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Aspects of colibacillosis in farm animals

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INTRODUCTION

It has been known for a considerable time that *Escherichia coli*, although a normal inhabitant of the intestinal tract, can also be associated with a variety of pathological conditions in man, farm animals and poultry.

When Escherich (1885) isolated from the faeces of a newborn baby an organism which is now accepted as *E. coli*, he considered it to be a harmless saprophyte. Laruelle (1889) was the first to suggest the possible pathogenicity of this organism, while Jensen (1893) showed that it was the cause of white scour in calves. The development of reliable serological methods facilitated the differentiation of strains and numerous workers have demonstrated an association between certain serological types of *E. coli* and various disease conditions in animals. Enteric diseases in young animals are an important cause of mortality and economic loss to the farming community.

There have been a number of reviews on various aspects of *E. coli* infection in farm animals (Sojka, 1971; Morris & Sojka, 1984; Smith, 1976; Sojka, Morris & Wray, 1979; Morris, 1984) since the comprehensive publication of Sojka (1965) and the emphasis of the present review will be the mechanisms by which *E. coli* cause disease in farm animals and how this knowledge may be applied to the prophylaxis and treatment of disease.

Disease syndromes associated with *E. coli* are usually referred to as colibacillosis and in farm animals these include:

(*a*) Enteric colibacillosis, which includes colibacillary diarrhoea and colibacillary toxaemia.

(*b*) Systemic colibacillosis which is caused by invasive strains of *E. coli*.

(*c*) Mastitis in adult cattle; of which a comprehensive account will be found in the review of Morris & Sojka (1984) and will not be considered further.

ENTERIC COLIBACILLOSIS

Colibacillary diarrhoea

Colibacillary diarrhoea occurs most frequently in calves, lambs and piglets 1–3 days after birth. Piglets, however, may also develop diarrhoea around weaning and this will be mentioned separately under weanling colibacillary diarrhoea.

Neonatal colibacillary diarrhoea is the most commonly diagnosed cause of enteric disease in young animals in England and Wales during their first week of life (MAFF, 1984). The disease is often acute; the enterotoxigenic *E. coli* (ETEC) cause severe diarrhoea which gives rise to fluid and electrolyte imbalances, dehydration

and death. Specific lesions are absent at post-mortem examination and the intestinal mucosa is undamaged. Large numbers of certain serotypes of *E. coli* ($> 10^8$ organisms) are found in the small and large intestines, often closely associated with the mucosa, while the numbers of other intestinal bacteria are normal (Smith & Jones, 1963). These *E. coli* belong to relatively few serological groups; in calves and lambs they usually belong to the same OK groups and in piglets the majority of such serogroups, which are often haemolytic, are seldom found elsewhere (Sojka, 1971).

ETEC are able to adhere to the mucoid surface of the villous epithelium of the small intestine and so overcome the mechanical clearance caused by peristalsis. The adherence of an *E. coli* is often associated with the presence of filamentous, proteinaceous, surface antigens, termed fimbriae and those associated with ETEC for different animal species tend to be antigenically distinct although they share a number of chemical and biological properties (Gaastra & de Graaf, 1982). Besides promoting colonization of the small intestine, most of these fimbrial antigens, with the exception of 987P, exhibit mannose-resistant haemagglutination of animal erythrocytes.

The properties of the more common adhesins found in ETEC strains of animal origin are shown in Table 1. Further information will be found in the review of Gaastra & de Graaf (1982).

The commonest adhesin of ETEC from piglets has been found to be the K88 antigen, of which three antigenic variations exist (K88ab, ac and ad). However *E. coli* that produce K88 do not adhere to the brush borders of intestinal epithelium from all piglets. A recent study involving the three K88 variants has shown that at least five different phenotypes of piglets could be distinguished with *in vitro* enterocyte brush border tests (Bijlsma, de Nijs & Frik, 1981). The phenotypes appear to be the product of two alleles at a single locus which are inherited in a simple Mendelian manner; the adhesive allele being dominant over the non-adhesive allele (Sellwood *et al.* 1975).

