A Review of Bovine Bluetongue

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Introduction

Bluetongue (BT) is an insect-transmitted, virus disease of domestic and wild ruminants. The disease was first described in South Africa, but has subsequently been recognized in a number of other countries, including the United States.[1,2] The first confirmed cases of BT within the United States were among sheep in California in 1952, although the disease had been earlier suspected in Texas.[3,4] The first isolate of bluetongue virus (BTV) from United States cattle came from a blood sample collected in Oregon during 1959.[5] Serological surveys indicate BTV infection is now widespread within the United States, most particularly in the South, West and South West states.[6-8]

Bluetongue virus is a member of the family Reoviridae, and the prototype virus of the genus orbivirus.[9] Twenty-one serotypes of BTV are currently recognized worldwide, and serotypes 10, 11, 13 and 17 are present in the United States.[10,11]

Transmission

Bluetongue is not contagious, rather it is usually transmitted by biting gnats. *Culicoides variipennis* is considered the most important vector within the United States.[12] Bluetongue virus must replicate within the gnat before it can be transmitted to a vertebrate host and after the gnat feeds, there follows an incubation period of some 10 days before the gnat can transmit the virus. *C. variipennis* is able to transmit BTV from infected cattle to sheep and vice versa.[12] *C. pallidipennis,* an important vector of BTV in Africa and the Middle East, exhibits a distinct host preference for cattle rather than sheep. Infection of gnats is usually lifelong, in which time individual insects may feed on 3 or 4 different hosts. Outbreaks of bluetongue in sheep often coincide with the peak vector season, which is usually late summer and fall. The gnat prospers in moist, warm conditions and succumbs to extremes of either cold or dryness. Thus outbreaks often cease after the first frost of the season. Shallow water contaminated with fecal material is favored as a breeding site for the gnat, particularly the still, muddy water about the margins of ponds, small streams, ditches, lagoons, sewage ponds, or water troughs.

Although culicoides are very important as transmitters of infection in a local area, viremic animals transported over long distances serve as a new source of infection when introduced into an area.[8] Of particular importance in this respect are cattle which may appear clinically normal; however, they may be viremic for 5 to 8 weeks. These infected animals if introduced into an area with a susceptible gnat population may readily introduce new virus or new viral serotypes into a susceptible population. If culicoides are active when the infected animal arrives, the gnats are available to biologically transmit virus between infected animals and in susceptible populations. Movement of animals during bluetongue season represents a very important means of disseminating BT infection.

Bluetongue virus has been isolated from the semen of infected bulls which is a cause of concern in the artificial breeding industry and to bluetongue free countries that import bovine semen as BTV can be transmitted to non-pregnant cattle by intra-uterine inoculation of virus.[13] Recent studies indicate that viral shedding in semen occurs only during the time that the bulls are viremic. This may last as long as 40 to 50 days following the initial infection.[15]

Epizootiology

BT is a seasonal infection with the limits associated with the activity of culicoides.[6,8] In the southern states these insects may remain active for long periods, whereas the more northern areas, infection occurs in the late summer and fall. In most of California, infections begin in July and continue until December or until the first frost. Similar patterns of infection have been observed in other western states. As a group, cattle appear to peak out with BT infection before the other species.[6] Epidemiological surveys have not confirmed the hypothesis that cattle are the overwintering host of bluetongue virus.[6,8]

Of the four recognized sero-types of BTV known to cause infection in the U.S., serotype 11 appears to be the most con-

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sistent cause of infection. Of the total number of 278 bovine BTV isolates, serotype 11 accounts for 51%, BTV-13, 26%; BTV-17, 17%; and BTV-10, 6%. In about one-third of the herds from which BTV was isolated, two or more BTV serotypes were isolated from different animals.[6] Often one serotype will preceed another serotype in a herd. In some instances 2 serotypes of virus were isolated from an animal at the same bleeding indicating dual infection.[40]

Infection of Cattle

Bluetongue virus infection of cattle is important for at least four reasons: a) Outbreaks of 1) infection and 2) clinical disease among infected cattle; b) Infected cattle may be reservoirs of BTV; c) Reproductive losses among pregnant cattle; d) Restrictions placed on importation and exportation of ruminants. In order to better define the biology of BT in cattle, we arbitrarily divide it into 1) subclinical infection and 2) bluetongue disease.

