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RECENT ADVANCES IN INTESTINAL PATHOLOGY OF RABBITS AND FURTHER PERSPECTIVES

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Introduction

Digestive disorders are the predominant cause of mortality in commercial rabbits (Biolatti & Capaldo, 1984, Lecerf, 1984, Morisse et al., 1984, Urosevic et al., 1986). Mortality rate is between 12 and 20 %, but may reach up to 50 %. Mainly weaned rabbits of 4 to 8 weeks of age are affected, although another peak may occur in suckling rabbits of 8 to 12 days old. Rabbits older than 3 months are rarely affected. Beside mortality, digestive disorders are responsible for important economic losses by growth depression and bad feed conversion. Most rabbit breeders underestimate the financial consequences of these hidden losses, which often surpass losses by mortality and which are often noticed too late.

For a long time, the classification of digestive disorders in rabbits has been hampered by the fact that, regardless of the cause, they all present the same clinical signs : anorexia, apathy and diarrhoea. At necropsy few typical lesions are found. Moreover, often different pathogenic agents are simultaneously involved or succeed each other in the time. Until recently the pathogenicity of most of these agents remained obscure. As also the feed composition may influence the course of these disorders, correct diagnosis of the factors involved becomes difficult, which often leads to disappointing results of treatment. Sometimes medication itself deteriorates the situation. The uncertainty about the exact causes of rabbit diarrhoea led Whitney (1976) to refer to enteric diseases in rabbits as the enteritis-complex.

Between 1982 and 1986 detailed information became available on the occurrence of parasites, bacteria and viruses in diarrhoeic commercial rabbits (Table 1). The presence of these

agents was related with clinical signs and gross and microscopic lesions. In most rabbitries three to four pathogenic agents were detected. Mixed infections were common (Peeters, 1987).

TABLE 1 Percentage occurrence of parasites, yeasts, viruses and pathogenic bacteria in the gut of diarrhoeic rabbits

Year	1982	1983	1984	1985	1986	Total
Number of field cases	130	138	187	185	154	794
Flagellates (1)	-	10.5	12.3	11.9	6.1	10.6
Cryptosporidium sp.	0.0	4.4	10.7	6.0	1.5	4.9
Eimeria spp.	18.5	29.0	52.4	54.1	63.6	45.4
Graphidium strigosum	0.0	0.0	0.0	0.5	0.0	0.1
Passalurus ambiguus	0.0	0.0	0.0	6.0	0.7	1.5
Trichostrongylus retortaeformis	0.0	0.0	0.0	0.5	0.0	0.1
Saccharomycopsis guttulata (1)	32.3	18.1	35.8	26.0	21.8	27.2
Adenovirus	0.0	0.0	0.5	0.5	0.0	0.3
Coronavirus	0.8	0.7	5.9	4.3	1.5	2.9
Enterovirus	0.0	0.0	0.0	0.5	0.0	0.1
Parvovirus	0.0	0.0	0.5	0.5	0.0	0.3
Rotavirus	35.4	18.2	23.5	16.8	5.4	19.4
Bacillus piliformis	2.3	10.9	9.6	1.1	4.4	5.7
Clostridium spiroforme	-	52.4	46.5	53.0	47.2	49.9
Enteropathogenic *E. coli* (EPEC)	40.0	30.4	35.8	26.5	25.0	31.4

(1) Presence of at least 6 organisms per microscopic field at 400 X

The availability of animals free of recognized infectious agents allowed to test the pathogenicity of different infectious agents associated with rabbit enteritis. According to the observations from the field and in the light of new evidence from recent literature we think that following classification of the enteritis problems in commercial rabbits may be proposed from a practical point of view :

1. **Specific enteritis caused by highly pathogenic agents.** These agents always cause high mortality (> 30 %), often in a short time and even in the presence of optimal conditions of hygiene, level of infection and/or nutrition. Drastic measures are necessary to combat the disease. Examples of such agents are :

   - some species of eimeria such as *E. intestinalis, E. flavescens, E. piriformis*
   - some types of enteropathogenic *E. coli* (EPEC) such as neonatal strains (O109/biotype 1+) or some weaned rabbit strains as O103/biotype 8+ or O15/biotype 3-

2. **Multifactorial enteritis.** In most rabbitries rotaviruses and moderately pathogenic strains of EPEC and/or coccidia are endemic. These and other agents act synergistically (e.g. *E. perforans* in upper small intestine, EPEC in lower small intestine) and may cause 5 to 20 % of mortality, beside growth depression and unfavourable feed conversion. Usually rate of mortality increases progressively during several months in relation to the increasing level of infection. The level of infection necessary to cause losses can only be reached in continuously occupated rabbit houses or in case of insufficient hygiene, resistance to the anticoccidials in the feed, immunodepression by excessive stress factors, etc. Also the feed and the environment may enhance the losses. Multifactorial enteritis is responsible for the majority of digestive disorders in commercial rabbitries.

3. **Iota-enterotoxaemia.** This is the result of a dysbacteriosis of the normal caecal flora and may be induced by stress, early weaning or antibiotics, and possibly by nutrition as well. Dysbacteriosis may lead to proliferation of *C. spiroforme*, production of iota-toxin and sometimes high mortality. Dysbacteriosis may also favour colibacillosis.

4. **Subclinical enteritis** : at low levels of infection different agents cause temporary growth retardation and bad feed conversion without visible or only slight clinical signs. Examples of such agents are rotaviruses, cryptosporidia and moderate infections by coccidia. Rise of the level of infection may lead to multifactorial enteritis.