Evidence from adhesion studies *in vitro* imply that *E. coli* with different fimbriae bind to different receptors in the small intestine (Isaacson *et al.* 1978). Thus isolated K88 fimbriae will not inhibit the attachment of K99 bacteria to epithelial cells and piglets which are genetically resistant to colonization by K88$^+$ETEC are fully susceptible to infection by K99$^+$ *E. coli* which readily colonize their small intestine. Runnels, Moon & Schneider (1980) suggested from the results of their *in vitro* studies that the piglet's small intestine develops resistance to K99-mediated adhesion with age, but that this was not the case with K88-mediated adhesion. Nevertheless diarrhoea in older pigs caused by K88$^+$ ETEC does not appear to be a problem and the resistance of older animals to *E. coli* diarrhoea is not related entirely to the presence or absence of receptors.

Pohl *et al.* (1982) found that 157 of the 401 *E. coli* from calves that they examined possessed an adherence antigen which they called Att 25 and they suggested that this antigen was similar to antigen 'y' which was described by Giradeau, Dubourguier & Contrepois (1980). Aning *et al.* (1983) found that some strains of *E. coli* O65:K? isolated from pigs caused mannose-resistant haemagglutination and adhered to isolated porcine enterocytes.

In some cases more than one different fimbrial antigen may be found on the same

Table 1. *Neonatal* E. coli *diarrhoea in piglets, calves and lambs*

	Adhesins found in enterotoxigenic E. coli *isolates*			
Adhesin	K88	K99	F41	987P
In ETEC isolates from	Piglets only	Calves, lambs (piglets)	Calves, lambs (piglets)	Piglets only
In ETEC isolates belonging to serological O groups	O8, O45, O138, O141, O147, O149, O157	O8, O20, O9, O64, O101	O101 and O9	O9, O20
Facilitates colonization of	Piglet's jejunum and ileum	Calf's, lamb's and piglet's posterior jejunum and ileum	Calf's, lamb's, piglet's posterior jejunum and ileum	Piglet's ileum
In vitro test: Mannose-resistant haemagglutination (MRH)	+(Guinea-pig RBC)	+ (Horse RBC)	+(Sheep RBC)	—
In vivo test: Adherence to piglet's villous epithelial cells (small intestine)	+ (Jejunum, ileum)	+ (Posterior jejunum and ileum)	+ (Posterior jejunum and ileum)	+ (Ileum)
Production of adhesin plasmid mediated	+	+	?	—

bacterium (Morris, Thorns & Sojka, 1980; Schneider & To, 1982). The genetic determinants of the K88 and K99 antigens are plasmid-mediated, whereas those for 978P and possibly F41 may be located on the chromosome.

Although colonization is an essential prerequisite for strains to produce diarrhoea, colonization *per se* does not cause diarrhoea and the strain must be enterotoxigenic. Two main classes of enterotoxins, which stimulate fluid secretion into the intestinal lumen, are recognized:

(a) Heat-labile (LT) which is inactivated by heating at 60 °C and exists as a high molecular weight protein that resembles cholera toxin both pharmacologically and immunologically. However, LT from *E. coli* strains associated with enteric disease in pigs and humans have been found to have antigenic differences. Like cholera toxin, LT binds to the GM1 ganglioside in the enterocyte membrane.

(*b*) Heat-stable (ST) enterotoxin has a low molecular weight and is poorly immunogenic and exists in two forms, STa and STb, which differ in their solubility in methanol.

Table 2 lists the properties of the enterotoxins.

Both enterotoxins act by altering the ion transport mechanisms of the mucosal epithelial cells without causing histological damage. LT activates adenylate cyclase to increase cyclic adenosine monophosphate (cAMP) within the epithelial cells of the small intestine (Evans *et al.* 1972). In contrast ST acts by stimulating guanylate cyclase producing increased levels of cyclic guanosine monophosphate (cGMP) which inhibits the absorptive mechanisms; whereas cAMP stimulates secretion as well as inhibiting absorption. Both processes result in a net secretion into the intestinal lumen.

