Clostridium perfringens Type C Enterotoxemia

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Abstract

Forms of enteric disease caused by *Clostridium perfringens* type C are critically reviewed with emphasis on practical aspects and recent research findings. Available data indicate that more animal species may be fatally infected by type C of this organism than by any other type of *C. perfringens*. Fatal cases have been recorded in pigs, cattle, sheep, horses and humans. Newborn animals are typically the most susceptible, possibly related to aspects of bacterial colonization, intestinal digestive functions, and to some other, unexplained, factors. Both beta toxin and the bacterial cells are required to initiate pathogenesis at the tips of jejunal villi, and subsequent massive adherence of these cells to necrotic mucosa is a characteristic feature. Although major lesions occur in the intestine, death is due to toxemia. The disease can be effectively controlled by vaccination of the dam. Epizootiology of this disease is a possible area for further studies.

Résumé

Clostridium perfringens type C entérotoxémie

On révise les formes de maladie entérique causée par *Clostridium perfringens* type C en insistant sur les aspects pratiques ainsi que sur les données récentes de la recherche. Les données actuelles indiquent que le type C de cet organisme peut causer une infection fatale chez plusieurs espèces animales plus que tout autre type de *C. perfringens*. On enregistre des mortalités chez le porc, la vache, le mouton, le cheval et l'homme. Le nouveau-né est particulièrement susceptible et ceci est relié à des facteurs de colonisation bactérienne, de la fonction digestive intestinale et à d'autres facteurs obscurs. La cellule bactérienne et la toxine bêta sont toutes deux nécessaires pour initier la pathogénèse au niveau de l'extrémité de la villosité jéjunale et l'adhérence massive subséquente de ces cellules à la muqueuse nécrotique est une observation caractéristique. La toxémie est la cause principale de la mort même si on observe des lésions intestinales sévères dans l'intestin. La maladie peut être contrôlée efficacement par la vaccination des femelles reproductrices. D'autres informations importantes pourraient être obtenues en étudiant l'épizootiologie de cette maladie.

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Introduction

In 1980, a review was presented on the role of *Clostridium perfringens* in animal disease (1). That review pointed out that, of the five universally recognized types of this organism, there were two toxigenic types that caused clearly defined enterotoxemias in Canadian livestock. These were type D, the causative organism of the classical enterotoxemia of sheep, and type C, the agent responsible for hemorrhagic enterotoxemia of neonatal calves. In the period from 1980 to the present, *C. perfringens* type C has been shown to be capable of causing serious enteric disease in the bovine, porcine, equine, ovine, and human species in many parts of the world. Accordingly, more reports have been published recently about type C than any other toxigenic *C. perfringens* type affecting animals.

This paper is a review of *C. perfringens* type C enterotoxemia with an emphasis on practical aspects of the disease in the light of recent knowledge of the present decade. The relationship of type C to other toxigenic types of this bacterium and the biological characteristics will not be discussed here; such information has already been published (2,3).

The Disease

Clostridium perfringens type C enterotoxemia, also known as hemorrhagic or necrotic enteritis, has been reported to affect virtually all common livestock species. The disease is most common in pigs and it occurs throughout the world with apparently focal prevalence in certain geographical areas. For example, sporadic outbreaks occur in several north-central states of the USA whereas only occasional cases have been seen in Canada (4). In a recent summary of common etiological agents of diarrhea in nursing pigs in Illinois, there was a prevalence of 11% of *C. perfringens* type C (5).

Piglets from birth to about a week old are the most susceptible to this infection, with the susceptibility decreasing rapidly with daily aging. The age of the host also influences the severity of this disease, which may range from peracute to subacute and chronic forms. The peracute form with hemorrhagic or no diarrhea occurs in one- or two-day-old piglets, most of which die within 24 h (6,7). The older the piglets the more the character of diarrhea changes from hemorrhagic and watery with necrotic debris, to intermittent yellow, with a corresponding lengthening of illness. The chronic form, affecting one- to two-week old or older pigs, may last for several weeks before terminating in death, often from dehydration and secondary bacterial infections. Recovery is rare, with survivors becoming unthrifty. The susceptibility, range of clinical signs, and number of piglets affected vary between herds, between litters and even between piglets in the same litter. Sometimes the disease may affect only a few pigs within the litter; in contrast, severe outbreaks with up to 80% morbidity and mortality may occur. The disease tends to recur in subsequent litters on those premises where no control measures are practised.

