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Experimental infection of piglets with cryptosporidium

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Piglets from five litters were dosed orally with cryptosporidium originally derived from diarrhoeic calves. The piglets were either nursed by the sow, artificially reared after sucking colostrum, or weaned on to creep feed. Colostrum-fed, artificially reared piglets obtained from two litters and exposed in the first week of life developed clinical signs of inappetence, vomiting and diarrhoea and shed oocysts in the faeces. Histologically the parasite was observed throughout the small and large intestine attached to epithelial cell surfaces and its presence was associated with extensive mucosal damage, particularly in the posterior small intestine, stunting and fusion of villi, immaturity of villous epithelial cells and oedema with increased cellularity of the lamina propria. Piglets from two other litters, both sucking and colostrum-fed artificially reared, exhibited similar but milder clinical signs. Histological lesions were less severe and cryptosporidium infection less extensive. When weaned piglets were exposed they remained clinically healthy although histologically there was evidence of cryptosporidium attachment in the small intestine and minor mucosal damage. There appears to be a good correlation between the extent of intestinal infection, the degree of mucosal damage and the severity of clinical disease induced by cryptosporidium in piglets.

ENTERITIS is a major cause of mortality in piglets in the first few weeks of life. The aetiology is complex and microorganisms thought to be responsible include: enterotoxigenic Escherichia coli (ETEC), which are the most frequently incriminated (Moon 1974, Pesti 1979), the coronavirus of transmissible gastroenteritis (TGE) (Woode 1969), rotavirus (Lece et al 1976, Bohl et al 1978) and possibly other viruses, eg, a coronavirus serologically distinct from TGE (Pensaert and De Bouck 1978), a rotavirus-like, a calicivirus-like and a small virus-like particle (Saif et al 1980). Isospora suis, a coccidian parasite, has also been implicated in piglet enteritis (Sangster et al 1976, Roberts et al 1980, Stuart et al 1980).

Recently cryptosporidium, another coccidian parasite, has been associated with diarrhoea in calves (Morin et al 1976, Moon et al 1978, Pohlenz et al 1978, Snodgrass et al 1980, Tzipori et al 1980c), lambs (Barker and Carbonell 1974, Berg and Peterson 1978), deer (Tzipori et al 1981a), humans (Meisel et al 1976, Nime et al 1976, Tzipori et al 1980b) and in other species (Kennedy et al 1977). Cryptosporidium has been shown to lack host specificity (Tzipori et al 1980a) and cross infection, sometimes associated with diarrhoea, is readily achieved between domestic and laboratory animals.

A previous report has described the gut histology of three clinically healthy six-week-old pigs incidentally found to be infected with cryptosporidium (Kennedy et al 1977). Bergeland (1977) reported the occurrence of cryptosporidium in one nursing piglet with focal ulceration of the ileal mucosa.

This communication describes experimental infection of piglets with cryptosporidium originally obtained from diarrhoeic calves.
Materials and methods

Experimental animals

Five litters of piglets originating from three different farms were used in these experiments. Sows were farrowed in individual isolation. In each case some of the piglets were removed from the sow, housed individually in cages and fed three times daily a diet of evaporated cows’ milk (Carnation Milk), reconstituted with mineralised water. Per feed each piglet received 200 ml during the first three days after birth, 300 ml up to eight days old and 400 ml thereafter. Piglets exposed to infection were kept in separate accommodation from control animals.

Source of inoculum

The cryptosporidium used in these experiments was obtained from a scouring calf which had been infected by surgical inoculation into the duodenum with faecal material from a field outbreak of diarrhoea attributed to cryptosporidium (Tzipori et al. 1980c). Ileal scrapings from this calf were homogenised 20 per cent v/v in phosphate buffered saline (inoculum A) and propagated once in specific pathogen free (SPF) rats and then in SPF lambs (Tzipori et al. 1981b).

