Pathology and Potential Pathogenesis of Typhlocolitis in Horses

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Summary

Typhlocolitis in horses is an acute sporadic disease which generally results in death. Cause and pathogenesis of this disease are incompletely understood. A brief overview describes the typical mucosal alterations and criteria which characterize this disease. Especially microcirculatory failure resulting in so-called exhaustion shock are pointed out. Shock most likely results from toxin absorption, when bacteria or their toxins are accumulated in the intestinal lumen, especially cecum and colon. Disease causes described in the literature which are salmonellosis, clostridiosis, Potomac horse fever, use of antibiotics, chemotherapeutics and anti-inflammatory drugs are discussed. Drug incuded alterations in the intestinal microenvironment are described in addition to potential failures in nutrition. Tissue alterations as described morphologically can result from either one of the discussed mechanisms, when the intestinal microenvironment is disturbed.

Pathologie und mögliche Pathogenese der Typhlokolitis beim Pferd

Die Typhlocolitis des Pferdes ist eine sporadisch auftretende akut und meist tödlich verlaufende Krankheit, die in ihrer Ursache und Pathogenese unvollkommen aufgeklärt ist. Im Rahmen einer kurz gefaßten Übersichtsdarstellung werden die dabei auftretenden Organveränderungen beschrieben und die Kriterien, die das Krankheitsbild charakterisieren, nämlich ein Versagen der Mikrozirkulation wie beim Schockgeschehen, herausgestellt. Als Ursache für dieses Schockgeschehen müssen wahrscheinlich Toxinabsorptionen angenommen werden, die nach Anreicherung mit bestimmten Bakterien oder deren Stoffwechselprodukten im Darm, vornehmlich Cäcum und Colon, erfolgen können. Die im Schrifttum diskutierten Ursachen einer Typhlocolitis werden nacheinander diskutiert. Es sind die Salmonellose, die Clostridiose, das „Potomac Horse Fieber" sowie Anwendungen von Antibiotika, Chemotherapeutika und schmerzstillende Mittel, ferner aber durch die vorgenannten Einwirkungen oder aber durch Fütterungsfehler hervorgerufene Störungen im „microenvironment" von Cäkum und Colon. Letztere sind verantwortlich für die Gewebsschäden.

In recent years typhlocolitis in horses has increasingly gained the attention of scientists in veterinary medicine and comparative gastroenterology as well as of nutritionists. Though in some cases the cause of this disease entity may become evident, there are still many incidences in which a causative agent remains undetected. It is most likely that only subtle changes in the colonic microenvironment will contribute to the development of severe colonic mucosal alterations resulting in acute disease and death. In this presentation, we want to focus on the acute disease with inpredictable current onset under special consideration of the disease syndrome which has been named "Colitis X" as described first by *Rooney* et *al.* in 1963. Whether this term is still useful has already been debated in 1981 by *Schiefer.*

Equine typhlocolitis is a severe, in most cases fatal, disease with sudden onset of lethargy and high body temperature when seen in the peracute phase. There is profuse watery diarrhea present within 12 to 24 hours after onset of symptoms. The prominent clinical characteristics of "the Colitis Syndrome" have been described already in 1963 by *Bryans.* In brief, these are: Accelerated thready pulse, sometimes impalpable, hypotension, depression; as intractable fetid watery diarrhea progresses, there is rapidly progressive hemoconcentration. Hemograms reveal extreme leucopenia and obvious neutropenia, associated with increase of hematocrit values. In case animals survive several hours, body temperture will fall below normal values. In early onset of disease blood glucose values have been shown to be elevated. Colic may be evident, and copious sweating may occur. Overall symptoms recorded are those as seen in an acute, more or less rapidly progressing shock. *Rooney* et *al.* have described this unusual disease syndrome as "exhaustion shock in the horse" in 1965. Commonly the case history refers to sudden environmental change of the animal, withdrawal of food, transport over long distances, lack of fluids for several hours and especially submission to a veterinary clinic and a history of surgery at any site of the body along with anaesthesia and application of antiinflammatory and/or antibiotic drugs (*Whitlock,* 1986; *Lauk* et *al.,* 1987). The disease may occur in animals at any age or many breed but is seen more often in horses older than one year. It rarely occurs in more than one or two animals at the same time and one single barn.