Certain conditions may increase the susceptibility of the rabbits to endemic pathogens, such as decline in maternal immunity, cold, early weaning, altered intestinal microflora (antibiotics) and incompletely developed homeostatic mechanisms (Lelkes, 1987).

The following discussion will clarify the proposed classification of digestive disorders in commercial rabbits.

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Infectious agents

Eimeria spp.

Different recent publications confirm that coccidiosis is still omnipresent in commercial rabbit units. The highest incidence occurs the first three weeks after weaning, with up to 100 % of the rabbits infected (Novinskaya et .al, 1983, Pote, 1985, Pinna & Scarano, 1985, Lipej, 1985, Hervouet & Nouaille, 1986, Cringoli et al., 1986, Peeters, 1987).

The significance of coccidiosis in juvenile rabbit enteritis is generally accepted. The losses are related to the species involved and to the level of infection. The 8 intestinal species can be classified in species with high pathogenicity (*E. intestinalis, E. piriformis* and *E. flavescens*), moderate pathogenicity (*E. magna, E. media*) and low pathogenicity (*E. perforans, E. irresidua* and *E. coecicola*). Hepatic coccidiosis (*E. stiedai*) seems rare in commercial rabbits, but may prejudice the marketing of the carcasses by causing white spots on the liver. Intestinal coccidiosis interferes with intestinal function : it causes villous atrophy (Peeters et al., 1984a) and reduces intestinal peristaltism (Fioramonti et al., 1981). This leads to bad feed conversion and growth depression varying from 40 to 350 g according to the species involved.

Coccidiosis plays an important role in all types of juvenile rabbit enteritis: the highly pathogenic species cause important losses even in the presence of good hygienic conditions, whereas the importance of the losses caused by species with low or moderate pathogenicity is determined by the level of infection and so by hygiene. Low oocyst numbers will cause no adverse reactions, higher numbers will lead to subclinical coccidiosis with slackening down of feed conversion (- 7 to 8 %) and sometimes growth depression (Peeters & Halen, 1980, Bernot, 1982), whereas still higher numbers may cause diarrhoea and low mortality. Often the evolution of this type of coccidiosis is progressive and, in the absence of an efficient anticoccidial programme, the phase with increased mortality will be reached after one year of continuous occupation.

The extent of the losses will also depend on the numbers of species present and from a possible synergistic effect : often *E. magna, E. media* and *E. perforans* are present at the same time. Each of these species on its own provokes only discrete clinical signs at low infection levels. If they occur together, compensation effects by unaffected parts of the gut are made impossible, as they will attack resp. lower, mid and upper small intestine. In most rabbitries at least 3 different species are present and so this situation is likely to occur (Francalanci & Manfredini, 1967, Catchpole & Norton, 1979, Zundel et al., 1980, Peeters et al., 1981 1987a, Cringoli et al., 1986). A synergistic action may also occur with other agents : as coccidiosis is

always attended by an increase of *E. coli* numbers in the caecum (Licois & Coudert, 1980), coccidiosis favours the impact of enteropathogenic *E. coli*. Although coccidiosis may disturb caecal flora, a favourable effect of coccidiosis on *C. spiroforme* proliferation and iota-enterotoxaemia has not been shown (Peeters et al., 1986e).

Only little information is available on the immunogenic properties of the different species of eimeria in rabbits. *E. stiedai* and *E. irresidua* were shown to induce substantial immunity after single inoculation (Rose, 1959, Norton et al., 1979) and *E. intestinalis* after repeated infections (Licois & Coudert, 1980). *E. flavescens* and *E. magna* proved not very immunogenic (Niillo, 1967, Norton et al., 1979). In the field *E. magna* and *E. perforans* seemed to induce the weakest resistance, whereas a more marked resistance was found for *E. intestinalis* and *E. irresidua*. *E. media* appeared to have an intermediate position (Peeters et al., 1983).

Since 1983 robenidine has been used as a major anticoccidial drug in a lot of European countries. This led to a clear cut modification of coccidial infection patterns : before the introduction of robenidine more than 10,000 oocysts per gramme of faeces were established in 40.4 % of Belgian commercial rabbits and this figure dropped to 2 % immediately afterwards. Similar observations have also been reported from France and Italy (Bernot,1982, Tacconi & Bartolini, 1984). The very pathogenic species *E. flavescens* and *E. intestinalis* disappeared almost completely since the incorporation of robenidine. After five years of continuous use higher oocyst numbers are being detected again in faecal samples and this rise in infection ratio is mainly due to an increase of *E. magna* and the less pathogenic species *E. media* and *E. perforans* . For *E. magna*, and presumably also for *E. media* and *E. perforans*, this rise may be attributed to drug resistance (Peeters et al., 1988a). The other species are still under control.

As *E. magna* causes growth depression and alters feed conversion, rabbitries should be monitored permanently in order to adopt the anticoccidiosis programme in time. As alternative anticoccidials in the feed 200-300 ppm clopidol/methylbenzoquate, 8-12 ppm narasin or 20 ppm salinomycin may be used, although the narrow therapeutic index of the ionophores has to be emphasized (Peeters, 1983, Morisse et al., 1986). Good results by the drinking water are still obtained with systemic sulfonamides (Dousek et al., 1987) or since recently also with toltrazuril. Administration of 25 ppm of this potent drug during two periods of two days separated by an interval of five days allows development of immunity (Peeters & Geeroms, 1986).

