

**ADVANCES IN
VETERINARY SCIENCE AND
COMPARATIVE MEDICINE**

Volume 24

ADVANCES IN VETERINARY SCIENCE AND COMPARATIVE MEDICINE

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Volume 24

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PREFACE

This volume of *Advances in Veterinary Science and Comparative Medicine* covers recent progress both on a number of economic diseases such as brucellosis, coccidiosis, and bovine lymphosarcoma, and on biocontrol in veterinary entomology. In addition, other timely subjects such as chromosome analysis, canine and feline reproduction, stress in animals, and the use of whole body autoradiography in toxicological studies are presented.

The complexities of the epidemiology of bovine brucellosis, particularly regarding the move of producers toward larger herds, are evident in increased exposure potential. The economic impact of coccidiosis has been poorly defined in the past. These protozoan diseases affect all classes of animals by producing either death or morbidity and may be of the greatest economic significance. Current technology does not allow for the reliable prediction of what the expected life of a new anticoccidial agent will be before resistance becomes a field problem. Unfortunately, little is known about both the biochemical mode of action of most anticoccidials and mechanisms of drug resistance. This situation only magnifies the need for research in this area.

The recent observation that leukemia virus infections are widespread has created a new interest in its mode(s) of transmission. It is apparent that this infection is now considered a most valuable and unique model system for studies on etiology, pathogenesis, and prophylaxis of leukemia in mammals, including man.

A number of microorganisms are presented in the chapter on biocontrol of arthropods and snails that are known to produce invertebrate pathology. These represent the best prospects for product development. General agreement exists for the effective use of microbial control only as part of an integrated control complex designed for both health and environmental acceptability.

New banding techniques as described now allow for definite identification of individual chromosomes and the diagnosis of chromosomal variations. Such cytogenetic techniques will soon allow for the determination of individual gene positions and systems. It is also evident that only through understanding the reproductive cycle by investigating new approaches to fertility control in dogs and cats can the overpopulation of these species be controlled by man. The measurement of the more commonly encountered stresses in animals during adverse situations is also reviewed. Organizing mechanisms enabling animals to respond homeo-

statically to stressors are dependent upon precise interactions between the nervous and endocrine systems.

The recent use of whole body autoradiography has allowed for new approaches to the study of maternal-fetal metabolism and teratology. It is now apparent that this technique ideally should be utilized early in the study of the toxicology of new molecules.

Appreciation is expressed to the staff of Academic Press for their outstanding help in compiling this volume. Without the continued advice and dedicated interest of the Advisory Board, such quality reviews would not be available. Special gratitude goes to Dr. Charles F. Simpson for his abiding interest and assistance in manuscript review during this past year.

The death of our beloved Senior Editor, Dr. Carl A. Brandly, represents a major loss to comparative medical science. His lifetime was dedicated to the scholarly pursuit of excellence in all of his many professional activities. Carl will be dearly missed as he leaves a lasting influence on both the veterinary medical profession as well as his many friends.

C. E. CORNELIUS



CARL ALFRED BRANDLY
1900-1979

CARL ALFRED BRANDLY 1900—1979

Carl Alfred Brandly was born on May 23, 1900, in Fairview, Kansas. He received his degree of Doctor of Veterinary Medicine from Kansas State University in 1923 and his Master of Science degree from the same institution in 1930. After receiving his veterinary degree, Carl was employed for four years by a company producing veterinary biologics and for a short period held a position with the United States Department of Agriculture. He was appointed Assistant Professor of Bacteriology at Kansas State in 1927, where he taught students in the veterinary medical curriculum and carried out research and diagnosis in poultry diseases.