Upon necropsy the carcass is dehydrated and subcutaneous blood vessels are filled with dark barely clotting tarry blood. There are petechiae and rarely ecchymoses all over the body, predominantly in the serosal surfaces of the abdominal and thoracic wall, the diaphragm and the epicardium. There is dilatation of the right heart with streaky appearance of the myocardium at several sites. The lungs are hyperemic and edematous, poorly retracted and froth is filling the trachea. There is petechiation in tracheal mucosa and pleural membranes and quite often an emphysema of peripheral areas is prominent. The adrenals are hyperemic and hemorrhages are seen especially at medullary cortical junction and in the cortex. Liver and spleen may be congestive and hyperemic.

Cecum and ventral right colon, in several cases all of the ascending colon, are dilated and filled with large quantities of fouly smelling fluid which sometimes appears foamy. Caecal and colonic wall are thickened, edematous, bluish to dark red in colour and covered at the serosal side by petechia and ecchymoses. The muscle layers are diffusely hemorrhagic. The submucosa is edematous and mucosal folds are swollen, hyperemic and hemorrhagic. In most cases the surface is covered by greyish fibrinous material. Sometimes mucosal erosions are present. In many instances

the gut associated lymphoid follicles are swollen and on a closer view protruding over the luminal surface. On rare occasions the lesions have been detected in the ventral colon only and have very seldom been present behind the pelvic flexure, where in a few occasions only mucosal hyperemia was present. The cecocolic lymphnodes are enlarged and edematous with severe hemorrhages. Small colon, rectum and small intestines are normally not involved in this disease syndrome except that the duodenum and ileum may be hyperemic and congested. In cases of salmonellosis however, small intestines are involved. Careful investigation of parasitic arteriitis will result in several cases with lesions present at the arteries, but equine typhlocolitis can be very well distinguished compared to alterations in thromboembolic colic.

Histologic lesions vary in intensity depending on the time of death after the onset of disease. In cases which clinically do not develop diarrhea, there is severe hyperemia and edema of mucosa and submucosa. The capillary bed is extremely dilated and lymphatics in submucosal tissues may appear like cysts (figs. 1, 4, 5, 6). In early stages there is sloughing of epithelial cells, later necrotic epithelial cells on surface (fig. 2) and in crypts are enclosed in fibrin and cellular debris containing neutrophils, macrophages and eosinophils (figs. 1, 7). Many degranulated mast cells are present in the L. propria and submucosa, arterioles are contracted with vacuoles in their muscle layers (fig. 3), and capillaries and venules are distended, often filled with fibrin and red blood cells. Submucosal vessels are plugged with thrombi and capillaries often contain microthrombi. Plasmadiapedesis and hemorrhages are common features (figs. 4, 5). In later stages colonic epithelial cells disappear nearly completely and cecal and ventral colonic mucosa are changed into fibrinonecrotic to diphtheric typhlocolitis (figs. 5, 6, 7). These morphologic descriptions have been summarized from several of the overview articles including personal experience with of more than 50 cases.

Lesions, seen in typhlocolitis, cellular necrosis, severe mucosal alterations along with severe edema, congestion and hemorrhages, arterial wall necrosis and constriction, and capillary and lymph vessel dilatation along with microthrombus formation are suggestive to the pathologist to be related to endotoxic effects. Experimentally, endotoxins and anaphylaxis will produce a syndrome as seen in colitis (*Whitlock*, 1975). Thus, it is not surprising that a typhlocolitis can be found along with acute salmonellosis and clostridiosis. Furthermore, there have been observed adverse effects after treatment with some antimicrobial drugs as well as with antiinflammatory drugs. In the following a few known disease entities in relation to acute typhlocolitis are briefly summarized.