A peracute form of hemorrhagic enterotoxemia in foals has been reported from Canada (8), USA (9-11), and Australia (12). The affected foals were one- to

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four-days-old and all died within 24 h of becoming ill. Clinical signs included weakness, recumbency, dysentery, and occasional signs of colic.

A peracute form of the illness, similar to that seen in foals, has been reported in calves in Alberta. It has recurred almost annually in the general area where it was first diagnosed in 1974 (13). An earlier report of the disease originates from Colorado (14). Most of the affected calves in these outbreaks were three- to four-days-old, but a few were in the range of two to ten days. None recovered.

The first and only cases of this disease in lambs were reported from Colorado (15). It occurred in lambs 12 to 72 h after birth. Despite the extensive losses (daily incidence of 12% to 20% of lambs on a ranch with more than 15,000 ewes) which indicated a rapid spread of the infection within a flock, extension of the disease to lambs in new territories has not yet been reported. The "struck" disease of adult sheep in England, first described in 1930, has not been reported in the literature for many decades.

The role of *C. perfringens* type C in necrotic enteritis of chickens is not quite clear. The disease has been produced experimentally in broilers with type C organisms when the birds were subjected to mild subclinical coccidiosis (16). However, similar lesions have been produced with *C. perfringens* type A in the presence of some intestinal damage (17). Therefore, it is not certain that beta toxin of type C is specifically involved as is the case in the mammalian disease.

As for human necrotic enteritis caused by *C. perfringens* type C, there are no recent case reports available, but the fact that research on this problem has been conducted lately, suggests that this disease still occurs in Papua New Guinea (18).

Pathogenesis

For the infection with *C. perfringens* type C in the newborn animal to occur, the organism must enter the digestive tract by ingestion. This occurs by suckling the dam which carries the organism, or by licking contaminated objects in the surroundings. The first bacteria to appear in newborn calves, lambs, piglets and small laboratory animals are *Escherichia coli, C. perfringens*, and streptococcus (19). Although *C. perfringens* type A is a part of normal intestinal bacterial flora, which begins to be established in the neonate within the first day after birth (19,20), type C is not commonly present in every animal and even carriers may harbor very small numbers of this type as compared to type A. It is apparent that the only time type C may predominate in the intestinal flora is close to, or during, the clinical disease it causes. The factors that cause an imbalance of the intestinal bacterial flora and allow type C to proliferate, produce toxin, and initiate pathogenesis of the disease are poorly understood.

From the taxonomic viewpoint, type C strains have been divided into five subtypes according to their minor toxin characteristics and epidemiological origin (21). However, the pathogenicity of the subtypes is not strictly limited to a particular host species (22).

Neonates are the most susceptible to this disease. This is apparent in all animal species affected, except humans, in which the disease affects mainly children rather than infants (23). It has been postulated and experimentally proven that shortage of trypsin in the small intestine, which usually would inactivate the beta toxin and act as a protective mechanism, allows this toxin to exert a pathogenic effect on the intestinal mucosa (23,24). By the use of trypsin inhibitors, such as soybean flour, the disease has been successfully reproduced in guinea pigs and lambs (25,26). There could be a short period after birth when the pancreatic secretion and proteolytic enzyme production in the neonate has not reached its full potential, and hence the host is at increased risk (24).

A trypsin inhibitor in sow's colostrum was demonstrated long ago (27), but no further investigation has followed the original report. If such an inhibitor is present in the colostrum, it would have a direct bearing on the pathogenesis of *C. perfringens* type C enteritis. Further research about this aspect is desirable.