Nine years later Carl moved to the University of Illinois to accept the positions of Associate Professor of Veterinary Medicine and Pathologist for the Illinois State Department of Agriculture. In 1939 he became Senior Pathologist at the United States Regional Poultry Laboratory at East Lansing, Michigan. During World War II he was Research Specialist and Director of the Huntington War Research Program in Exotic Diseases at Harvard Medical School in Boston. When this assignment was completed in 1946, he moved to the University of Wisconsin in Madison, where he was Professor of Veterinary Science and Chairman of the Department of Veterinary Science. In 1956 he was appointed Dean of the College of Veterinary Medicine at the University of Illinois where he remained until retirement in 1968.

From the beginning of his career and despite many other demanding responsibilities, Carl's primary interest was research on animal diseases. He communicated this interest with great dedication to his students and colleagues. Many of his working hours were devoted to gaining federal and state support for investigations in his department and college. His research was concerned chiefly with diseases of poultry and the epidemiology of animal diseases. Seizing on Goodpasture's observation that fowl pox could be cultivated in chicken embryos, Carl Brandly studied the growth of equine encephalitis, infectious laryngotracheitis, fowl pest, and Newcastle disease in embryonating eggs. He was the first to use egg-grown virus to immunize animals against virus diseases, in 1934. His work with Newcastle disease and fowl plague laid the foundation for subsequent studies. With his associates, he demonstrated that immunity was transmitted transovarially in these diseases and established the significance of yolk-borne immunity in the epizootiology of other avian dis-

eases as well. His studies also include the first investigation in the United States of a living Newcastle disease vaccine. He also participated in the development of a new, effective, and safer distemper vaccine for ranch foxes.

His work on botulism in mink led to management methods that reduced the problem; his studies on lead poisoning in pheasants and vesicular stomatitis in cattle were directed to understanding the epizootiology of the disease. He considered prevention of disease to be primarily a problem of management, with the use of vaccines as valuable but supplemental measures. In this belief that vaccines and drugs often lack effectiveness outside a rational program of animal management, Carl Brandly was clearly ahead of his time. His research findings are described in over a hundred papers on which he was author or coauthor.

One of Carl's administrative policies as Dean of the College of Veterinary Medicine was that all teachers should be engaged in research projects to sharpen their teaching skills. He believed strongly that conduct of research without public communication of the results was unethical. Furthermore, he emphasized that such communications were not to be considered casually. All of his students and many of his colleagues remember manuscripts that he edited and returned to them with more editorial notations than text. One new graduate student protested to him, "But Dr. Brandly, this passage that you corrected is the one you rewrote in the last draft." Dean Brandly replied, "I have never seen a passage of mine or of anyone else that could not be improved by revision."

It was natural that Dean Brandly should be selected (first with Jungheer and later with Cornelius) to edit *Advances in Veterinary Science and Comparative Medicine*, a serial publication now recognized throughout the world.

In order to emphasize the diseases of animals transmissible to man, Dr. Brandly established the Illinois Center for Zoonoses Research, where research and graduate training in the zoonoses were the main objectives. He instituted interdisciplinary cooperation with other colleges and departments of the University. During his tenure, leaders in all aspects of medical and biological science came together at the University of Illinois to formulate programs for improving the health of living beings, regardless of species. In this, he was again far ahead of his time.

His accomplishments have been recognized by Kansas State University with the distinguished alumni award in 1955, by the Illinois State Veterinary Medical Association with the "Veterinarian of the Year" award in 1958, and by the American Veterinary Medical Association with its Twelfth International Congress Prize in 1966. He received an honorary degree from the Tierärztliche Hochschule, Hannover, Germany, and was

honored by the Royal College of Veterinary Surgeons, London, England. The national organization of Research Workers in Animal Diseases dedicated its 1978 meeting to Carl Brandly in recognition of his contributions to veterinary research.

Carl Brandly served as consultant to many national and international agencies. He was a member of several special commissions, including two White House Conferences, and he went on missions to Russia, India, and South America. He was a consultant to the Colleges of Veterinary Medicine at both the University of Florida and Kansas State University. The Microbiology Study Section of the National Institutes of Health, the U.S. Foot and Mouth Disease Committee, the War Research and Development Board, and the U.S. Public Health Service all made use of his services. Another of his responsibilities was membership on the Board of Consultants of the Plum Island Animal Disease Center of the USDA, which was established to protect the United States from foreign animal diseases; in this, as in all other consultancies, he served with distinction.