Salmonellosis:

Within the large amount of identified salmonellae species as causative agents of infectious diarrhea Salmonella typhimurium var. copenhagen is the most frequently isolated serovar. The pathogenicity of different serovars and within serovars is obviously varying and there seems to be a higher virulence of S. typhimurium compared to other serovars (*Carter* et *al.*, 1986; *Palmer* et *al.*, 1982; *Traub-Dragatz* et *al.*, 1990). Most often salmonellosis develops in debilitated horses (*Traver*, 1979) or is reported in association with stressful circumstances like transport (*Owen* et *al.*, 1983), medical treatment (*Owen* et *al.*, 1983), surgery or changing feeding conditions (*Gibbons*, 1980). The pathogenesis of salmonella enterocolitis is not fully understood. The organism is taken up orally, adheres to the mucosa and invades the intestinal wall. Depending on the host's ability of immunological reaction, the severeness of inflammatory response is varying (*Martens* and *Scrutchfield*, 1982). On the one hand, bacterial toxins like lipopolysaccharides, enterotoxins, cytotoxins and porins are playing a major role, on the other hand, additionally an unappropriate host response with influx of inflammatory cells and production of mediators are contributing to the pathogenesis of typhlocolitis (*Murray* et *al.*, 1989). In an in-vivo study in isolated colon segments inoculated with Salmonella typhimurium culture lysate and viable Salmonella typhimurium, *Murray* et *al.* (1989) were able to demonstrate marked histological changes with edema in the mucosa and submucosa of the colon, PMN infiltration in the submucosa, depletion of goblet cells and, on the surface of the epithelium, a thick mucous layer with erythrocytes and neutrophils, respectively. With the culture lysate they were able to induce an increased fluid secretion into the lumen, which might be, in this case, a result of passive secretion. Passive secretion, in contrast to cAMP or cGMP induced active secretion as it is common along with colonisation of intestinal mucosa with gramnegative bacteria, is a result of microvascular alterations.

Clostridiosis:

Several clostridia species are described to be responsible for induction of enterocolitis in horses. *Wierup* (1977) observed an increase of Clostridium (Cl.) perfringens type A in horses with enterocolitis; and the resemblance of the alterations with colitis X *Led Swerczek* (1980) to the conclusion, that this disease entity should be named "Equine clostridial typhlocolitis".

Whereas Cl. perfringens exists only in small amounts in the normal colonic flora (*Smith*, 1965; *Gautsch*, 1990; *Kropp*, 1991), clostridial growth and pathogenetical significance of clostridia is considered to be of multifactorial origin. Only under certain circumstances the bacteria are able to experience massive growth and produce sufficient amounts of enterotoxins. Especially sudden changes of the diet, administration of antibiotics and other drugs (*Bader*, 1985) and stress conditions are regarded as important effects on bacterial growth and toxin production (*Swerczek*, 1979). In contrast to several reports on a growth promoting effect on clostridial population after administration of oxytetracycline, *Kropp* (1991) could not find a clinical or intestinal effect of increased clostridia concentrations.

Cl. perfringens type A enterotoxin is a product which is released within the process of sporulation (*Duncan*, 1973) and is, together with other clostridial exotoxins, able to induce an acute hemorrhagic gastroenteritis after intravenous injection in Shetland ponies (*Ochoa* and *Kern*, 1980).

Other clostridia species found in association with typhlocolitis are Cl. cadaveris (*Prescott* et *al.*, 1988), which was isolated in one case. Cl. difficile, known to produce pseudomembranous, antibiotic-associated colitis in humans, is identified as probable causative agent for enteritis in foals in single cases (*Jones* et *al.*, 1988). Important bacterial toxins of Cl. difficile are a cytotoxin and an enterotoxin.