1. Subclinical Infection

When considering the clinical signs of BT in cattle, it must be emphasized that most infections are inapparent. This is most graphically illustrated by a popular method of BT control employed by South African sheep farmers: Cattle are grazed in close proximity to sheep because *Culicoides pallidipennis* prefers to feed on cattle rather than sheep. Apparently this technique reduces the incidence of ovine BT yet cattle losses to BT are not sufficient to discourage the practice.

As early as 1905 it was recognized that cattle could become infected with BTV, but until the descriptions of BT in cattle by Bekker *et al* in 1934, BTV was thought to produce overt disease only in sheep.[16] Numerous descriptions of disease in cattle, associated with BTV infection, have followed that initial report.[2,17-21] In areas where BTV is enzootic most infections are not clinically obvious, and viremia and seroconversion may be the only evidence of infection. For instance, BTV infection of cattle in Northern Australia is widespread, but disease has not been reported in either naturally or experimentally infected cattle. BT infection of cattle is common in southern and western U.S.; however, clinical bluetongue disease is rare.

2. Bluetongue Disease

Descriptions of the acute BT disease in cattle include an initial fever and stiffness of gait, followed by hyperemia and subsequent ulceration of the nasal and oral cavities which is accompanied by profuse salivation and inanition, crusting and sloughing of the muzzle, dermal edema and vesicles and necrosis of the skin; severe coronitis and eventual alopecia.[16,18-21] Mortality is usually low but convalescence may be prolonged and milk production will fall or cease in lactating animals. A chronic ill-thrift syndrome associated with persistent BTV infection has been described. Bulls may have temporary infertility as a result of the initial infection; however they appear to recover with no subsequent loss in reproductive capacity.

A number of other diseases of cattle may mimick BT, and 2 are of particular interest. Ibaraki virus, another orbivirus, has been associated with outbreaks of severe, bluetongue-like disease among cattle in Japan. Mycotic stomatitis is a bovine disease of unknown etiology, but with clinical signs very similar to those of bluetongue. It also occurs most commonly in the late summer or fall, and outbreaks often cease after the first frost. Morbidity and mortality are low. Mycotic stomatitis has not been experimentally reproduced or transmitted, thus its relationship to BT is speculative.

Adequate descriptions of necropsy lesions in cattle with BT are somewhat lacking, perhaps because of the low mortality in affected cattle. Cattle with BT that are necropsied may have severe ulceration throughout the nasal and oral cavities, trachea, udder, interdigital space and skin, plus irregular congestion and hemorrhage in the gastrointestinal tract and some parenchymatous organs.

Studies on the pathogenesis of BT in cattle have been hampered by the difficulty encountered in experimental reproduction of the disease. The severity of disease may depend upon a number of factors, including the pathogenicity of a particular virus, the host's inate susceptibility at the time of challenge, and environmental factors such as solar irradiation.

The lesions observed in cattle with BT suggest the virus has a predilection for the skin and the mucosa of the nasal cavity and the upper gastrointestinal tract. However the pathogenesis of BT has been adequately investigated only in species other than the bovine. For instance, lesions in infected deer are secondary to small vessel thrombosis and subsequent disseminated intravascular coagulation.[22,23] Lesions in affected sheep may also be secondary to vascular lesions.

In some natural outbreaks of BT older cattle are more commonly affected than young ones. Metcalf hypothesized that BT is a hypersensitivity disease, and the disproportionate incidence of overt disease in older animals was a reflection of their increased likelihood of having experienced multiple exposures to BTV. Recent studies indicate that a hypersensitive condition can occur with BT antigens. Experimental evidence shows that once the sensitized cattle are reexposed to live BT virus of the same serotype, the cattle develop clinical bluetongue. The clinical signs appear to be the result of an IgE mediated immune disease. It has been possible to transfer to noninfected recipients through serum the skin reactive (IgE) antibody which then reacts with BT virus resulting in an immediate hypersensitivity. The clinical manifestation includes weaping, ulcerative dermatitis, vesicular and ulcerative lesions of the oral cavity, coronet, and stiffness and lameness.

b) Virus Reservoir

Cattle have been proposed to be a reservoir host for BTV for a number of reasons: viremia is often prolonged in infected cattle; Some experimental cattle infected with BTV, may develop prolonged infections; the majority of infected cattle exhibit no clinical signs of disease and mortality is