Sudden change of diet may profoundly alter the intestinal flora, particularly in piglets (28), and along with possible changes in the digestve enzymes would, in turn, increase the host's susceptibility to the infection and explain why some of the cases occur at weaning time (29).

The first pathogenic effect of *C. perfringens* type C, as observed in piglets, begins at the tips of the villi of the small intestine. Both the bacterial cells and their toxin are needed to produce the disease (6,26,29). The cells adhere to the villus epithelium and massive attachment of these cells to the necrotic mucosa in the later stages is a regular histologial feature (4,8,10,11, 26,29). The mechanism of this process is unclear. It was shown experimentally that *C. perfringens* type C cells first adhered to and proliferated on the jejunal villi of pigs and thus provided their toxin an intimate contact with the host tissue (30). Recent ultrastructural studies, however, have shown marked damage to microvilli, degeneration of mitochondria, and further damage to terminal capillaries as a primary lesion prior to any bacterial adhesion to the villus epithelium (31). Similar ultrastructural changes were oberved in cell-free beta toxin intoxication, the effects of which remained limited to the epithelium (32). Therefore, an ultrastructural toxic damage of the epithelial cells may precede adhesion of the bacteria and thus initiate the pathogenesis of progressive necrosis of the mucosa. The reason the disease begins at the tips of the villi may be the presence of mature epithelial cells which, with their demanding digestive and absorptive functions (33), are more likely susceptible to damage by beta toxin than are the young undifferentiated crypt cells.

The subsequent stages of pathogenesis follow a regular self-propagating pattern (6,31,34): destruction and desquamation of epithelial cells, further invasion by bacteria, proliferation and more localized toxin production for massive necrosis, structural tissue breakdown, and hemorrhage. Beta toxin is a potent necrotizing agent and large amounts of it are released into the intestinal lumen which in turn can promote rapid extension of the pathogenic process along the small intestine. At the same time, necrosis extends through the