Potomac Horse Fever:
In the late seventies a new disease in horses was recognized

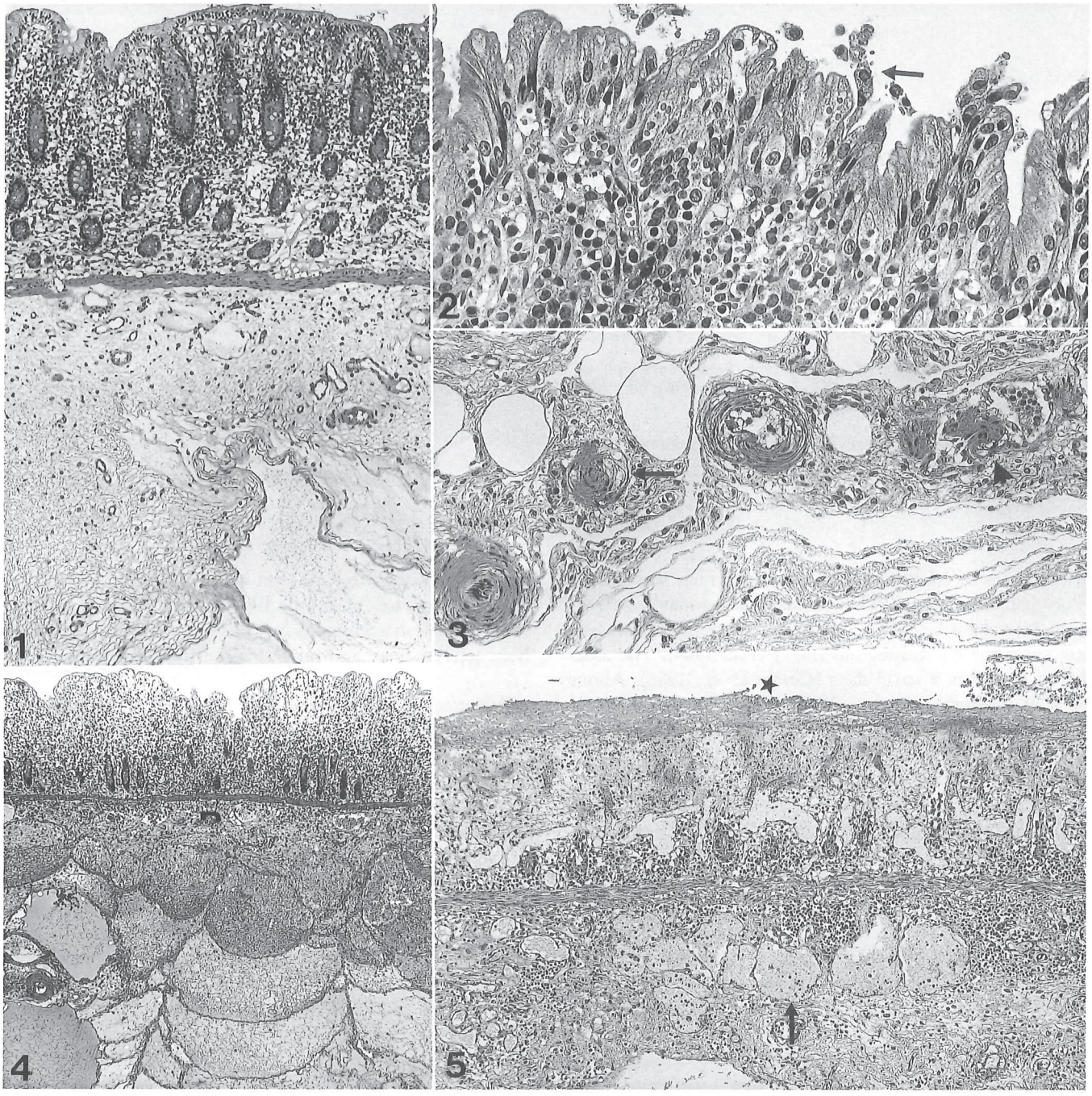


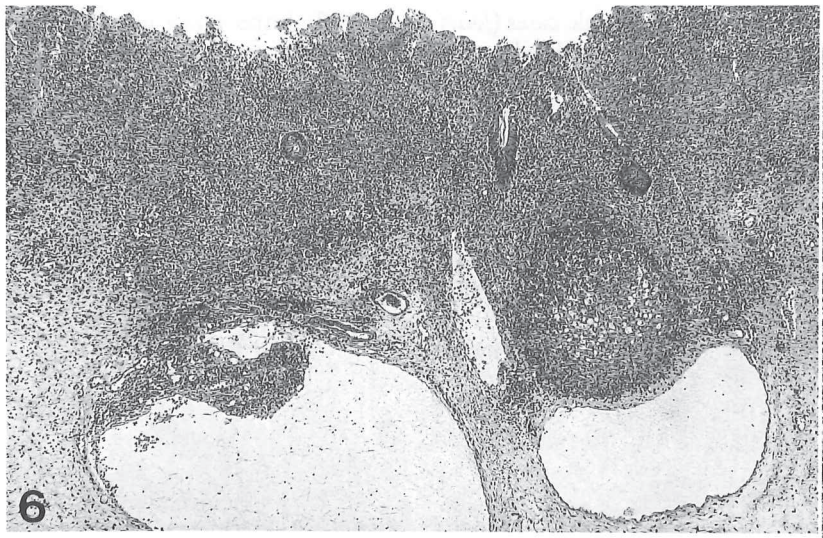
Fig. 1: Acute colitis with inflammatory cellular infiltration in the surface epithelium, dilation and filling of lymph vessels with proteinaceous fluid. Horse, colon, H – E, x 10.

Fig. 2: Early alterations in acute colitis with sloughing of necrotic cells into the colon lumen (arrow) and hydropic epithelial cell degeneration. Horse, colon, H – E, x 10.

Fig. 3: Constriction of arteries and degenerative changes in the vascular wall (arrow), leucocytosis in venules and constriction of venous cuffs (arrow head). Horse, colon, H – E, x 40.