Table 2. *Properties of enterotoxins*

		E. coli		
			ST	
	V. cholerae choleragen	LT	ST_A	ST_B
Ileal hypersecretion	+	+	+	+
Mol. weight	84×10^3	$10^4 - 10^6$	$4{\cdot}5 \times 10^3$	$10^3 \times 10^4$
Stable 65 °C	−	−	+	+
Stable 100 °C	−	−	±	+
Immunogenic	+	+	−	−
Ganglioside receptor	+	+	−	?
Methanol-soluble	−	−	+	−
Plasmid	−	+	+	+
Biological activity				
Neonatal piglet		+	+	−
Weaned piglet		+	−	+
Calf		?	+	?
Suckling mouse		−	+	−

Kohler (1971) investigated the effect on piglets of crude ST (broth culture) and crude LT (whole cell lysate). With LT, diarrhoea developed later than with ST, was more persistent and more piglets died; with ST none of the piglets died. Enterotoxin production is plasmid-mediated and the transmissible nature of these virulence factors was exploited by Smith & Linggood (1971) to assess their role in the pathogenesis of neonatal diarrhoea in piglets. Removal of the K88 plasmid from a porcine ETEC was accompanied by a loss in its ability to cause diarrhoea. The introduction of the K88 plasmid from another *E. coli* isolate restored its virulence. A non-enteropathogenic strain of *E. coli* was rendered enteropathogenic by implanting the K88 and Ent plasmids. The K88 antigen enables the organism to colonize the anterior small intestine while the enterotoxin is responsible for the profuse diarrhoea. A $K88^+$ Ent^- recombinant colonized the small intestine and diarrhoea, which was not severe, occurred in some cases. Likewise transfer of K88 and Ent plasmids to an *E. coli* K12 strain did not convert the strain to enteropathogenicity suggesting that other factors may be of importance.

Most of the *E. coli* strains enteropathogenic for calves, lambs and piglets produce ST; in the case of the first two species it is usually STa and in piglets it may be either STa or STb. $K88^+$ strains of *E. coli* from piglets generally produce both LT and STa.

Sivasvamy & Gyles (1976) found that most ETEC from calves were mucoid and possessed the A type of K antigen. Isaacson, Nagy & Moon (1977) reported that both capsule and pili were involved in the colonization of the porcine intestine by some strains of ETEC. They speculated that the capsule may either protect the organism in the intestine or it may be involved in the adhesion to the mucosa. Our own experiments, (Sojka, Wray & Morris, 1978) showed that non-capsulated variants of the ETEC strain, B44, were relatively avirulent when used to challenge lambs.

Non-toxigenic (invasive) *E. coli*, which have a shigella-like pathogenicity, and

are associated with colitis and dysentery-like syndrome in both older children and adults, have been described on a number of occasions (Formal *et al.* 1971; Sakazaki & Namioka, 1957). Recently *E. coli* causing dysentery have been described in calves (Pohl *et al.* 1983; Chanter *et al.* 1984).

Investigations of outbreaks of neonatal diarrhoea have shown that in addition to ETEC other agents such as rotaviruses and the protozoa cryptosporidium may also be isolated (Acres *et al.* 1975; Morin, Lariviere & Lallier, 1976). Stair *et al.* (1973) suggested that *E. coli* may aggravate the outcome of illness brought on by rotavirus and McNulty (1978) pointed out that it is not clear whether death is caused by rotavirus infection alone or whether it is due to secondary bacterial infection. Experimental co-infection with ETEC and rotavirus in gnotobiotic calves have shown both a synergistic interaction producing a fatal disease (Gouet *et al.* 1978) and an interaction in which rotavirus aided ETEC colonization occurs but with little disease enhancement (Runnels *et al.* 1980). Experiments in lambs (Wray *et al.* 1981, 1984) showed that co-infection with ETEC and rotavirus produced a higher mortality rate than when either of the agents was administered alone and the results suggested that the agents may act synergistically. On the other hand, Tzipori *et al.* (1981) found that rotavirus and ETEC co-infection of gnotobiotic lambs failed to induce diarrhoea. Thus, while the exact nature of the interaction between rotavirus and ETEC is still debatable, it should be borne in mind when investigating diarrhoea outbreaks that both agents may be frequently isolated.