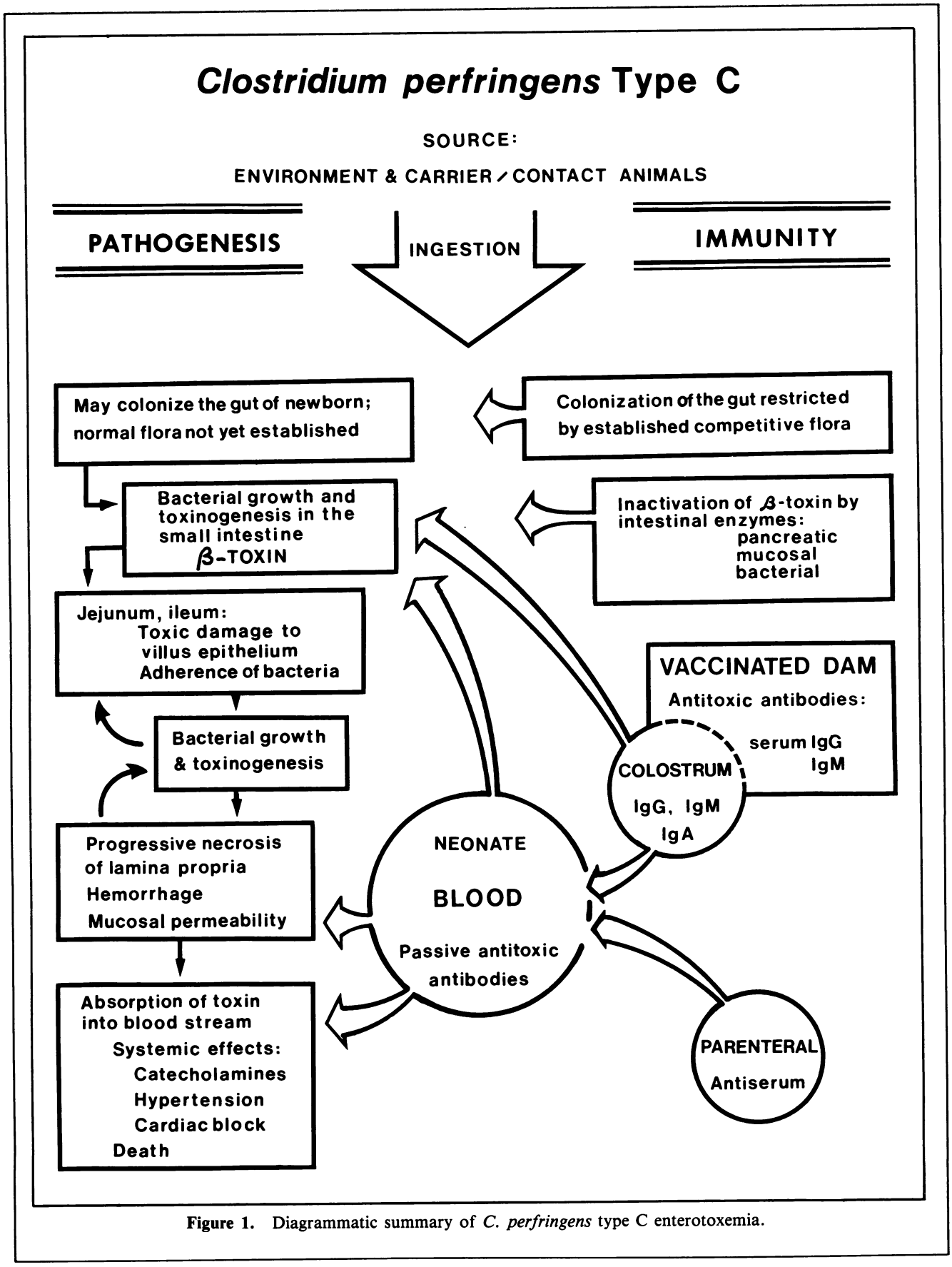

Figure 1. Diagrammatic summary of *C. perfringens* type C enterotoxemia.

mucosa, involving the crypt epithelium, mesenchymal elements of lamina propria, and muscularis mucosa (6,31). The necrotic tissue is heavily infiltrated with *C. perfringens* cells which tend to appear in layers. Clostridial spores have been observed in the lamina propria (35), but their role in pathogenesis is likely insignificant.

The intestinal lesions vary from necrotic to hemorrhagic. The entire range of variation has been observed in pigs (6,7), while the cases in other animals have been predominantly the peracute, hemorrhagic type. Generally, the gross pathological picture closely corresponds to the clinical course: the peracute disease manifested in hemorrhagic enteritis, while subacute and chronic cases show primarily necrotic characteristics.

In acute and peracute cases, there is a massive increase in membrane permeability which allows the passage of blood proteins into the intestinal lumen (36) as well as the passage of beta toxin into the blood stream with subsequent toxin exudation into peritoneal and other serous cavities (29,37,38). Therefore, the terminal stages in the acute course can be interpreted in the context of systemic effects, i.e. toxemia. Experimentally, purified beta toxin has caused a rise in blood pressure and a simultaneous fall in heart rate, accompanied by electrocardiographic disturbances suggestive of atrioventricular block (39). The rise in blood pressure was thought to be induced by a release of catecholamines.

In chronic and subacute cases, production and absorption of beta toxin are reduced, and tissue damage is limited in extent and severity. Thus, systemic effects are avoided and prospects for the host's survival are increased. An example of this form is necrotic enteritis in humans where prognosis for survival can be increased by surgical removal of necrotic sections of the intestine (38,40).

Figure 1 is a diagrammatic summary of enterotoxemia caused by *C. perfringens* type C, showing the usual steps in the pathogenesis of the disease and possible factors involved in the protective mechanisms of the host.