Cryptosporidium sp.

Cryptosporidia are unicellular organisms belonging to the same order as the genus *Eimeria.* They develop in the brush border of small intestinal epithelial cells, cause epithelial desquamation and villous atrophy and reduce the absorptive and digestive capacities of the gut (Tzipori, 1983). They were detected for the first time in rabbits by Inman & Takeuchi in 1979. Between 1983 and 1986 they were detected in 2 to 11 % of weaned diarrhoeic Belgian rabbits from 7 of 29 rabbitries examined. Worth noting is the increased frequency of this parasite since the withdrawal of sulphaquinoxalin as anticoccidial drug in 1982. Since Angus et al. (1984) showed that sulphaquinoxalin reduces oocyst output in experimentally infected mice, it is quite possible that also rabbit strains of *Cryptosporidium sp.* are partially susceptible.

Experimental infection of suckling rabbits with an isolated rabbit strain showed the parasite to cause high mortality and liquid diarrhoea in three-day-old rabbits. In weaned rabbits no mortality and very discrete diarrhoea were established, but weight gain and feed conversion were deteriorated significantly during the second week post infection. Histology showed serious villous atrophy at the same time, explaining the observed growth depression (Peeters et al., 1986a). This confirms the observations from the field, where cryptosporidiosis causes subclinical enteritis in weaned rabbits. In suckling rabbits field outbreaks are rarely detected, but when they occur they are associated with high mortality.

More than 40 antimicrobial drugs have been tested against *Cryptosporidium.* Most of these drugs were ineffective. Only arprinocid caused a marked reduction in oocyst excretion in experimentally infected mice and hamsters (Angus et al., 1984, Kim, 1987). No data with this drug are available in rabbits

Saccharomycopsis guttulata

Proliferation of *S. guttulata* can regularly be established in the gut of diarrhoeic rabbits. However, no specific gross or microscopic pathology can be assigned to this organism. *S. guttulata* is considered to be a part of the normal intestinal flora of weaned rabbits (Shifrine & Phaff, 1958). Experimental infection of rabbits with large numbers of blastospores does not induce any clinical sign (Burgisser, 1961, Richle & Schöler, 1961). However, it is not excluded that abundant growth of *S. guttulata* in rabbits with intestinal disorders might aggravate enteric disease.

Escherichia coli

Already since the 1970's studies have indicated a dramatic increase of *E. coli* -numbers in the intestines of rabbits with enteric disease. The lack of convincing evidence linking *E. coli* to juvenile rabbit enteritis eventually led most investigators to conclude that *E. coli* overgrowth was a secondary manifestation rather than the primary cause of enteric disease.

In contrast with most other mammalian species, only low levels of *E. coli* are present in the gut of weaned rabbits (Matthes, 1969, Gouet & Fonty, 1973). This is due to the inhibitory influence of the non dissociated volatile fatty acids (VFA) in the caecum (Prohaszka, 1980). When caecal pH increases from its normal value of 5.8 above 6.5, the VFA dissociate and lose their inhibitory effect, which may lead to a huge proliferation of *E. coli* or colidysbacteriosis. Among other factors, coccidiosis is known to cause a temporary increase of caecal pH and colidysbacteriosis.

In 1977, Cantey and Blake first confirmed the existence of enteropathogenic *E. coli* (EPEC) in rabbits. The strain they isolated belonged to biotype O15 and was called RDEC-1. Experimental infection with as few as 1.5 x 10^2 cells of RDEC-1 caused liquid diarrhoea and high mortality. In recent years, other authors as well established the existence of enteropathogenic strains of *E. coli* in rabbits and confirmed the pathogenic nature of these strains by infection experiments (Prescott, 1978, Renault et al., 1983, Peeters et al., 1984c,e, Okerman et al., 1985, Camguilhem et al., 1986a). Experimental infections with saprophytic strains of *E. coli* by these authors did, on the contrary, not induce any clinical sign, nor lesion. According to the results of an epidemiologic survey in Belgium, colibacillosis is responsible for 25 to 40 % of digestive disorders in weaned rabbits (Table 1). Important epidemics of colibacillosis have also been reported from France (Camguilhem, 1986, Mureau, 1987) and from the Netherlands .

Opposed to saprophytic strains of *E. coli* in the rabbit gut, EPEC are able to attach to the intestinal mucosa. This protects them against elimination from the gut by intestinal peristaltism. EPEC cause effacement of the epithelial brush borders and are therefore also called attaching effacing *E. coli* (AEEC). Effacement is followed by destruction of the absorptive epithelial cells and by villous atrophy (Cantey & Blake, 1978, Prescott, 1978, Takeuchi et al., 1978, Cantey & Inman, 1981, Peeters et al., 1985b). This results in a reduction of the digestive and resorptive capacities of the gut with liquid diarrhoea, bad feed conversion, weight loss and mortality. Rabbit EPEC do not produce any known thermostable or thermolabile enterotoxins and are not entero-invasive either (Cantey & Blake, 1978, Prescott, 1978, Okerman et .al.,

1982, Peeters et al., 1984e). The damage they cause to the enterocytes seems to be related to the production of a *Shigella dysenteriae* - like enterotoxin (O'Brien et al., 1982).