Weanling colibacillary diarrhoea

The sudden changes of environment and microflora that occur in older piglets at weaning may lead to the multiplication of *E. coli* in the small intestine which may give rise to colibacillary diarrhoea or colibacillary toxaemia. The isolates of *E. coli* from both syndromes most frequently belong to OK groups O 141 : K 85ab or O 141 : K 85ac or to OK group O 138 : K 81 (Sojka, 1971).

It has been suggested that other factors may be involved and Lecce *et al.* (1982) induced weaning diarrhoea in piglets by infecting them with rotavirus followed by haemolytic *E. coli*. They suggested that the rotavirus damaged the epithelium of the small intestine and produced an environment which favoured the selection and growth of the *E. coli*. The dietary regimen was also believed to play an important role (Lecce *et al.* 1983). Miller *et al.* (1984) suggested that post-weaning diarrhoea may be precipitated by a transient hypersensitivity reaction to dietary antigen. They found that piglets fed on a protein diet developed intestinal hypersensitivity which predisposed to the multiplication of *E. coli* and the development of diarrhoea, whereas piglets fed on pre-digested protein diet remained healthy.

Colibacillary toxaemia in pigs

Three syndromes, which involve the relatively small number of *E. coli* serogroups mentioned previously, have been described:

(*a*) Shock in weaner pigs. (*b*) Haemorrhagic enteritis. (*c*) Oedema disease.

In shock in weaners, one or two piglets in a litter die suddenly (Schimmelpfennig, 1970); oedema is observed in the intestine, lungs and kidneys as well as in the CNS.

Serous exudate is common in the body cavities and in severe cases blood may pass into the intestinal lumen. Schultz, Brass & Nussel (1961) suggested that the intestinal changes are due to permeability disturbances.

Haemorrhagic enteritis, a form of enteritis in post-weaning piglets, is characterized by sudden death, and haemorrhagic lesions of the mucosa of the gastrointestinal tract and associated lymph nodes (Thomlinson & Buxton, 1962). Diarrhoea may sometimes occur. The pathogenesis of this and the previously mentioned syndrome may be related and involve the rapid absorption of endotoxin from the gut.

Oedema disease is an acute disease of young pigs occurring about a week after weaning. As the name implies extensive oedema occurs in the subcutaneous tissue of the head, the sub-mucosa of the stomach and mesentery of the colon. Affected piglets show neurological disturbances such as ataxia and convulsions. Histologically characteristic lesions of angiopathy affecting the small arterioles may also be present.

The mechanisms involved in the pathogenesis of the above three syndromes is still uncertain. Thomlinson & Buxton (1962) believe that each of these syndromes are the manifestations of an anaphylactic reaction to endotoxin. According to this hypothesis small amounts of *E. coli* polysaccharide are constantly absorbed from the small intestine and this results in the production of tissue-sensitizing antibodies. At weaning, a rapid multiplication of *E. coli* may occur, leading to the accumulation of endotoxin and in the sensitized animals a hypersensitivity reaction may develop. The type of lesions depend upon the degree of hypersensitivity and the amount of endotoxin absorbed.

Erskine, Sojka & Lloyd (1957) found that intravenous injection of cell-free extracts from *E. coli* strains associated with oedema disease resulted in a condition indistinguishable from field cases. Schimmelpfennig (1970) suggested that the first two syndromes represent different degrees of the reaction to endotoxin absorption and that oedema disease is caused by a neurotoxin. Nielsen & Clugston (1971) compared the effect of intravenous injection of a partially purified freeze-thaw extract of *E. coli* (referred to as 'Edema Disease Principle', EDP) and phenol/water extract from the same strain (endotoxin). The clinical responses induced by EDP and endotoxin were similar initially, but EDP produced additional delayed neurological symptoms of ataxia, which were characteristic of oedema disease.