Fig. 4: Acute colitis with necrosis on surface, loss of crypts, extreme dilatation of submucosal vessels, and severe hemorrhages. Horse, colon, H – E, x 2.5.

Fig. 5: Diphtheroid colitis, on the surface of the colon fibrin and cellular debris (asterix), lymphangiectasia and stasis of proteinaceous, fibrinous fluid in lymph vessels of the mucosa and submucosa (arrow). Horse, colon, H – E, x 5.



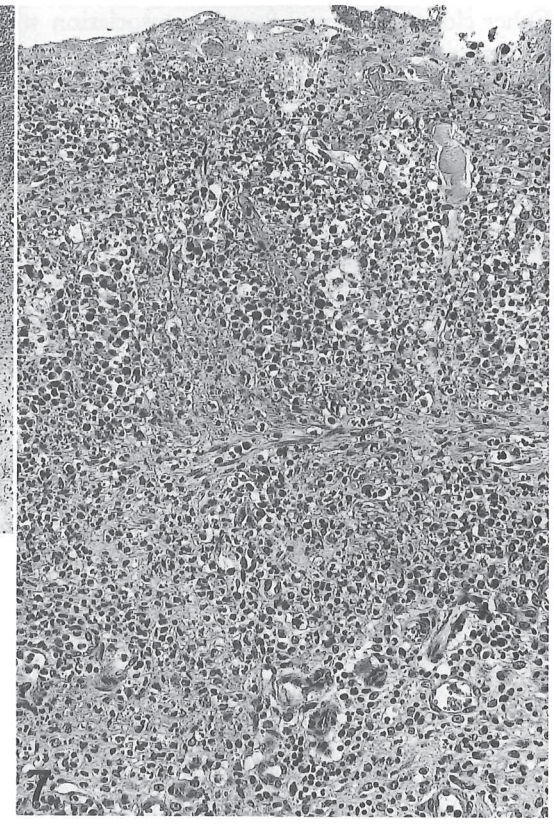


Fig. 6: Acute necrotising colitis, note extreme dilatation of lymph vessels and destruction of the lamina epithelialis, centrifollicular necrosis of a mucosal lymphfollicle. Horse, colon, H – E, x 5.