Final diagnosis of EPEC is rather cumbersome and based on histological demonstration of adherent *E. coli* to the intestinal mucosa. As histology is expensive and not available in every veterinary laboratory, EPEC may also be screened by biotyping and serotyping. Since *E. coli* is inconsistently present and only in low numbers in the intestines of weaned rabbits, colibacillosis may also be screened by semiquantitative evaluation of *E. coli* numbers in the gut of freshly killed non treated diarrhoeic rabbits : a 89 % correlation has been shown between histological confirmation of entero-adherent *E. coli* and confluent growth of *E. coli* in mid small intestine (Peeters et al., 1986b). Demonstration of confluent growth in mid small intestine makes differentiation from coccidiosis induced colidysbacteriosis possible, as coccidiosis only produces an increase of *E. coli* -counts in the caecum and sometimes in terminal small intestine.

EPEC-strains may be differentiated in serotypes with different tropism. Experimental infection studies indicated that some serotypes (O109:K-:H2) are mainly pathogenic for suckling rabbits and to a lesser degree for weanling rabbits (Okerman et al., 1982, Peeters et al., 1984b,c), whereas other serotypes (O2:K1:H6, O15:K-:H-, O20:K-:H7, O103:K-:H2, O128:K-:H2, O132:K-:H2, O153:K-:H7) are mainly pathogenic for weaned rabbits and to a lesser degree for suckling rabbits (Cantey and Blake, 1978, Varga & Pesti, 1982, Peeters et al., 1984e, Camguilhem et al., 1986b). These serogroups may also be differentiated in groups with different pathogenicity. EPEC belonging to serotypes O15:K-:H- and O103:K-:H2 are highly pathogenic and low numbers may cause 50 % mortality and more, even in rabbitries with good hygienic standards. The other serotypes show moderate pathogenicity and require higher levels of infection to cause clinical signs. As moderately pathogenic *Eimeria*-species, they may induce bad feed conversion without clinical signs. Mortality mostly occurs in rabbitries only after 6 to 12 months of continuous occupation.

Most EPEC belonging to a certain serotype also show analogous biochemical characteristics : based on the fermentation pattern of four carbohydrates and motility, they can be divided in different biotypes (Okerman & Devriese, 1985). Most motile EPEC-strains of biotype 1+ and 2+ are O109:K-:H2 and O132:K-:H2 resp., whereas all immotile strains tested of biotype 3- were O15:K-:H- and all motile strains of biotype 8+ , O103:K-:H2 (Peeters et al., 1988b). This indicates that specific clones of EPEC are involved in juvenile rabbit enteritis.

In suckling rabbits EPEC colonize the full length of small and large intestine (Coussement et al., 1984, Peeters et al., 1984b), whereas in weaned rabbits EPEC colonization mostly is

limited to distal small intestine, caecum and colon (Cantey & Inman, 1981, Peeters et al., 1984c). Only EPEC belonging to serogroup O103:K-:H2 also colonize proximal small intestine in weaned rabbits. In suckling rabbits colibacillosis mainly affects rabbits of 3 to 12 days of age. At necropsy small intestine may be lightly congested, whereas caecal contents is liquid and yellowish. The stomach is filled with curdled milk, indicating the rapid fatal evolution of the disease. EPEC belonging to serogroup O109:K-:H2 mostly will kill all animals of the affected litters within 24 to 48 hours after the first appearance of a yellow diarrhoea. Other serotypes seem less pathogenic and half of the litter mates may survive. Two successive litters of the same doe are rarely affected (Okerman et al., 1982).

In weanling rabbits the first clinical signs appear 5 to 14 days after weaning. At necropsy moderate to severe caecal oedema becomes evident and caecal content is foul-smelling, watery and brown. The mesenteric lymph nodes are markedly swollen. Mortality is mostly between 5 and 12 %, but may reach 50 % and more, when highly pathogenic strains are involved (Licois et al., 1982, Peeters et al., 1984d, Camguilhem et al., 1985, Banerjee et al., 1987). There is a 5 to 7 day growth retardation in surviving animals and huge numbers of EPEC are being excreted during 14 days (Cantey & Hosterman, 1979).

Challenge experiments of rabbits surviving a previous infection with O15:H- strains (RDEC-1 and U83/39) showed that protection provided by previous colonization was complete. Cantey (1984) found large amounts of high titer sIgA antibody postdelivery in the milk of doe rabbits that had been immunized during gestation by the orogastric route with live RDEC-1 bacteria. He was able to show that the immune sIgA prevented colonization and diarrhoea due to the RDEC-1 bacterium, confirming the role of sIgA in the protection against infection with this *E. coli* strain. Until now, single s.c. vaccination with formalized U83/39 bacteria or oral administration of this inactivated vaccine during 5 successive days to weaned rabbits has given disappointing results : although mortality was reduced, weight gain remained too low (Peeters, 1984). Similar results have been obtained for EPEC belonging to serotype O103 after i.d. (Camguilhem, 1986) or oral (10 successive days) vaccination (Renault, 1984, Mureau 1987). Intra-peritoneal vaccination of rabbits with a subunit vaccine based on AF/R1 fimbriae of RDEC-1 on the contrary gave rabbits a good protection against challenge with RDEC-1. This was not the case after s.c. vaccination (Vandenbosch H., 1987).