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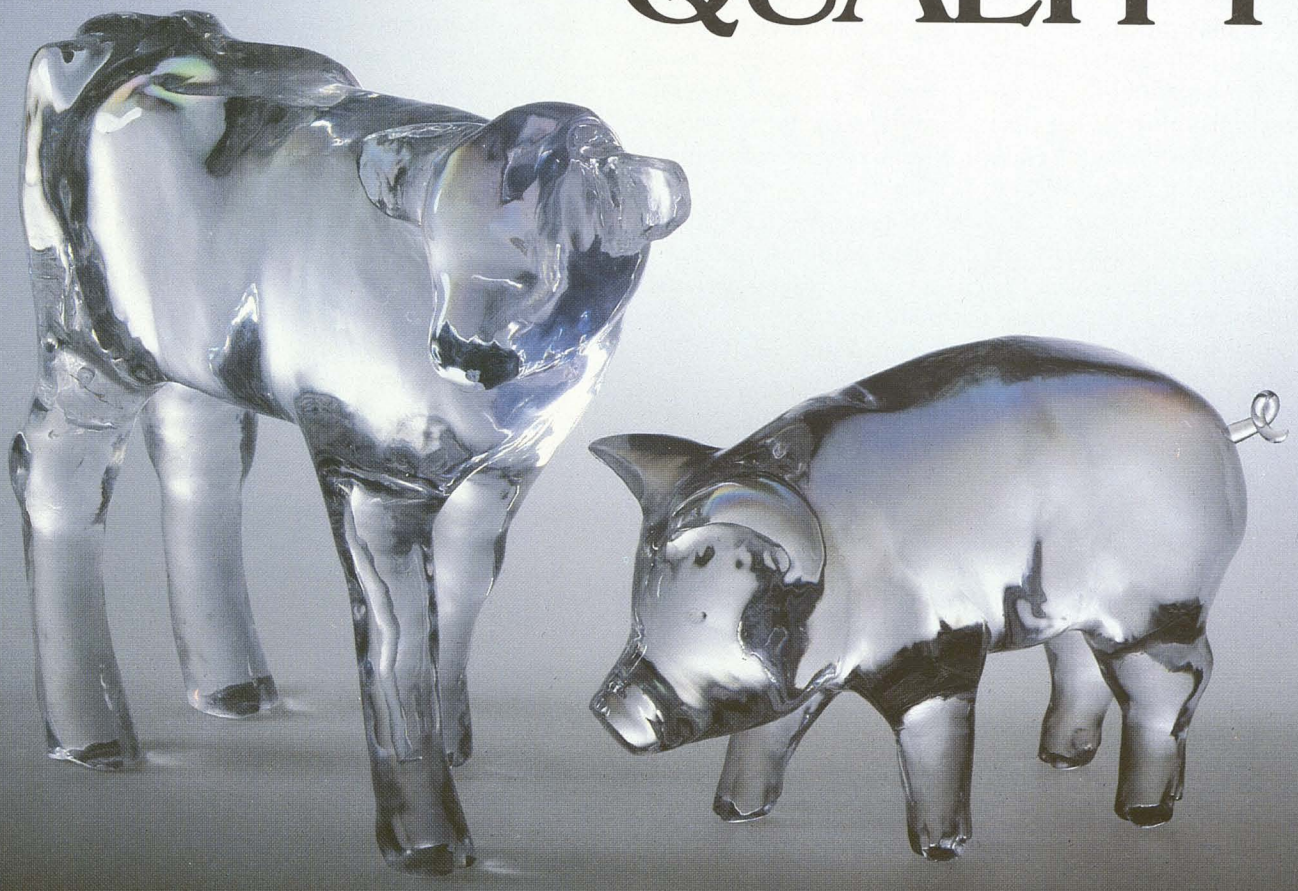

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usually minimal.[24]

Viremia

The virus is cell associated during viremia. Pini *et al* concluded that bloodborne virus was associated with the buffy coat rather than plasma, and found the spleen and mesenteric lymph nodes to be the organs most suitable for virus isolation.[25] Luedke found that washed erythrocytes contain 10 to 100 times more virus than an equal volume of cells from the buffy coat, and the plasma contained significantly less virus than either cell fraction.[26] Often when BTV was isolated from red blood cells taken from cattle, it could not be isolated from buffy coat, cells or plasma in the same blood sample. There is little agreement among investigators as to the duration of viremia in infected cattle, but to some extent this may reflect the sensitivity of the different methods used for virus isolation. Viremia is often prolonged lasting as long as 50 to 70 days. [24]

The process responsible for clearance of BTV from infected cattle is yet to be defined. Antibody alone is apparently unable to clear the virus, because infectious virus and its specific neutralizing antibody may coexist in the blood of infected animals for prolonged periods. Luedke suggested that virus circulates in a site protected from antibody.[24],[26] It is not known if virus that is associated with red blood cells is absorbed to the red cell membrane or has an intraerythrocytic location, as does Colorado tick fever virus which is also an orbivirus.

