitro infectivity assay which permits the detection of BLV in animals as well as in cell cultures (*22, 23*).

BLV infection can also be diagnosed by demonstrating serum antibodies against the virus. Several serologic methods have been developed for this purpose, the most sensitive ones being the seroneutralization (*23, 24*), radio-immunoprecipitation (*20, 27*), and immunofluorescence (*15, 16, 25*) tests. Antibodies against BLV can also be detected by the agar gel immunodiffusion (AGID) test, using as antigen the major internal viral protein (*16, 26*). This test is relatively simple but yields negative results for a high percentage of infected cattle that are positive in other serologic tests (*9, 24, 27*). Therefore, because of their limited sensitivity, the immunodiffusion test is not indicated in situations where it is important to rule out BLV infection, such as in eradication programs or in selecting breeding stock and animals for export.

It has been recently reported (*28*) that the sensitivity of the immunodiffusion test can be increased by using as antigen a glycoprotein which is present in the supernatant fluids of a fetal lamb kidney cell line experimentally infected with BLV (cell line FLK-



Electron micrograph of a cluster of BLV particles (× 90,000)



Electron micrograph of a BLV particle budding from the cell membrane (× 140,000).

BLV). However, since recent studies by Dr. R. Schultz (Cornell University, Ithaca, New York) and Dr. M. Van der Maaten (National Animal Disease Center, Ames, Iowa) have shown that cell line FLK-BLV is also infected with the bovine viral diarrhea virus, the specificity of the immunodiffusion test with the glycoprotein antigen must be carefully evaluated.

## BLV Infection, Lymphosarcoma, and Persistent Lymphocytosis

Research conducted on well-characterized herds has demonstrated that 60 per cent of the BLV-infected cattle are asymptomatic carriers; that is, they are negative according to the hematologic keys (*9, 25, 29*). These carrier animals can be identified by the infectivity assay or by a sufficiently sensitive serologic test.

BLV infection is common in the cattle population of the United States, particularly in dairy herds (*9, 29–31*); according to our preliminary studies, it is common in several Latin American countries as well.

## Natural Mode of Transmission of BLV

BLV is transmitted predominantly by contact and occasionally *in utero* (*32, 33*). It is probable that tabanids, ticks, and other hematophagous insects play an important role in the spread of the virus. It is still unclear whether or not BLV is transmitted through the sperm. The transmission of the virus through milk has been suggested by the observation of structures resembling C-type virus particles in milk from cows in a high-incidence herd (*34*). In addition, it has been shown that two out of six chimpanzees fed from birth with milk from infected cows developed leukemia (*35*). In this study, however, it was not possible to carry out the

tests required to conclude with certainty whether or not the virus was responsible for leukemia in the two chimpanzees.

### Possible Implications for Man

We have recently obtained preliminary evidence of permanent infections in chimpanzees that were inoculated with the virus at birth. It has also been conclusively demonstrated that the virus can readily infect human or other primate cells in vitro (*21, 22*). These findings have raised the possibility that BLV represents a threat to human health. Thus far there is no direct evidence in favor of this possibility, but studies with sensitive techniques which will permit its critical evaluation have not yet been carried out.

### Conclusions

The economic importance of bovine leukemia is determined in part by the number of animals that die with the disease. Although in general the incidence of bovine lymphosarcoma does not seem to be very high, it is important to consider existing evidence that the disease is increasing steadily, at least in the United States. In addition, the tendency of the disease to aggregate in certain herds may result in important ecomonic losses for some farms. In fact, there are several countries, most notably Denmark and Germany, where the disease resulted in complete destruction of many multiple-case herds.

From the economic point of view it is quite possible that BLV infection will be a more serious problem than that of the disease itself, particularly if future studies show that this agent is infectious for man. In addition, the virus could cause important losses for countries that export cattle or sperm. In this regard, it is worth noting that several countries already request evidence that imported cattle are BLV-free.

The fact that BLV is transmitted predominantly by contact indicates that eradication of BLV infection, and therefore of the disease, is feasible through programs based on isolation of the infected animal. As was mentioned before, there are already several highly sensitive diagnostic methods which can be standardized and simplified for large-scale use. The development of a vaccine is, of course, a fundamental element in these programs and constitutes one of the research objectives of our laboratory.

## SUMMARY

Bovine leukemia, a malignant neoplastic disease, affects cattle of both sexes and all breeds. Statistics of the U.S. Federal Meat Inspection Service show a steady rise in the frequency of bovine leukemia in the United States.

A leukemia-causing virus closely associated with bovine leukemia was recently discovered and characterized. Known as the bovine leukemia virus, it belongs to the C-type oncornavirus group—which also includes the leukemia viruses of other animal species. A highly sensitive and specific *in vitro* infectivity assay has been developed which permits detection of this virus in animals as well as in cell cultures. The identification of cattle infected with BLV can also be accomplished by serologic test.

Some experiments have raised the possibility that the virus might pose a threat to human health. Thus far, however, there is no direct evidence to support this theory. Studies with sensitive techniques which will permit critical evaluation of this question have not yet been carried out.

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## AWARDS OFFERED IN MEMORY OF NATHALIE MASSE

Two biennial awards—a fellowship and a research prize—are now being given in honor of Dr. Nathalie Masse, former Director of Teaching at the International Children's Center in Paris. Dr. Masse, who died in 1975, held this position for 18 years and was an important contributor to the international improvement of child health. In 1976 Dr. Masse's friends endowed a memorial fund to perpetuate her memory, which led to creation of the present fellowship and international prize.

*The Nathalie Masse Research Fellowship,* granted in even-numbered years, has just been awarded for the first time for research on nutrition education in a socially deprived area of South America. Like this fellowship, the one to be awarded in 1980 will be geared to helping young research workers with projects addressing problems in social and preventive pediatrics.

*The International Nathalie Masse Prize,* awarded in odd-numbered years, will be given for the first time in 1979. Intended as compensation for an original work on child health by an institution or an individual under age 40, it also seeks to encourage studies by young professionals and researchers.

Winners of the fellowship and prize are chosen without regard to nationality. Detailed rules governing these awards, as well as application forms, can be obtained by writing to the Memorial Committee, Centre International de L'Enfance, Château de Longchamp, Bois de Boulogne, 75016 Paris, France.