Carl had a great interest in sports, particularly hunting, football, and golf. He was on the varsity football team at Kansas State, playing half-back on both defense and offense, and played professional football after graduating. His many friends enjoyed with him his enthusiasm for the game of golf.

Carl's outstanding work in teaching and research, his vision, and his leadership helped to develop the College of Veterinary Medicine, University of Illinois, into a leading professional and graduate institution. His inspiration and guidance in the birth and development of America's first Center for Zoonoses Research attest to his selfless dedication to the improvement of animal and public health. The profession of veterinary medicine and people throughout the nation who are concerned with animal and human health will long reap the benefits of Carl Brandly's devoted service.

Many students and colleagues are indebted to Carl for his friendship and unwavering support. He habitually shared his knowledge for their development in teaching, research, and public service.

Perhaps even more importantly, all of us have felt the strength of his human qualities. He was a devoted husband and father, a good neighbor, and a concerned citizen. Carl Brandly's wisdom and friendship will continue to live within all of us.

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I. Introduction

Bovine lymphosarcoma, presently recognized as the most common neoplasia of cattle, was described for the first time by German workers in the last part of the nineteenth century. German workers also appear to have been responsible for the initial studies on the demographic aspects of bovine lymphosarcoma and, in the early 1900s, reported its spread along the Baltic seacoast. In subsequent years it became apparent that the disease was prevalent in most of Europe, where it was the cause of important economic loss, as well as in North and South America and in the U.S.S.R. The observation that lymphosarcoma often occurs in striking familial aggregations was interpreted originally as evidence for the heritable nature of the disease. However, this view began to dwindle during the 1950s as the viral etiology of the avian and murine leukemias became well established. Discovery of a mammalian leukemogenic virus and the observation that the predominant form of bovine lymphosarcoma has an enzootic occurrence led European veterinarians to speculate that the disease in cattle also has a viral etiology. Investigators in several countries were thus motivated to undertake extensive studies aimed at uncovering the virus responsible for bovine lymphosarcoma. These efforts culminated in the discovery and characterization of an indigenous bovine leukemogenic virus which is now regarded universally as the causative agent of the enzootic form of the disease. It is also well established now that, as in many other infectious diseases, infection with the virus alone is not enough to cause lymphosarcoma, but that host genetic constitution plays an essential role in determining whether or not an infected animal will develop the disease. Thus, although bovine leukemia virus infection is widespread in the cattle population of most countries, tumor development is a relatively rare event.

In light of recent developments it has become apparent that bovine

lymphosarcoma and bovine leukemia virus infection are not only important problems in veterinary medicine, but also provide a most valuable and, in some respects, unique model system for studies on the etiology, pathogenesis, and prophylaxis of leukemia in mammals, including man.

Although most of the vast numbers of papers published since the discovery of the bovine leukemia virus have been summarized in recent articles, a need still exists for a critical evaluation and interpretation of the new information on this system. This article represents an attempt to accomplish this objective and, most particularly, to identify those solid contributions on which future progress on this subject will depend.

II. The Disease

1. DEFINITIONS—CLINICOPATHOLOGICAL AND EPIDEMIOLOGICAL PROPERTIES

Bovine lymphosarcoma is a systemic malignancy of the lymphoreticular system. With the possible exception of ocular squamous cell carcinoma, it is the most frequently diagnosed neoplastic disease of domestic cattle. It affects both sexes and all breeds, but many more cases have been reported in dairy cattle (Marshak *et al.*, 1962; Theilen *et al.*, 1963; Bendixen, 1965b; Jarrett *et al.*, 1966; Anderson and Jarrett, 1968).