Diagnosis

There are only a few clinical signs that can be considered indicative of *C. perfringens* type C enterotoxemia. If an affected newborn animal is found alive, it may show depression, listlessness, weakness, disinclination to suckle, subnormal body temperature, and possibly bloody diarrhea. Sometimes an animal may die before diarrhea develops. Age of the animal is important. A few days after birth is the most probable period for an acute or peracute form of the disease to occur. Chronic forms are difficult to diagnose clinically. Knowledge of previous outbreaks on the premises is helpful as the disease tends to recur.

The characteristic postmortem feature is one of severe hemorrhagic enteritis in acute cases. In piglets, it may involve mostly the jejunum and sometimes extend to ileum and beyond. In calves, lambs, and foals, the entire small intestine may be involved. There may be fibrin clots and necrotic tissue casts mixed with hemorrhagic luminal contents, which usually are dark brown rather than bright red. Clear or straw-colored exudate may be present in peritoneal, pericardial, and pleural cavities (6,38). Lesions of chronic cases in piglets may be confused with other enteric disease conditions, such as coccidiosis or colibacillosis.

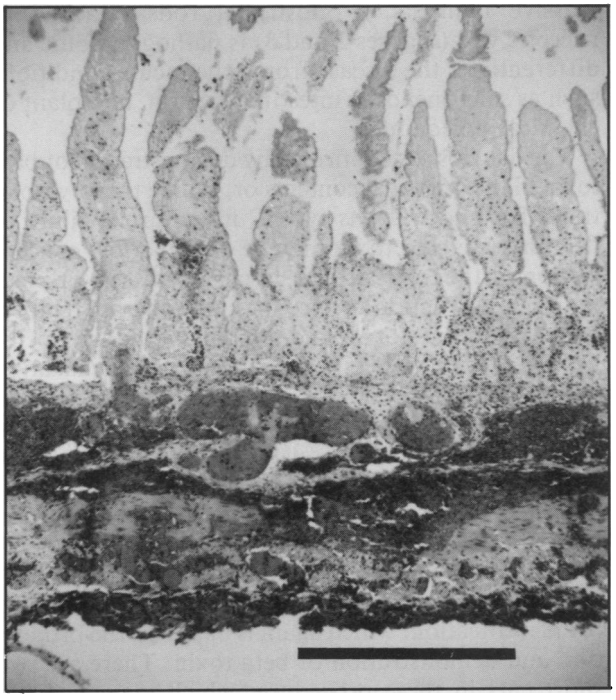

Figure 2. A typical section of jejunal mucosa of a three-day-old calf with the peracute form of *C. perfringens* type C enterotoxemia. The villi and lamina propria are necrotic and stain poorly. Cellular detail is lost. Dark borders on villi are layers of adherent bacteria. Congestion and massive hemorrhage in deeper tissues. H & E. Bar = 500 μm.

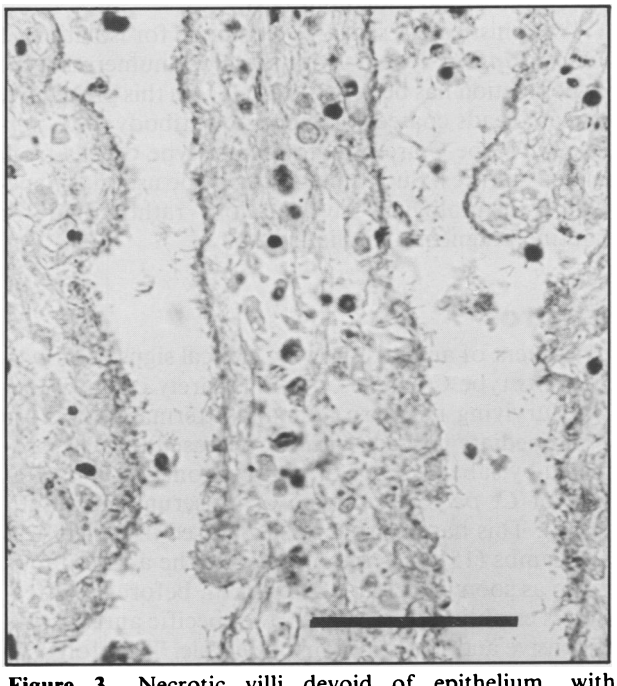

Figure 3. Necrotic villi devoid of epithelium, with characteristically adherent bacterial rods. H & E, phase contrast. Bar = 50 μm.