Identification of the specific response that enables infected cattle to clear BTV, is a prerequisite to the development of a logical method of prophylaxis.

Persistent Infections

Luedke *et al* reported that cows inoculated with BTV at 5 or 7½ months of gestation give birth to calves with BTV specific antibody, although virus and antibody did coexist in the blood of some calves at the time of birth.[27],[28] However, infection of pregnant heifers at gestation day 60 or 120 subsequently lead to the birth of some calves that were persistently infected with BTV and apparently immunologically incompetent to BTV.[27] Unfortunately it is not known at what stage of gestation virus actually crossed the placenta and infected the fetuses. Feeding of *C. variipennis* on a persistently infected bull was sometimes associated with a dramatic rise in the titer of circulating virus. Such an animal would be an ideal reservoir of BTV, available to vectors whenever they emerge after periods of adverse climatic conditions. However, attempts by others to experimentally reproduce similar infections have not been successful.[15] It is not known if persistently infected cattle that are immunologically tolerant to BTV occur in nature because in extensive surveys virus isolations have not commonly been made from cattle in spring, when persistently infected cattle might be expected to shower virus after exposure to the increasing gnat populations that appear at that time.[6],[8] Further, fetuses exposed to BTV in early gestation during the BT season would be delivered in Spring, and BTV has not been commonly isolated from Spring calves.

c) Reproductive Losses

Infection of pregnant cattle with BTV has reportedly caused fetal malformation or abortion, however the spectrum of such fetal aberrations has not been adequately defined and their significance is unresolved. Natural BTV infection of 2 pregnant cattle was associated with abortion of 1 animal and malformation of the fetus born to the second.[29] Experimental BTV, serotype 13, infection of 60 and 120 day pregnant heifers lead to abortion or mummification of 2 fetuses and malformations of fetuses born to some of the others. Abortion has also followed infection of cattle in an advanced stage of pregnancy, but in this outbreak virus isolation was not reported from aborted fetuses and abortion can be a sequalae of maternal viral illness rather than infection of the fetus. In view of the very limited number of reported instances in which abortion has been associated with proven BTV infection, the role of BTV in bovine abortion must be considered as dubious until more comprehensive studies are undertaken.

Bluetongue virus has been incriminated as a cause of hydranencephaly in the bovine, following either direct fetal inoculation or after transplacental transmission of virus in the course of natural infections of pregnant cattle.[30] The lesions in the brains of term calves might sometimes be mistaken for a non infectious hydrocephalus, however the real incidence of BTV-infected hydranencephaly is unknown. Of considerable significance is the fact that calves affected with hydranencephaly would not survive and thus they could not function as virus reservoirs in nature, even if they were born persistently infected. Thus hydranencephaly and prolonged persistent infection are mutually exclusive potential sequelae of infections in early gestation.

A number of other teratogenic defects have inconsistently been attributed to BTV infection in utero.[28] Malformations described include arthrogryposis, agnathia, prognathia, and gingival hyperplasia. However these lesions were mild and their relationship to BTV infection is somewhat speculative. The condition described as gingival hyperplasia is a consistent, normal finding in newborn calves.

The influence of BTV infection on early embryonic mortality is an area that requires investigation. Preliminary research in this laboratory suggests that BTV-serotypes 10, 13, and 17 cause hydranencephaly if infection occurs between 85 and 125 days gestation. If BTV does cause embryonic loss its effects are likely to be subtle and seasonal. If BTV caused any dramatic embryonic mortality, obvious differences in fertility would be expected between BTV endemic and non-endemic areas during the U.S.'s BT season of late summer and fall.

Diagnosis of Bluetongue Virus Infection

The diagnosis of BT infection is difficult because the clinical syndrome is poorly defined and it is often confused with clinical bovine virus diarrhea (BVD) and infectious bovine rhinotrachectis (IBR). The most definitive means of

diagnosing infection is by virus isolation: collection of heparinized blood samples, which are then refrigerated during shipment to the laboratory is the best means of isolating virus. These samples are then inoculated into embryonating chicken eggs. [31,32] Identification of BTV by either fluorescent antibody with anti BTV serum or serotyping of the specific viral isolates on tissue culture confirm the viral isolates as BTV.