Success in medicating rabbits with colibacillosis depends on the strains involved : moderately pathogenic EPEC are easily controlled by most antibiotics and the disease can be eradicated if medication is followed by hygienic measures to reduce pression of infection. Highly pathogenic strains of EPEC on the contrary appear extremely difficult to control. Only neomycin and to a lesser extent chloramphenicol are active, while sulphonamides, tetracycline,

furaltodone, flumequine and colistine proved inactive (Camguilhem & Tournut, 1986, Peeters et al., 1986a). Administration of feeds rich in fiber or of acetic acid in the drinking water shows no effect in reducing clinical signs by highly pathogenic EPEC (Lebas & Camguilhem, 1986). Medication has to be attended by elimination of healthy looking carriers, because up to 24 % of healthy looking does may carry the bacterium. Individual animals may be succesfully cured by oral administration of an antidiarrhoeic drug as loperamide hydrochloride 0.1 mg/kg body weight for 5 days, associated with oral rehydration with electrolytes and glucose (Banerjee et al., 1987)

Clostridium spiroforme (iota-enterotoxaemia)

The first reports mentioning the presence of *C. perfringens* type E iota -like toxin in caecal contents of diarrhoeic rabbits date from 1978 (Katz et.al., 1978, Patton et al., 1978, Lamont et al., 1979). The bacterium producing this toxin has not been isolated until 1982, when Carman & Borriello (1982) first established that *C. spiroforme* was responsible for the production of the iota-like toxin and the observed diarrhoea. This toxin causes destruction and desquamation of caecal enterocytes, hemorrhagic typhlitis and high mortality.

Careful faecal examination of 8-week old healthy rabbits may reveal up to 46 % of rabbits carrying low numbers of *C. spiroforme* (Peeters et al.,.1986e). First infection seems to occur around weaning age, as only 9 % of five-week old rabbits excreted the bacterium. Toxinogenic strains were isolated in 24 rabbitries of 29 tested. Since toxic strains of *C. spiroforme* appear to be omnipresent, other factors seem necessary to determine *C. spiroforme* - mediated enterotoxaemia, as only 7.4 % of diarrhoeic rabbits in our 1986 survey succumbed to iota enterotoxaemia. Carman & Borriello (1984) showed that experimental infection of very young rabbits (500 to 600 g of weight) causes watery diarrhoea from 3 to 10 days p.i. with significant growth depression and low mortality, whereas infection of older animals does not result in adverse reactions. In these animals, faecal *C. spiroforme* output quickly decreases to a very low level after experimental infection. This indicates that the normal intestinal physico-chemical environment of weaned rabbits is not permissive to mass colonization by *C. spiroforme.*

The hypothesis that *C. spiroforme*-mediated enterotoxaemia requires a disturbance of normal intestinal flora is further sustained by the fact that the administration of clindamycin or lincomycin may provoke fatal iota-enterotoxaemia in at least 50 % of medicated animals (Lamont et al., 1979, Regh & Pakes, 1982, Borriello & Carman, 1983, Maiers & Mason, 1984). But also other antibiotics may favour iota-enterotoxaemia : in the field prolonged administration of well tolerated antibiotics such as chloramphenicol and tetracycline increases caecal *C. spiroforme* numbers. Medication of colibacillosis with neomycin is often followed

by iota-enterotoxaemia in variable numbers of animals (less than 20 %). The influence of other factors remains unclear. Although iota-enterotoxaemia is often associated with other pathogenic agents, iota-enterotoxaemia was not induced by combined infections of *C. spiroforme* and *E. magna* or enteropathogenic *E. coli*. No influence of diets rich in quickly available carbohydrates (10 % of saccharose) was established either, nor of diets with a low or high energy/protein ratio.

Until now, complete eradication of *C. spiroforme* from a rabbitry is difficult. The bacterium only seems sensitive for the expensive vancomycine (Katz et al., 1978). The currently used tetracyclines have no influence on *C. spiroforme*, on the contrary they rather promote its proliferation (Carman & Evans, 1984). Several authors were able to cure *C. spiroforme*-mediated diarrhoea with imidazoles, although the disease did not disappear completely : dimetridazole, ipronidazole and ronidazole were successful in the field (Eaton & Fernie, 1980, Harris & Portas, 1985). Patton et al. (1982) showed that 400 ppm of copper in the diet may protect against diarrhoea and mortality in weanling rabbits. This effect may be explained by the findings of Grobner et al. (1986), who showed that copper at levels of 250 ppm or more inhibits toxin production and growth of *C. spiroforme* in vitro.

Bacillus piliformis (Tyzzer's disease)

Tyzzer's disease was first described as an infectious disease causing overwhelming diarrhoea and high mortality in Japanese waltzing mice by Tyzzer (1917). Only in 1965 was the disease also detected in another species, the rabbit (Allen et al., 1965) and since then the range of susceptible animals has been extended to numerous other mammalian species (Licois, 1984). Most cases of Tyzzer's disease in rabbits described in literature were established in laboratory units. Only few reports deal with outbreaks in commercial rabbitries. Since 1982 the disease has been reported from Belgian (Peeters et al., 1985a), French (Licois, 1984), German (Scharmann, 1985), Hungarian (Vetesi, 1982) and Indian (Rai et al., 1984) commercial rabbits. During our epidemiological survey the disease has been detected in 1.1 to 10.9 % of diarrhoeic rabbits from 8 out of 29 rabbitries examined (Table 1). As diagnosis is rather difficult, it is probable that Tyzzer's disease is more common in commercial rabbitries than these figures suggest.