Ileal scrapings from the SPF lambs were prepared as described for inoculum A, designated as inoculum B and passed five times in SPF mice. Ileal scrapings from the SPF mice, prepared as described for inoculum A, were designated as inoculum C. Inocula were maintained at 4°C until use. As the experiments were conducted over a five month period, storage times varied and were as follows:

litter 1, inoculum A, stored for 64 days
litter 2, inoculum B, stored for 14 days
litter 3, inoculum C, stored for 131 days
litter 4, inoculum B, stored for 136 days
litter 4, inoculum C, stored for 117 days
litter 5, inoculum B, stored for 40 days.

Aliquots of 2 ml from inoculum A, B or C were used to dose pigs orally. The inocula were judged by culture to be free of ETEC and no enteric viruses were detected by electron microscopy.

Microbiology

Daily faecal samples from each piglet were examined for (a) ETEC by routine culture and a proportion of colonies screened for pilus antigens (K88, K99, 987P) by slide agglutination, (b) for cryptosporidium oocysts by examination of Giemsa-stained faecal smears, (c) for rotavirus by enzyme linked immunosorbent assay (ELISA) and (d) for other enteric viruses by electron microscopy.

Clinical observations

Each piglet was bled and weighed before dosing and at necropsy. Observations were made at least twice daily for signs of illness and the milk intake was recorded.

Necropsy

Piglets chosen for necropsy were anaesthetised, the alimentary tract exposed and five segments taken from areas equally spaced along the small intestine (sites 1 to 5), one from the caecum (site 6) and one from the spiral colon (site 7). One portion from each segment was fixed in 10 per cent phosphate buffered formal saline and processed for histology and scanning electron microscopy. Blocks of mucosa, approximately 2×1×1 mm, were fixed in 2·5 per cent glutaraldehyde in 0·1 M cacodylate buffer and processed for transmission electron microscopy. The contents of the mid-small intestine were cultured routinely for ETEC.

Immunofluorescent studies (IF test)

Pre- and post-exposure sera from the piglets were examined for cryptosporidial antibodies using the indirect IF test described elsewhere (Tzipori and Campbell 1981). Briefly, sections of lamb gut heavily infected with calf cryptosporidium were incubated with piglet sera, counterstained with fluorescein isothiocyanate-conjugated anti-pig IgG and examined for fluorescence in the brush border.

Experimental design

Experiment 1. Sixteen piglets from two litters (litters 1 and 2) were weaned 36 to 72 hours after birth on to the milk diet described above and 10 of these were dosed orally 24 hours later with either inoculum A or B (Table 1). Six piglets, two from litter 2 and four from litter 1, were maintained separately as unexposed controls.

As part of other investigations some of these piglets, both those dosed with cryptosporidium and controls, were also exposed to Campylobacter sputorum subsp. mucosalis after the initiation of clinical symptoms in the cryptosporidium group. There was no indication that these bacteria influenced the results of the cryptosporidium infection.

Experiment 2. Six piglets from a litter of 11 (litter 3) were weaned 48 hours after birth leaving five piglets suckling the sow. The five suckling and four of the six artificially reared piglets were dosed at 48 hours of age with inoculum C. Two artificially reared piglets were
maintained separately as controls. This procedure was repeated one month later with another litter of 11 piglets (litter 4). However, in litter 4 the five sucking and four artificially reared piglets were dosed twice; at four days of age with inoculum B and at nine days with inoculum C.

Experiment 3. Six piglets of litter 5 were allowed to suck the sow for 12 days, with creep feed without antibiotic (Finisher creep; Seafield Mill) available from two days of age. At 12 days the sow was removed and the artificial milk diet was fed until 15 days old, after which only creep feed and water were available ad libitum.

At 22 days the piglets were divided into two groups of three and maintained in separate buildings with separate attendants and one piglet was killed as a pre-exposure control.

At 25 days of age the five surviving piglets were dosed orally with C. parvum subsp. C. parvum. There was no evidence that these bacteria influenced the results of the cryptosporidium exposure described below.

At 26 days of age three piglets in one group were dosed orally with cryptosporidium (inoculum B). The two littersmates were maintained as controls not dosed with cryptosporidium.