Following Dunn's classification (1954), workers in comparative cancer research have used the term leukemia (leukos, white; haima, blood) in a broad sense to encompass all systemic malignant processes of the blood-forming tissues, irrespective of whether or not there is an increase in the number of peripheral blood leukocytes. Accordingly, the disease in cattle is also referred to as bovine leukemia, even though the blood picture in most cases is normal.

The term leukosis, which means proliferation of the leukocyte-forming tissue, was originally used by Ellermann and Bang (1908) as a general designation for both leukemic and pseudoleukemic disorders of the leukocyte-forming tissues of chickens. Later, Dobberstein (1934) proposed this term for the corresponding disorders of cattle, namely, lymphosarcoma and persistent lymphocytosis, the latter a benign condition that frequently occurs in association with the adult form of the disease.

Two main forms of bovine lymphosarcoma are recognized:

(1) *The enzootic form.* This is by far the most frequently encountered type in the United States (Marshak *et al.*, 1962; Perman, 1962; Theilen *et al.*, 1964; Sorensen *et al.*, 1964; Marshak and Abt, 1968b), continental Europe (Dobberstein, 1934; Schöttler and Schöttler, 1934; Fornter, 1953;

Gotze *et al.*, 1954; Olson, 1961; Bendixen, 1965b), and Venezuela (Marin *et al.*, 1978). Typically, this form occurs in geographic and herd aggregations (Bendixen, 1965b; Reisinger, 1963; Marshak and Abt, 1968b; Marshak *et al.*, 1966). Herds may be classified as multiple-case herds, lymphosarcoma-free herds, single-case herds, and contact herds. The criteria for defining these various herd categories have been described by Marshak (1968). Enzootic lymphosarcoma is seen almost invariably in cattle older than 3 years and, therefore, is often referred to as the adult form of the disease. This form has a peak incidence in cattle between 5 and 8 years of age and often occurs in familial aggregations (Schaper, 1938; Karlson, 1942; Weischer, 1944; Henrickson and Olson, 1962; Marshak *et al.*, 1962, 1966; Bendixen, 1965b; Croshaw *et al.*, 1963; Marshak and Abt, 1968b).

The disease is characterized by a proliferation of neoplastic lymphocytes that results in the formation of discrete solid tumor masses and/or the diffuse infiltration of various tissues and organs. The neoplastic process almost invariably involves the lymph nodes, but the abomasum, heart, uterus, and other organs are frequently affected. Clinical manifestations depend on the particular organ(s) involved, the rate of tumor growth, and the degree of dissemination of the neoplastic process. The typical clinical picture is one of emaciation, weight loss, anemia, decreased milk production, and enlargement of one or more peripheral lymph nodes. Lymph nodes in the pelvic area are also frequently involved and infiltration of tissues in the orbital cavity may cause exophthalmos. Signs of circulatory, respiratory, digestive, reproductive, urinary, and neurological disorders may occur when these specific tissues are involved. Only one-third of the cases show true leukemia, i.e., an increase in the number of blood leukocytes. In these cases there is usually a high proportion of atypical lymphoblasts with abnormal karyotypes in blood (Marshak *et al.*, 1962; Hare *et al.*, 1967).

The disease is almost invariably fatal, with death occurring several weeks or months after the onset of clinical signs. Cattle with heart involvement may die suddenly while in apparent good health.

Hare *et al.* (1967) showed that 75% of cattle with the adult form of the disease have chromosomal abnormalities. While the disease is not characterized by a consistent chromosomal change, neoplastic cells obtained from peripheral blood and from different tumor sites in each individual case show the same abnormal karyotype. This suggests that the disease is unicentric in origin. As in human lymphosarcoma, the most conspicuous chromosomal change in cattle is hyperploidy.

It has long been recognized that herds with a high incidence of the adult form of lymphosarcoma often contain many clinically normal cattle with *persistent lymphocytosis* (PL) (Gotze *et al.*, 1954; Marshak *et al.*,