Fig. 7: Acute necrotising colitis with complete destruction of the epithelial layer and diffuse inflammatory cell infiltration, destruction of lamina muscularis mucosae. Horse, colon, H – E, x 20.

in the states of Maryland and Virginia which was named "Potomac horse fever (PHF)". This disease today is known to be caused by Ehrlichia ristici organisms. The disease is infectious but not contagious (*Perry* et *al.* 1984). The incubation period is 9 to 15 days (*Cordes* et *al.*, 1986). About 30 % of infected animals will die after an acute onset of diarrhea. In this disease onset of clinical symptoms and intensity are less severe as described, in cases of typhlocolitis of unknown origin, but infected animals may acutely die after 2 to 5 days after onset of diarrhea. As described in experimental reproduction of this disease by *Cordes* et *al.* (1986), the most consistent gross changes were found in the large colon and cecum and, to a lower extent, in the small intestine which is different compared to the acute typhlocolitis but is consistent with findings as seen in acute salmonellosis. Cecal and colonic lesions seen at necropsy are very similar as described in acute typhlocolitis. The infectious agent (Ehrlichia organisms) is detectable in epithelial cells of small and large intestine, from macrophages and from mast cells by either an immunoperoxidase technique or by a modified "Steiner silver stain technique" (*Steel* et *al.*, 1986) or less specific, by a toluidin blue or Giemsa stain. It is incompletely understood why predominantly cecum and colon are infected, but it is possible that the general infection alters ingesta passage and the upper large intestines are functionally affected. Another point of discussion should focus towards the involvement of macrophages and intestinal mast cells, especially mast cell degranulation which might interact with colonic microcirculation and promote a shock-like microcirculatory disturbance. Ehrlichia ristici has, to our knowledge, not yet been shown to be involved in European cases of equine Ehrlichiosis, which is a different disease, characterized by subcutaneous edema, hemolysis, icterus, fever and no gastrointestinal disorders.

Antibiotics, Chemotherapeutics and Anti-inflammatory Drugs

In 1971, *Anderson* et *al.* were the first ones to report on antibiotic associated diarrhea in horses due to application of tetracycline. Since then, several other antibiotics and chemicals which interact with bacterial growth were found to induce diarrhea. Lincomycin, for instance, which is used as food additive in pigs, has been observed as potential cause of enteritis, and clindomycin, known from human medicine to produce necrotising colitis, have been investigated (*Tedisco* et *al.*, 1972; *Unger* et *al.*, 1975). In accidental poisoning of horses with Monensin early circulatory disturbances in cecum and colon were evident 36 hours after exposure to this substance (personal observation). In a recent literature review, *Kropp* (1991) has reported on microbiological investigations in relation to the composition of intestinal flora of horses and the influence of chemotherapeutics.

There are different ways of interaction with the colonic microenvironment discussed in relation to the development of mucosal lesions. *Owen* (1975) discussed that salmonella in chronic carriers may be exacerbated by tetracyclines when normal colonic bacterial flora is disturbed. Since tetracyclines are concentrated in liver and excreted via bile flow, they easily may interact with intestinal flora.

High concentrations of intraluminal antibiotics within a short period of time kill bacteria; and bacterial wall fragments may be present to be absorbed and interact with secretory processes in the colonic mucosa.

In 1981 *Snow* et *al.* reported a pheynlbutazone toxicosis in horses, describing severe colitis. *Meschter* et *al.* (1990) experimentally reproduced this disease comparing morphological, ultrastructural and biochemical data. In these experiments a dose approximately 50 % greater than the recommended dose of 8.8 mg/kg bodyweight was used by intravenous application daily for 4 days. Early mucosal lesions in cecum and ventral colon consistent with alterations seen in typhlocolitis were present in animals killed 48 hours after phenylbutazone injection, but not in animals investigated 24 hours past treatment. In animals investigated 96 hours after application more severe lesions were present than at 72 hours. Mucosa of cecum and colon contained extensive dark red miliary foci along with severe colonic congestion. Mucosal necrosis was predominantly present at the right ventral colon. The cause of lesions detectable by light microscopy has been interpreted to be related to microvascular injury which consists of vascular swelling, stagnation and occlusion of blood flow, fibrin formation, perivascular leakage resulting in severe edema, thrombosis and tissue necrosis. Whether well documented increases in rate of shedding of surface cells (*Max* and *Menguy,* 1969) or the accelerated expulsion of mucous granules, which may disrupt the epithelial barrier mechanism (*Reinsford* et *al.,* 1982), are supportive to lesion development is probable, but needs further experimental work in the equine species.