Kurtz & Short (1976) produced angiopathy in piglets by injecting bacterial autolysates or haemolysin intravenously. Lipopolysaccharide caused acute endotoxin shock but no angiopathy. Typical clinical symptoms of oedema disease were not observed consistently in any of the groups of piglets. Schimmelpfennig & Weber (1978) isolated crude oedema disease neurotoxin from *E. coli*, which caused fits and paralysis in mice. The toxin was thermolabile, sensitive to formalin and poorly immunogenic.

Dobrescu (1983) and Smith, Green & Parsell, (1983) found that strains of *E. coli* from oedema disease produced a toxin which showed a cytopathic effect on Vero cells. The properties of the oedema disease toxin differed from other *E. coli* toxins active on Vero cells. Smith, Green & Parsell (1983) transferred the Vero toxin genes from a human *E. coli* strain to *E. coli* K12 and found that when cell-free cultures were inoculated into pigs they produced a disease clinically and pathologically similar to oedema disease.

SYSTEMIC COLIBACILLOSIS

Systemic colibacillosis occurs frequently in calves, lambs and poultry. Bacteraemic strains of *E. coli* pass through the mucosa of the alimentary or respiratory tract and enter the blood stream where they may cause either (*a*) a generalized infection (colisepticaemia) or (*b*) a localized infection such as meningitis and/or arthritis in calves and lambs, or air sacculitis and pericarditis in poultry.

Systemic colibacillosis in calves and lambs

This occurs commonly in hypogammaglobulinaemic calves, usually in colostrum-deprived animals, but it may also occur in some colostrum-fed animals which have failed to absorb the immunoglobulins. If colostrum is to be effective it must be ingested within a few hours of birth because little or no absorption occurs after 24–36 h. In lambs systemic colibacillosis occurs most commonly 2–3 weeks after birth.

Generalized infection follows an acute, usually fatal course. Diarrhoea may occur but it is not a constant feature. Shock-like symptoms, possibly caused by endotoxin, may also be seen (Tennant *et al.* 1978). The external appearance of animals that die is normal but internally splenomegaly and organ congestion with petechiation are commonly found. The course of disease is more chronic in some animals and the *E. coli* localises in the joints and meninges.

In generalized infection pure cultures of *E. coli* can usually be isolated from most organs and tissues, whereas in localised infection *E. coli* may only occasionally be isolated from the infected sites. The *E. coli* belong to a small number of serological groups; the commonest being O78:K80(B) which is frequent in calves and lambs as well as poultry.

Experimental studies (Penhale *et al.* 1970; Logan & Penhale, 1971) showed that the main factor which predisposes a calf to systemic colibacillosis is gamma-globulin deficiency and that the IgM fraction of serum gamma-globulin prevented colisepticaemia.

Systemic colibacillosis in poultry

Many manifestations of *E. coli* infection in poultry have been described (Sojka, 1965) but the most common is systemic colibacillosis. Colibacillosis is primarily a disease of 5- to 12-week-old broiler chicks with a maximum incidence at 6–9 weeks (Gross, 1972) but it can also occur in newborn chicks and turkeys.

The main clinical characteristics are respiratory distress and sneezing, depression, severe green diarrhoea and often lameness. Death usually occurs within 5 days of the onset of signs and at autopsy the most frequent lesions are fibrinous pericarditis and perihepatitis with thickened air-sacs which contain yellow caseous exudate. The infecting strain of *E. coli* can often be isolated in pure culture from the pericardium of birds which have died but in killed birds the lesions may be resolving and sterile. In chronic cases the infecting organism may be localised in affected joints. The strains of *E. coli* belong to relatively few serological OK groups; the commonest being O78:K80, O1:K1 and O2:K1 (Sojka & Carnaghan, 1961).