Different stages of Tyzzer's disease occur in the field and only acute outbreaks may be confirmed with certainty. During the acute stage of the disease, mortality may reach 40 % during the first weeks of the outbreak. In surviving animals, there is a chronic evolution with sometimes extreme cachexia. Multifocal hepatic necrosis, focal myocardial necrosis, patches of mucosal necrosis in ileum, caecum and colon and marked caecal oedema are most prominent at

autopsy of acute deceased animals. When the disease becomes endemic in a rabbitry, these lesions are absent in most animals. In most cases Tyzzer's disease is the result of reactivation by stress or by immunosuppression, which is perhaps the reason why most outbreaks of Tyzzer's disease are reported after purchase and transport of breeding animals or as a complication of other diseases. Moreover, also transplacental transmission of *B. piliformis* has been shown (Fries, 1978).

Very few antibiotics are active against *B. piliformis*. Treatment of experimentally infected mice and rabbits showed that penicillin G, streptomycin, neomycin, polymyxine B, chloramphenicol, sulfadimidin and sulfadimethoxin are useless. Only chlortetracycline and oxytetracycline are sufficiently active (Licois, 1984) Good results have also been obtained with high doses of erythromycin (100 mg/kg i.m.)(Thunert, 1982).

Viruses

Until now, 5 different viruses have been established in diarrhoeic rabbits. Rotaviruses are most common. They were present in 19 of 29 rabbitries of our field survey and this was in agreement with serological evidence. Also data from Canada (Petric et al., 1978), England (Bryden et al., 1978), France (Morisse et al., 1982), Hungary (Kudron et al., 1982), Italy (Castrucci et al., 1984, 1985), Japan (Takahashi et al., 1979) and the U.S.A (DiGiacomo & Thouless, 1984,1986, Schoeb, 1986). indicate that rotaviruses are endemic in most commercial rabbit units. Rotavirus infection seems most common in winter season (Hervouet & Nouaille, 1986).

In suckling rabbits rotavirus-infection is characterized by sudden onset, rapid spread and high morbidity and mortality (Peeters et al., 1982, Schoeb et al., 1986). Mostly 1 to 3 week old rabbits are affected. They die within 2 days after the onset of a watery yellowish diarrhoea. In weanling rabbits rotavirus infection is associated with watery diarrhoea. In uncomplicated infections, diarrhoea stops spontaneously 2 to 3 days after the onset of the symptoms and mortality is quite low. Weight gain and feed conversion is badly altered during one week. Lesions are limited to watery or liquid caecal contents, moderate to severe small intestinal villous atrophy and epithelial desquamation. These lesions are in agreement with preliminary experimental infection studies in weaned rabbits (Petric et .al., 1978).

The significance of the other viruses in rabbit diarrhoea is unclear. In literature only mild symptoms or no symptoms at all were reported after experimental infection with adenoviruses (Bodon & Prohaszka, 1980), coronaviruses (Osterhaus et al., 1982, Descoteaux et al., 1985)

and parvoviruses (Matsunaga & Chino, 1981). Probably they aggravate other enteric infections by synergistic action.

Nutritional factors

Data from the field and from experimental studies clearly indicate a relationship between nutrition and juvenile rabbit enteritis. Presumably the diet may disturb the caecal ecological system in certain circumstances. However, until now there is a lack of substantial experimental evidence on the possible mechanisms involved. Crude fiber, carbohydrates and protein as the way of feeding may be of importance as well.

Several authors (Colin et al., 1976, Laplace, 1978, Spreadbury & Davidson, 1978, Pote et al., 1980) have noted that dietary fiber may protect weanling rabbits from diarrhoea. However there is conflicting evidence on the levels of crude fiber needed. Franck & Coulmin (1978) and De Blas et al. (1986) showed increased mortality after feeding rations with 9 % of crude fiber, whereas Licois et al. (1980) were not able to induce mortality with rations containing as little as 3.3 % of fiber. Whatever, most authors agree that administration of feeds with less than 9 % of crude fiber is followed by significantly lower weight gain (Colin et al., 1976, Lebas & Laplace, 1977, Cheeke & Patton, 1978, Licois et .al., 1980, Champe & Maurice, 1983). Lebas also stresses the importance of the digestibility of the crude fiber. This depends on the source of crude fiber used (Maertens & De Groote, 1984).

Also other components of the feed may be involved. Hens (1987) showed that administration of iso-energetic feeds (2500 kcal of apparent digestible energy) causes increased mortality by digestive disorders in weanling rabbits, when they contain more than 18 % of raw protein. Different hypotheses have been put forward to explain the influence of fiber and carbohydrates on caecal metabolism. According to Cheeke et al. (1986) the diarrhoea promoting effect of low fiber diets is based on two factors. Feeds low in fiber cause a reduction of caeco-colonic motility (Laplace, 1978). This results in increased caecal retention time of ingesta. As low fiber diets are a priori rich in readily available carbohydrates, the increased caecal retention of carbohydrates may allow proliferation of *Clostridium spiroforme*. The presence of glucose arising from starch digestion which is necessary for iota toxin production by *C. spiroforme* (Borriello & Carman, 1983), may favour iota-enterotoxaemia. If this hypothesis is correct, also pathogenic agents affecting the integrity of small intestine and causing intestinal hypomotility (coccidiosis, Fioramonti et al., 1981) may provoke increased concentrations of carbohydrates in the caecum. Yet, combination of coccidia or enteropathogenic *E. coli* and *C. spiroforme* did not produce such effects, nor were feeds rich in readily available carbohydrates.