Serological tests are used to identify those animals that have been exposed to BTV antigens; however it does not indicate that the animals are infected. In one study, 40% of the cattle from which BTV was isolated did not have demonstrable agar gel precipitating antibody.[6] In those instances where serum samples were collected a few weeks later, most, but not all of the cattle seroconverted.

The most useful serologic tests are those that identify the group specific antigens of all 21 serotypes and on occasion to epizootic hemorrologic disease virus (EHD). These tests are the 1) bluetongue immunodiffusion test (BTID) which is a modification of the 2) micro agar gel immunodiffusion test (AGID or AGD), 3) the complement-fixation test (CF) and 4) the enzyme-linked immunosorbent assay (ELISA).[33-37] Either the BTID and/or CF test results are the principle tests results that are accepted by most countries of the world which import ruminants. Cattle may maintain AGID antibodies for varying lengths of time. In our experimental studies where only one exposure to BT virus was known to occur, demonstrable antibodies lasted from 6 to 20 weeks. In a few instances BTID antibodies were transient, lasting only one week. On the other hand cattle followed in edidemiologic studies remained BTID positive for 3 years.

CF and ELISA tests are for antibodies to group antigens.[35,36] The CF test does not appear to be as sensitive as the BTID and therefore it is not used as frequently as the BTID.[34] The ELISA test has the potential of developing into a useful quantitative test can be used to identify antibodies to group antigens.[37]

Neutralizing antibodies are specific for the serotype of virus causing infection.[38,39] There maybe a limited degree of cross reactivity; however serotype specific antibodies are highest to that virus causing infection. Neutralizing antibody tests can be used to get an impression of the serotypes of virus active in a group of cattle at any one time. These antibodies last much longer than the BTID and CF antibodies.

Control

Control of BT infection is difficult since no vaccines exist for cattle. The modified live virus vaccines available for use in sheep should not be used in cattle.

The best means of controlling infection in cattle is through control of the culicoides vector. This can be accomplished by frequent application of larvicides to water sources such as ponds, lagoons, etc. Variation of lagoon or pond water levels at weekly intervals will reduce the breeding sites of the culicoides. Application of insecticides at weekly intervals to cattle may reduce an insect population sufficiently so that the infection rate is reduced.

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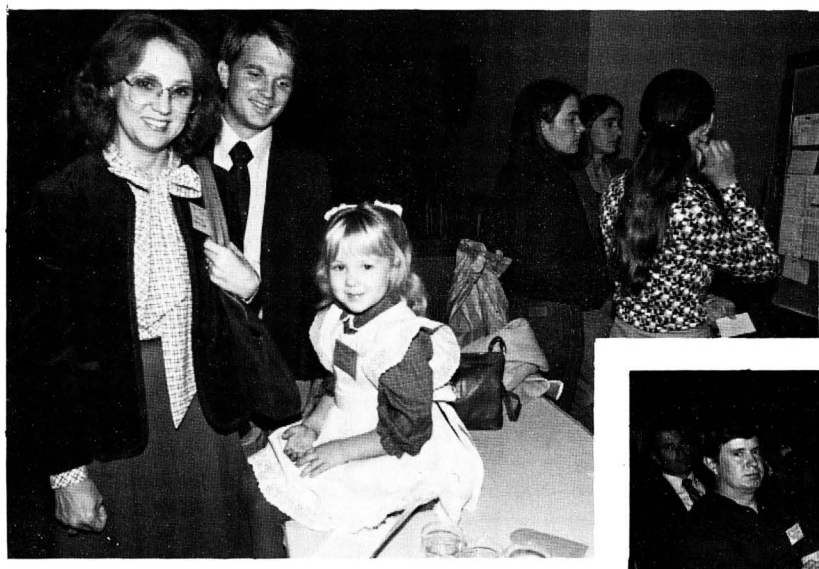