Harry & Hemsley (1965) reported that in normal chickens *E. coli* were restricted to the upper respiratory tract whereas in diseased birds pathogenic *E. coli* were isolated from the air-sacs and trachea. They concluded that the production of

colisepticaemia depended on factors other than the presence of a bacteraemic strain of *E. coli* in the upper respiratory tract. Gross (1957) found that many outbreaks of colisepticaemia occur in flocks affected with respiratory disease such as infectious bronchitis and *Mycoplasma gallisepticum*, although in some outbreaks *E. coli* may be the sole agent.

Virulence determinants in bacteraemic E. coli. A high proportion of *E. coli* isolated from calves, lambs or chickens produce Colicin V (Smith, 1974). By transferring the Col V plasmid from virulent field isolates into non-pathogenic strains of *E. coli*, such as strain K12, Smith found that the acquisition of the Col V phenotype was always accompanied by an increase in lethality. This was not associated with toxic activity but with a greater ability to survive in blood and peritoneal fluids. Smith also pointed out that although the genes associated with the increased survival were present on the Col V plasmid his results did not indicate whether the Col V genes themselves or other genes were responsible. The determinants for serum resistance and Col V production have been found to be closely linked (Binns, Davies & Hardy, 1979) and Williams & George (1979) reported that Col V plasmids specify an efficient iron-sequestrating mechanism that may play a key role in their pathogenicity.

Smith (1974) also described another independent plasmid, Vir, which was found in an *E. coli* strain isolated from a lamb. Vir^+ *E. coli*, however, appear to be far less common in nature than Col V^+ *E. coli* and have only been isolated from calves and lambs (Lopez-Alvarez & Gyles, 1980). Isogenic bacteria containing the Vir plasmid were toxic when injected into mice and chickens as were culture filtrates and ultrasonicates. In chickens the toxin produced characteristic lesions of fluid accumulation in the peritoneal cavity and pericardial sac similar to those caused by a chick lethal toxin produced by *E. coli* isolated from colisepticaemia in poultry (Truscott, 1973).

The Vir phenotype is characterized not only by the synthesis of a toxin but also the production of a surface antigen which could be demonstrated serologically (Smith, 1974). He showed that although Vir^+ organisms were agglutinated by specific antiserum the toxic activity was not neutralized which suggested that they may represent products of different genes located on the same plasmid. Morris *et al.* (1982) demonstrated that Vir^+ strains of *E. coli* attached *in vitro* to a number of cell preparations.

THE ROLE OF MANAGEMENT

Environmental factors are believed to play an important role in the aetiology of colibacillosis (Inglis, 1960; Loosmore, 1964). Thus it has been shown that the incidence of diarrhoea and mortality increased the longer a calf house was occupied (Roy *et al.* 1955; Wood, 1955). They believed that this was due to the natural selection of virulent *E. coli* strains, because at the beginning of their experiments a heterologous group of *E. coli* were present but as the occupation time increased certain types became dominant. Smith (1960) indicated that the pens were the most likely source of *E. coli* found in calves. Similar findings were recorded during farm investigations by Wray & Thomlinson (1975), who noted that, of the environmental factors studied, the use of new calf houses appeared to have the greatest influence on disease patterns. Likewise, the environment of piglets is heavily contaminated

at birth and it has been shown that an increased excretion of enteropathogenic *E. coli* by the sow occurs around farrowing (Arbuckle, 1968; Shreeve & Thomlinson, 1971). Thus high standards of husbandry and hygiene are important in the control of colibacillosis and, as the size of production units increase, high standards of management will be of paramount importance.

PROPHYLAXIS OF *E. COLI* INFECTIONS

Immunity

Young farm animals acquire maternal antibodies by ingestion of their dam's colostrum. The gamma-globulins in colostrum must be ingested within a few hours of birth because little absorption of protective immunoglobulins takes place after 24–36 h; in some animals it may be as little as 6–8 h.