On microscopy, smears of the intestinal contents usually contain tissue debris and epithelial cell casts, red blood cells, and clostridial rods among particles of ingesta. The clostridia in smears are not necessarily numerous. In some cases, the clostridia may from less than 10% of the total bacterial flora seen in smears. In histological sections, however, the presence of massive numbers of clostridial rods attached to necrotic villi (Figures 2 and 3) is pathognomonic and differentiates the disease from other acute conditions such as salmonellosis, intestinal torsion, and plant or chemical poisoning.

The diagnosis is confirmed by demonstration of beta toxin in the intestinal contents or, failing this, by isolation of *C. perfringens* type C in culture. Failure to demonstrate beta toxin may be due to a low concentration of the toxin present in chronic cases, or postmortem destruction by enzymes at moderate temperatures or during storage and shipping of the specimens. Demonstration of beta toxin is done by neutralization with specific *C. perfringens* type C diagnostic antiserum in mice or guinea pigs. Attempts to develop an *in vitro* test for this purpose have so far been unsuccessful.

Basic requirements pertaining to specimen selection in clostridial diseases and appropriate laboratory procedures are well described by Sterne and Batty (38). If *C. perfringens* is isolated in culture, it must be typed for identification, which again is based on the production and demonstration of beta toxin. There are two short cuts in these procedures which may facilitate laboratory diagnosis. One is the toxin demonstration in mixed *C. perfringens* culture (41) which is advantageous when type C organisms are mixed with, or overgrown by, type A strains. The other technique is a presumptive identification of type C by demonstration of delta toxin (if the strain in question is capable of producing it) by the use of type A antiserum on sheep blood agar medium (22).

A sophisticated, sensitive technique for isolation of *C. perfringens* type C from the more numerous type A population has been reported (18). In this procedure, silicate beads coated with specific antibody to *C. perfringens* type C are used to extract type C cells from mixed cultures. Such a method may be useful for special epidemiological investigations rather than for routine diagnostic applications.

Control

Treatment of animals showing clinical signs of *C. perfringens* type C enterotoxemia is rarely of any benefit. Surviving newborn animals (littermates or those in immediate contact with the diseased) can be protected by subcutaneous or intraperitoneal administration of *C. perfringens* type C antiserum (beta antitoxin). This has been successfully used in piglets (29) and lambs (15). It is important that the antiserum be given as soon as possible after birth, before the infection is established. However, the specific antiserum is expensive and not commonly available. Therefore, the usual approach in the prevention of this disease has been vaccination of the dam to provide protective antibody to the newborn via colostrum.

Vaccination trials to investigate and quantitate specific antibody response to *C. perfringens* type C have been conducted in pigs (42–45), cattle (46–48), and sheep (47). The vaccines have been either single or multicomponent bacterin-toxoid mixtures against several clostridial pathogens. Up to eight components can be found combined in commercial vaccines, and they are presently considered practical in overall disease control.

Satisfactory antibody responses were obtained when pregnant sows were vaccinated twice, allowing two to five weeks between doses with the second injection given two to three weeks before parturition (42–45). Longer intervals between vaccine doses, e.g. inoculation of gilts at or near breeding time and again two to three weeks before farrowing, have yielded higher beta antitoxin titers in the colostrum (44). The serum antitoxin titers of neonatal pigs were directly proportional to colostral titers of their dams (45) and were found to be highest on the second day after birth (43). The application of vaccination programs under field conditions have been very successful in preventing the disease (4,29). To maintain a vaccination program, sows with subsequent pregnancies would only need a booster dose two to three weeks before farrowing.