In many discussions referring to the development of typhlocolitis feeding habits, food quality and composition of daily food are incriminated as causative factors. The equine large intestine consists of different compartments, which are functionally distinct. As to *von Engelhardt* et *al.* (1989) and *Coenen* et *al.* (1990) the volume of equine colon measured in kg accounts for up to 15 % in relation to bodyweight, which is in the porcine only 5 % and in the rabbit 7 – 8 %. About 75 % of horses energy needs are derived from volatile fatty acids produced in the large intestine (*Argenzio* and *Hintz,* 1972). Thus a well balanced microbial environment needs continously to be maintained. This again depends on balanced digesta flow and mixing of cecal and colonic contents which requires intact intestinal motility, secretion and absorption. Feed material is normally retained in the ventral colon for 2 to 7 days, and in the dorsal colon for 2 to 10 days. Once digesta reaches the dorsal colon, retrograde movement to the ventral colon does not occur. Cecum, ventral and dorsal colon are the sites of the majority of microbial fermentation of carbohydrates to volatile fatty acids (*Argenzio* et *al.,* 1974). Half of the ingested soluble carbohydrate (starch) is converted to volatile fatty acids in the cecum and large colon and fermentation of the insoluble carbohydrate (cellulose) is facilitated predominantly in the ventral and dorsal colon (*Argenzio,* 1980). Ingesta passage necessary for intraluminal digestion, fermentation, mucosal absorption and scretion depends on fluid transport. As to estimations resulting from *Argenzio's* experiments (*Argenzio* et *al.,* 1974), equine cecum and colon of a horse of about 450 kg bodyweight are required to absorb 75 to 80 l of water per day, which represents more than three times of the horse's plasma volume (*Murray,* 1988). Fluid absorption and secretion in the intestine is regulated through intact intestinal mucosal barrier, which consists of surface epithelium with its mucous layer, crypt epithelium and lamina propria, and submucosa. Structure of highly specialized capillaries appears to be one of the main features of proximal colonic microcirculation, where fenestrated capillaries are present, in contrast to the descending colon (*Murray,* 1988; *Zahner,* 1991).

To maintain intact cecal and colonic function, a few basic requirements are needed: sufficient colonic microflora which depends on an even colonic pH of about 6.8, an unaltered epithelial barrier, an intact capillary function including arterial blood supply, venous backflow, as well as lymphatic drainage. Change in feeding habits may alter these conditions as demonstrated in a few examples: It is well understood that increase of cecal colonic acidity will result in alterations of colonic microflora. Under these circumstances endotoxins are released to produce laminitis, a condition in which predominantly capillaries are involved (*Garner* et *al.,* 1978, 1979, 1982).

Food rich in energy fed only will increase bacteria in the colonic lumen and increase amounts of volatile fatty acids in cecum (*Willard* et *al.,* 1977) compared to animals fed hay only. Sudden changes from hay diet to concentrated ratios will alter microbial flora of large intestine associated with an increase in lactobacilli (*Goodson* et *al.,* 1988).
In conclusion, main features of typhlocolitis in horses are alteration in colonic epithelium, inflammatory reaction in the lamina propria predominantly in cecum and ventral colon associated with severe hemorrhage, and edema resulting from capillary failure. All of these features of intestinal mucosal lesions may be associated either with alterations of the bacterial flora and enteropathogenic microorganisms or an inadequate diet, resulting in microvascular alteration. Use of antimicrobial drugs may increase an alteration of colonic flora resulting in severe release of bacterial toxins. Changes in colonic microenvironment are most likely the most important factors in the development of typhlocolitis. To initiate the different chains of events one or two factors are probably enough to introduce the following functional dearrangement: Increase of fermentation which results in increase of volatile fatty acids. This coincides with a decrease of cecal and ventral colonic pH. From this condition an increase of lactobacilli is facilitated which again results in further decrease of pH. Decrease of pH, however, will immediately kill parts of the normal intestinal flora with release of endotoxins. Endotoxins are absorbed and will result in reactions as seen in shock phenomena. All of these conditions resulting in a shock-like syndrome can be initiated by all events which interact with capillary integrity.

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