In sow's colostrum, the immunoglobulins associated with *E. coli* antibody belong to the IgA and IgM classes, of which the former is synthesised in the udder (Porter, 1969). During the first week of lactation, the IgG and IgM content of sow's milk falls to one fifth of the amount present in colostrum, whereas the IgA level is only halved (Porter, Noakes & Allen, 1970), which suggests that IgA functions to provide protection in the alimentary canal. In the ruminant, however, the major immunoglobulins in colostrum and milk are of the IgG and IgM classes (Lascelles & McDowell, 1974; Butler, 1974). Within the ruminant alimentary tract the concentration of IgG is greater than that of IgA and in some cases IgG1 predominates (Logan *et al.* 1974).

Oral administration of hyperimmune serum, prepared against porcine strains of *E. coli* associated with diarrhoea, to piglets during their first week of life has given variable results in terms of disease prevention. Saunders *et al.* (1960) obtained disappointing results, whereas Murphy & Ryan (1958) and Kohler & Bohl (1966) claimed that it protected piglets from the loss of body fluid and diarrhoea associated with experimental infection. Logan & Penhale (1971) fed colostral whey to hypogammaglobulinaemic market calves and observed that, although the whey had a protective effect against diarrhoea it was not comprehensive. Logan, Pearson & McNulty (1977) suggested later that since the calves were several days old infection may have preceded the feeding of colostrum and showed experimentally that in order to be effective prophylactically, colostrum must be fed prior to infection.

A more recent approach has been the use of monoclonal antibodies specific for the K99 antigen and Sherman, Acres & Sadowski (1983) reported that treated calves were protected when challenged at 12 h of age with a virulent *E. coli* strain. The mortality in the calves receiving the monoclonal antibody was 29 % compared with 82 % mortality in the controls.

The more usual approach to provide passive protection has been by vaccination of the dam. Thus vaccines have been prepared with K88 antigen for use in pigs (Dam, 1971; Rutter & Jones, 1973) and K99 antigen for use in cattle and sheep. (Myers *et al.* 1973; Contrepois *et al.* 1978; Acres *et al.* 1979; Sojka, Wray & Morris, 1978). Under the experimental conditions high levels of protection were obtained when animals from vaccinated dams were challenged with virulent ETEC. Under field conditions, their use has not always been successful and Söderlind *et al.* (1982)

& Schipper *et al.* (1984) reported adverse results. The former suggested that the use of the vaccines apparently selected *E. coli* strains bearing other adhesins.

Another approach has been to prepare vaccines against the enterotoxins. Thus Dobrescu and Huygelen (1976) prepared a vaccine against LT and Fürer *et al.* (1982) immunized sows with procholeragenoid, a toxoid of cholera toxin which is related immunologically to LT. Both groups of workers found substantial passive protection of neonatal piglets against colibacillosis.

ST is not immunogenic in its natural form but has been rendered immunogenic by coupling it to a protein carrier (Frantz & Robertson, 1981; Giannella, Drake & Luttrell, 1981). However conflicting results have been reported when ST coupled to a protein carrier has been used as a vaccine. Rats actively immunized with a protein-coupled STa antigen were protected against challenge with STa (Klipstein, Engert & Clements, 1981). Whereas piglets sucking dams which had been immunized with coupled-ST were not protected against challenge with a porcine ETEC that produced heat-stable toxin only (Moon, Baety & Giannella, 1983).

Oral immunization has also been used to stimulate protective antibodies in milk and a local immune response in the intestine of weaned pigs. Oral immunization of sows with a live enteropathogenic strain of *E. coli* (Kohler, 1974) and oral dosing of piglets with heat killed ETEC (Porter, Kenworthy & Allen, 1974) has given encouraging results.

As our knowledge of the pathogenic mechanisms of *E. coli* increase, more effective vaccines are likely to result.

Other prophylactic methods

Other prophylactic measures have been dietary manipulation to prevent *E. coli* colonization. Thomlinson & Lawrence (1981) found that the addition of lactic acid to the drinking water decreased the gastric pH of pigs and delayed the multiplication of pathogenic *E. coli* at weaning with a corresponding reduction in the incidence of diseases. Underdahl, Torres Medina & Dorster (1982) fed *Streptococcus faecium* (formerly *Lactobacillus acidophilus*) to gnotobiotic pigs before challenge with virulent *E. coli* strains and found that the incidence of diarrhoea and mortality was reduced.