In yearling calves, good beta antitoxin response was found two weeks after the first vaccination with a single dose, and a greater response was recorded when a second dose was given two to six weeks after the primary dose (46,47). Pregnant cows vaccinated with an eight-component bacterin six and two weeks prepartum had a significant passive transfer of humoral immunity to their calves (48). Isotypic beta antibody was found to be predominantly IgM in dams' sera; IgA predominated in colostra and calves' sera. There are no reports available about efficacy of the vaccines in cattle under field conditions.

Only one study has been published on *C. perfringens* type C vaccine in sheep (47). A bivalent vaccine, composed of type C and type D fractions, gave antibody responses similar to those in cattle (47). Experiments done at this Institute (unpublished data) showed that circulating beta antitoxin protected actively immunized lambs against intraduodenal challenge with *C. perfringens* type C, and that the protection was apparently directed against beta toxin in the intestinal lumen.

The mechanism of protection is not well explained by our present knowledge. It may be speculated that mucosal permeability increases in contact with beta toxin, thus allowing leakage of beta antitoxin (as in parenterally injected antiserum) into the intestinal lumen and subsequent neutralization of the toxin. Intraluminal neutralization of the toxin may also occur through a direct action of the antitoxin contained in the ingested colostrum, prior to absorption (Figure 1). In practice, immunization against *C. perfringens* type C enterotoxemia is feasible, practical, and effective.

Discussion

It is evident that there are still areas of meager knowledge and uncertainty, both applied and basic, where more research is required. These include information

on predisposing factors to the infection in the newborn, development of a carrier state in the adult, behavior and toxinogenesis of *C. perfringens* type C organisms *in vivo* (e.g. why some type C strains lose toxigenicity upon isolation from clinical cases [12,22,49]), mechanism of immune protection, and improved diagnostic methods together with simplified monitoring and control procedures.

A new area for further research is the behavior and interaction of bacterial populations in the intestinal flora. There has been considerable interest in manipulation of developing bacterial flora, by the principle known as "competitive exclusion", to protect newly hatched chicks against intestinal colonization by *Salmonella* organisms (50,51). Research workers in France have used a similar approach in which they demonstrated certain bacterial antagonistic effects against *C. perfringens* types A, B, C and D in piglets and laboratory animals (52–54). Such studies may help to explain, at least partly, the high susceptibility of newborn animals and the relative resistance of adult animals to type C enterotoxemia. CVJ

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BOOK REVIEW

RECENSION DE LIVRE

Companion Bird Medicine. E.W. Burr, ed. Published by Iowa State University Press, Ames, Iowa. 1987. 247 pages. Price $34.95.

Interest in avian medicine, particularly as it applies to pet birds, has increased exponentially since the beginning of the decade. Practitioners can currently avail themselves of several books in the subject area, each with its own set of shortcomings. This new book with contributions from Australian, British, French, Indian, Canadian, South African and American authors attempts to bridge the gap "between the theoretical and practical aspects of avian medicine" in less than 250 pages — a formidable task! The international scope of the authors fosters varied viewpoints and a sense of looking at familiar problems in a slightly different light, certainly a benefit for North American readers.

Specific chapters on Clinical Examination, Dermatology, Parasitology, Zoonoses and Herpesvirus Infections are well illustrated and provide good reviews of currently available information. Other chapters, such as those on Clinical Pathology and Orthopedics contain much material that has appeared elsewhere. Occasional sections, for example those on Anesthesia/Surgery and Antibiotic Therapy, are poorly referenced and lack important recent information such as the availability and use of isoflurance anesthesia and aspects of pharmacokinetics in avian species.

The index is easy-to-use and thorough. Illustrations and photographs are used liberally, but in some sections are not as effective as they could be. There are ten color plates provided but unfortunately some of the pictures, particularly those of the blood films, are not of sufficient quality to be illustrative.

While this book has certain uneven qualities, it can be recommended as a useful addition to the library of the veterinary student or practitioner with a serious interest in pet bird medicine. For those wishing a more comprehensive text, Harrison's *Clinical Avian Medicine and Surgery*, published in 1986, likely remains the most useful single source.

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