Morisse et al. (1985) on the contrary argue that a diet high in fiber and low in starch promotes diarrhoea, while a diet high in readily available carbohydrates gives a low incidence of enteric disease. Their hypothesis is that a high level of fermentable carbohydrates results in vigorous production of volatile fatty acids (VFA) in the caecum. This maintains an acidic pH of about 5.8, which is optimal for the normal bacterial flora, and to acid for proliferation of *Clostridium spp.* A diet higher in fiber and lower in fermentable carbohydrate results in lower VFA production, a higher caecal pH, an increase in ammonia (because less N is being used by digestive bacteria) and proliferation of *Clostridium spp.* because of the suboptimal growth of normal flora and the favourable pH and ammonia levels for *Clostridium* growth. Moreover, VFA-concentration and composition may also play a role in inhibiting *C. spiroforme* as shown for *C. difficile* in hamsters (Rolfe, 1984). Another effect of low VFA production and higher caecal pH is the dissociation and the loss of the inhibitory influence of non dissociated VFA on *E. coli.* This may lead to *E. coli* dysbacteriosis and may favour proliferation of enteropathogenic *E. coli.* Different authors showed that caecal pH and VFA-composition may be influenced by the feed (Champe & Maurice, 1983, Morisse et al., 1985) and by the feeding method (Maertens & Peeters, 1988).

Both hypotheses warrant further investigation. For these experiments rabbits free from recognized infectious agents or rabbits carrying known disease agents should be used. It is striking from the literature that a lot of feeding experiments are carried out without examining the presence of potential pathogenic agents. As in most rabbitries, experimental units included, rotaviruses, coccidia and *C. spiroforme* may be endemic, their absence from these experiments would be surprising. Since these agents influence at least in part intestinal motility (coccidia) and starch digestion (rotaviruses) and may cause caecal dysbacteriosis, their presence should be investigated systematically to exclude possible interference with the experiments. Therefore, more sensitive methods have to be developed to detect these agents more easily.

Mucoid enteropathy

Beside nutrition, also other factors may lead to a modification of caecal biochemistry. Different stress factors (cold, pneumonia,...) may lead to gut stasis. This is often followed by an accumulation of mucus in the colon, a syndrome called mucoid enteropathy. Already in 1976, Sincovics showed that caecal ligation also induces mucoid enteropathy. By using the same technique Toofanian and collaborators were able to show that such stop of transit is followed by different biochemical changes : decrease of caecal acetate and butyrate (Toofanian & Hamar, 1986) and decrease of small intestinal disaccharidases (Toofanian, 1985). As VFA seem involved in the control of *E. coli* and *C. spiroforme* in the caecum, also factors causing gut stasis may alter caecal microflora. Moreover, Toofanian and Targowski (1986) also

demonstrated that caecal filtrates from rabbits with experimental mucoid enteropathy stimulated mucus secretion and discharge from colonic goblet cells. According to Buckwell (1987) gut stasis in rabbits may be treated by an i.m. injection of 250 mg metamizole with 2.5 mg methindizate HCl and 1 mg dexamethasone sodium phosphate.

Further perspectives and conclusions

From the preceding discussion it becomes clear that juvenile enteritis in rabbits is a complex disease and that a lot of unknown factors still exist. Nevertheless, in recent years good progress has been made in understanding some of the factors involved, although a lot of work still has to be done. It is evident that nutrition and stress factors are important, but their role may not be over-emphasized. Indeed, in close rabbitries with good hygienic standards, losses are limited and only slightly influenced by different commercial rations. In such rabbitries problems often start after the introduction of a new batch of animals, stressing the importance of infectious agents and healthy looking carriers. In rabbitries with high animal density, any infectious agent multiplies rapidly and may threaten the indigenous population.

This means that prevention has to be based in the first place on excellent hygiene and good control of newly acquired animals. This is particularly important to avoid the introduction of highly pathogenic agents. So, there is an urgent need for quick methods to trace healthy looking carriers. This problem should be solved as quick as possible in order to guarantee the further expansion of meat rabbit production in the near future. There is also a need for vaccines, in order to reduce the risks, associated with the introduction of new animals to a healthy stock. Moreover, the anticoccidials with proved activity have to be registered for incorporation in rabbit feeds.

The moderately pathogenic agents are omnipresent and have to be controlled by adequate hygienic procedures : compartimentation of rabbit houses, evacuation systems which keep faeces as dry as possible, regular disinfection of the compartments after each slaughtering of a new batch of finished animals ore at least once a year. These measures are necessary to keep levels of infection low and to avoid losses by bad feed conversion by subclinical enteritis. As the feed may enhance losses by subclinical enteritis or may perturbate intestinal flora, further studies on the influence of feed composition on caecal parameters (pH, VFA, *E. coli* - and *C. spiroforme* proliferation) are necessary in order to develop low risk feeds. This research has to take in account the possible interaction of disease agents.

Finally, medication of juvenile rabbit enteritis has to start from an exact inventory of the pathogenic agents present. Therefore several living diarrhoeic rabbits have to be submitted for

detailed laboratory analysis before any medication. Autopsy alone gives insufficient data on the possible agents involved. Medication in accordance with laboratory results gives mostly satisfactory results. Each medication has to be followed by hygienic measures and if necessary, by a detailed follow up of the management in the rabbitry. Replacement of high risk feeds may sustain treatment.