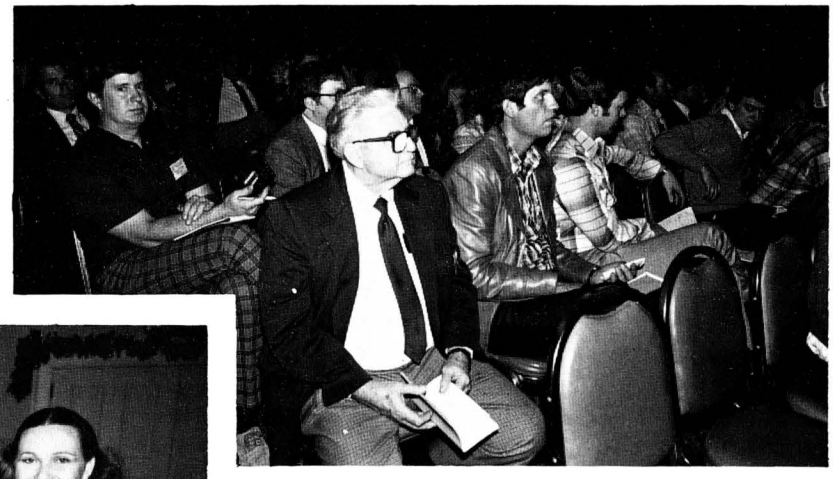

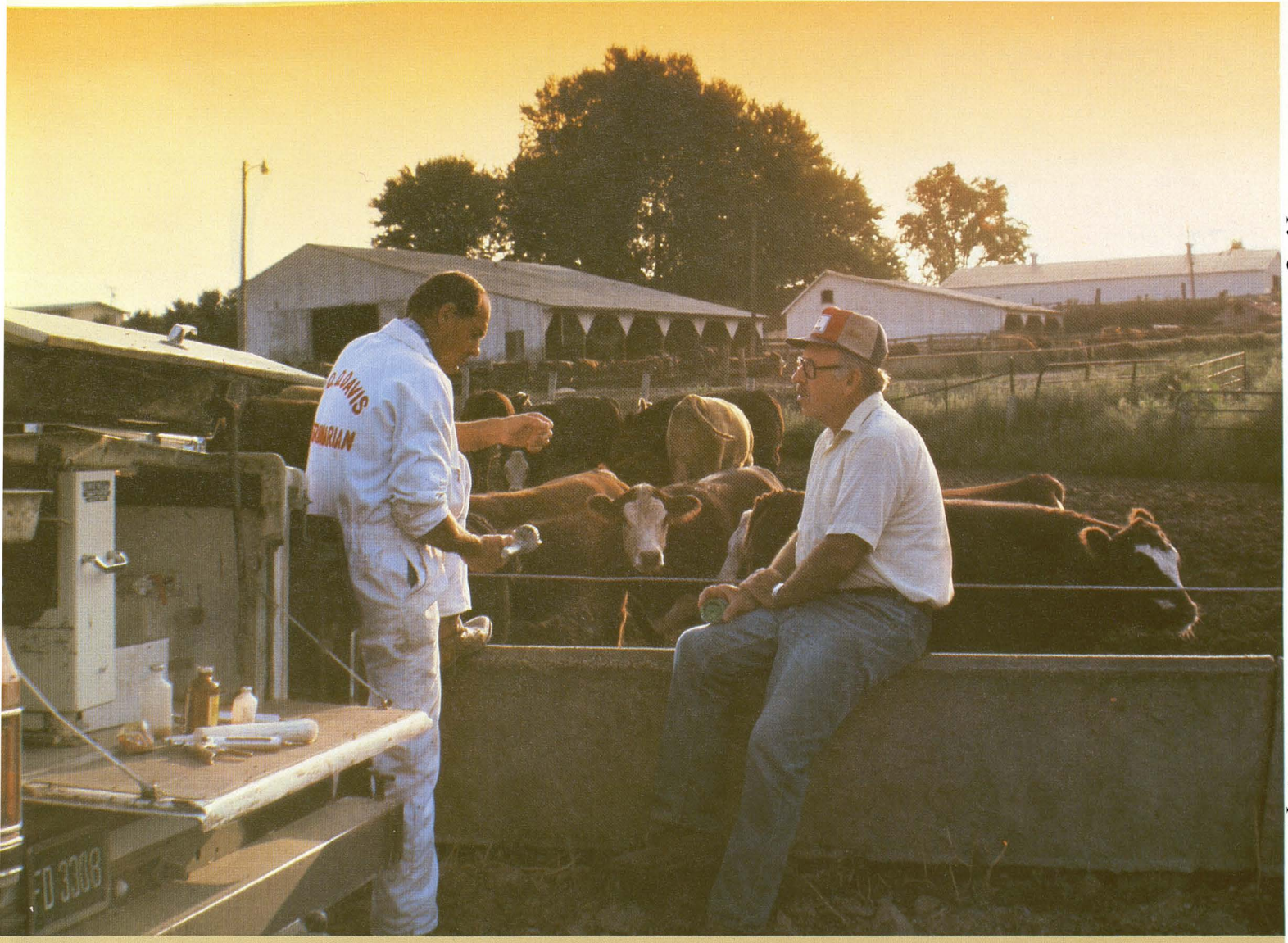

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