It may also be possible to breed disease-resistant live-stock. Some piglets are genetically resistant to colonization by K88$^+$ *E. coli* (Sellwood *et al.* 1975) and this resistance is due to a recessive gene inherited in a simple Mendelian manner.

THERAPY OF *E. COLI* INFECTION

Many different antibiotics have been used both for the prevention and treatment of diarrhoea in farm animals (see Sojka, 1965).

Varying degrees of success have been claimed and there seems to be little reason to doubt the efficacy of antibiotic therapy under certain conditions. Thus Bywater (1977) found a significant reduction in mortality and duration of diarrhoea when calves were experimentally infected with an ETEC and treated with antibiotics. On the other hand, Radostits *et al.* (1975) found no significant benefit from the use of antibiotics for the therapy of acute undifferentiated diarrhoea in newborn calves. Many of the clinical trials have been poorly designed and Buntain & Selman (1980) pointed out the non-specific nature of many outbreaks of diarrhoea and the

importance of knowing the immunoglobulin levels of the animals. The main drawback to the use of antibiotics is the rapidity with which *E. coli* develop resistance (Smith & Crabb 1957); many strains of *E. coli* isolated from farm animals show multiple antibiotic resistance (Jackson, 1981).

Another therapeutic approach has been the use of bacteriophage; Smith & Huggins (1982) successfully treated experimental *E. coli* infections in mice using phage and found it to be superior to antibiotic therapy. In farm animals, Kaszubkiewicz *et al.* (1982) used phage to control an outbreak of diarrhoea in piglets and Smith & Huggins (1983) found phages to be effective in treating experimental *E. coli* diarrhoea in calves, piglets and lambs.

The major therapeutic approach of recent years has been to combat the pathophysiological effects of the *E. coli* enterotoxins, which act by altering the ion transport mechanisms of the mucosal epithelial cells. Heat-stable toxins inhibit absorption; both toxins, however, cause a net loss of fluid and electrolytes into the intestinal lumen. Oral administration of electrolyte solutions containing glucose have been used for treatment because the absorption of glucose is accompanied by water and sodium (Nalin *et al.* 1970). In animals, the successful use of oral glucose-electrolyte solutions to combat diarrhoea has been reported by Bywater, (1977) and Jones, Phillips & Cleek (1984).

As our knowledge of the actions of enterotoxins increases there has been a corresponding interest in the pharmacological control of secretion. Drugs which have been of interest are those designed to reduce cyclic nucleotide levels or bind to the calcium dependent regulator.

Nicotinic acid, which reduces cAMP levels in adipose tissue was reported to inhibit the effect of cholera toxin in rabbit Thiry–Vella loops (Turjman, Gotterer & Hendrix, 1978) and to reduce the incidence of diarrhoea in piglets (Newsome, 1980). Aspirin was one of the first drugs to be shown to inhibit the effects of cholera toxin and Johannsen *et al.* (1979) reported that a dose of 0·5–1 g per piglet reduced the incidence of diarrhoea during a large field trial. Chlorpromazine, a drug used as a tranquillizer, affects cAMP levels and Lonnroth *et al.* (1979) reported that the use of chlorpromazine during a field trial significantly reduced the duration of *E. coli* diarrhoea. Bismuth subsalicylate, whose action depends on its inhibition of prostaglandin synthesis with a consequent reduction in fluid and electrolyte secretion, has been used in high doses to treat traveller's diarrhoea (DuPont *et al.* 1977) but there appear to be no record of its use in animals. Likewise absorbents such as charcoal and kaolin have been used for many years for the treatment of diarrhoea in animals and man. However, results in clinical studies have been disappointing in human infectious diarrhoea (Nalin & Cash, 1970) and there appears to be no evidence to support their use in animals.

CONCLUSION

It is now a 100 years since Escherich described the organism which bears his name. Its role as a pathogen in man and other animals is now well established and increasing knowledge of the pathogenic processes will lead to better prohylaxis and treatment.

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