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Summary

Digestive disorders are the predominant cause of mortality in commercial rabbits. Besides mortality, they also cause important economic losses by growth depression and bad feed conversion. Detailed laboratory analysis of diarrhoeic commercial rabbits indicated that juvenile enteritis is mostly associated with coccidia, enteropathogenic *Escherichia coli* (EPEC), rotaviruses and/or *Clostridium spiroforme* mediated iota-enterotoxaemia. Also cryptosporidia, worms, *Bacillus piliformis* (Tyzzer's disease) and viruses other than rotaviruses may be involved. In most rabbitries 3 to 4 pathogenic agents are present. There are indications that the feed composition may influence the course of enteric disease.

Experimental infections of rabbits free from recognized infectious agents allowed to test the pathogenicity of the different infectious agents isolated. Some species of eimeria (*E. flavescens, E. intestinalis*) and some strains of EPEC (serotype O109/biotype 1 in suckling rabbits and serotypes 015 (biotype 3-) and O103 (biotype 8) in weanling rabbits cause 50 % mortality and more. Other species of eimeria, other EPEC strains, cryptosporidia and viruses induce growth retardation, bad feed conversion and low mortality. Iota-enterotoxaemia requires preceding intestinal dysbacteriosis. Dysbacteriosis may be induced by early weaning or by certain antibiotics and possibly by nutrition. There is a lack of substantial experimental evidence on the relationship between nutrition and juvenile rabbit enteritis.

According to the observations from the field and in the light of the new experimental data from recent literature, following classification of the digestive disorders in commercial rabbits has been made :

1. Specific enteritis induced by highly pathogenic agents : losses are mainly determined by one agent and are independent from nutritional and environmental factors
2. Multifactorial enteritis associated with several synergistically acting infectious agents, often enhanced by nutritional or environmental factors
3. Iota-enterotoxaemia, resulting from intestinal dysbacteriosis
4. Subclinical enteritis by moderately pathogenic agents and associated with bad feed conversion and growth depression without obvious clinical signs

As the introduction of new batches of reproduction stock is often followed by enteric disease, there is an urgent need for quick and reliable methods to trace healthy looking carriers of highly pathogenic agents. Also effective vaccines are needed. As some feeds may enhance losses by subclinical and multifactorial enteritis or may perturbate intestinal flora, further studies on the influence of the feed composition on caecal flora are necessary in order to develop low risk feeds and in order to guarantee the further expansion of rabbit industry.

Résumé

Les troubles digestifs sont la première cause de mortalité dans l'élevage rationnel de lapins. En dehors des mortalités, ils sont aussi responsables de pertes économiques considérables en causant une diminution de la vitesse de croissance et une mauvaise conversion alimentaire. Des examens de laboratoire détaillés de lapereaux présentant de la diarrhée ont montré que ces troubles sont souvent associés à la présence de coccidies, de *Escherichia coli* entéropathogènes (EPEC), de rotavirus et/ou de l'entérotoxémie iota (*Clostridium spiroforme*). *Cryptosporidium sp.*, des vers, *Bacillus piliformis* (maladie de Tyzzer) et des virus autres que les rotavirus peuvent également intervenir. Dans la plupart des élevages 3 à 4 agents pathogènes sont présents. Il y a des indications que la composition des aliments influence l'évolution des problèmes digestifs.

L'infection expérimentale de lapereaux exempt de facteurs pathogènes reconnus a permis de tester la pathogénicité des différents agents pathogènes isolés. Certaines espèces d'eimeria (*E. flavescens, E. intestinalis*) et certaines souches d'EPEC (sérotype O109/biotype 1 chez les lapereaux sous la mère et les sérotypes O15 (biotype 3-) et O103 (biotype 8) chez les lapereaux sevrés) provoquent une mortalité de 50 % et plus, alors que d'autres espèces d'eimeria, d'autres

EPEC, des cryptosporidies et les virus causent seulement un retard de croissance, une mauvaise conversion alimentaire et une mortalité moins élevée. Une dysbactériose intestinale précède l'entérotoxémie iota. Cette dysbactériose peut être provoquée par un sevrage précoce, certains antibiotiques et peut-être aussi par l'alimentation. A l'heure actuelle il y a un manque de données expérimentales claires sur la relation alimentation-entérite.

Sur base des observations du terrain et des données expérimentales nouvelles de la litérature récente, les troubles digestifs peuvent être classés comme suit :

1. Entérites spécifiques causées par des agents hautement pathogènes : les pertes sont principalement déterminées par un agent spécifique indépendamment des facteurs nutritionels et environnants.
2. Entérites multifactorielles associées à différents agents infectieux avec action synergique, souvent aggravées par des facteurs nutritionels et/ou environnants.
3. Entérotoxémie iota, faisant suite à une dysbactériose intestinale
4. Entérites subcliniques causées par des agents pathogénes modérés et associées à une mauvaise conversion alimentaire et un retard de croissance sans qu'il y ait des signes cliniques clairs.

Comme l'introduction d'un nouveau lot de reproducteurs est souvent suivie par des problèmes digestifs lors de l' engraissement quelques semaines ou quelques mois plus tard, des méthodes de diagnostic fiables et rapides doivent être développées d'urgence pour détecter des porteurs sains d'agents hautement pathogènes. Le développement de vaccins efficaces doit aussi être entrepris. Comme certains aliments peuvent aggraver les pertes par les entérites subcliniques et multifactorielles ou peuvent perturber la flore intestinale, des études sur l'influence de la composition alimentaire sur la flore intestinale sont nécessaires en vue de la mise au point d'aliments à bas risque et garantissant l'expansion de la production cunicole.