Results

Experiment 1

One to three days after dosing nine of the 10 piglets developed inappetence (lasting three to six days), diarrhoea (three to five days) and five of them vomited (one to two days). Two piglets (1 and 3) were killed at the onset of the clinical illness and another (piglet 4) died three days after dosing. Cryptosporidium oocysts appeared in the faeces one to three days after the onset of clinical illness and were shed for five to nine days (Table 1). The extent of cryptosporidium infection and the severity of mucosal damage are correlated in Table 2. Infection varied between sites and indeed between adjacent villi. Often a number of different forms of the life cycle of the parasite could be seen on the same villus (Figs 1 to 3). In some heavily infected areas the organisms were seen attached deep within the crypt glands. In more severely affected piglets the large bowel was also infected, both in surface areas and deeper in the crypts (Fig 4).

Piglets 1, 4, 5 and 6, killed at the height of the clinical illness, exhibited identical intestinal lesions. These included: villous stunting with fusion and cross-bridging between adjacent villi (Figs 5 and 6), and oedema with inflammatory cell infiltration of the lamina propria. Sloughing of villous tips was apparent accompanied by an outpouring of inflammatory cells (Fig 7). These changes increased in severity towards the terminal ileum where loss of healthy vacuolated villous cells and their replacement by immature enterocytes also became more evident. Some patchy areas of bacterial adherence to the damaged mucosal surface were observed in some areas of the terminal ileum of piglets 5 and 6. Cecal surface cells exhibited rounded luminal borders and were cuboidal rather than columnar in piglets 1, 4 and 5.

In piglet 3, which was killed shortly after the onset of clinical illness, the histological lesions were mild

| Piglet number | Clinical illness (duration in days) | Shedding of oocysts |
|---------------|------------------------------------|---------------------|
|               | Incubation | Vomiting | Diarrhoea | Inappetence | First detection in faeces (day post-dosing) | Duration (in days) |
| 1*            | 3          | 1        | 1        | 1t          | -                                   | -               |
| 2*            | 3          | 2        | 5        | 3           | 4                                   | 8               |
| 3t            | 2          | 0        | 1        | 1t          | -                                   | -               |
| 4t            | 1          | 0        | 1        | 2t          | -                                   | -               |
| 5t            | 2          | 2        | 5        | 3           | 4                                   | 4t              |
| 6t            | 2          | 1        | 5        | 5           | 5                                   | 5t              |
| 7t            | 3          | 0        | 3        | 5           | 4                                   | 5               |
| 8t            | 2          | 0        | 3        | 6           | 4                                   | 7               |
| 9t            | 3          | 2        | 4        | 4           | 5                                   | 8               |
| 10t           | 0          | 0        | 0        | 0           | 5                                   | 9               |

* Piglet dosed with inoculum A
† Piglet dosed with inoculum B
‡ Piglet killed
§ Piglet died
- Not applicable

Six littersmates (control piglets) remained healthy throughout the experiment.
**TABLE 2:** Correlation between clinical diarrhoea, degree of infection with cryptosporidium and extent of mucosal damage in the small intestine (sites 1 to 5), caecum (site 6) and spiral colon (site 7).

| Piglet number | Day of necropsy post dosing | Intestinal contents | Degree of infection* | Degree of mucosal change† | at intestinal sites sampled |
|---------------|-----------------------------|---------------------|---------------------|--------------------------|---------------------------|
|               |                             |                     | 1                  | 2                        | 3                        |
| 3             | 2                           | Fluid               | + +                | +                        | +                        |
| 4             | 3                           | Fluid               | +                  | +                        | +                        |
| 5             | 6                           | Fluid               | +                  | +                        | +                        |
| 6             | 9                           | Fluid               | +                  | +                        | +                        |
| 7             | 11                          | Normal              | −                   | −                        | −                        |
| 8             | 13                          | Normal              | −                   | −                        | −                        |
| 9             | 16                          | Normal              | −                   | −                        | −                        |
| 10            | 16                          | Normal              | −                   | −                        | −                        |
| 2             | 17                          | Normal              | −                   | −                        | −                        |

* Degree of cryptosporidial infection: + + + heavy; + + moderate; + light; − no cryptosporidium detected
† Degree of mucosal damage: + + + stunting and fusion of villi, replacement of enterocytes by immature cells, increased cellularity of lamina propria; + + only the first two of above; + only the first one above; − no mucosal changes.
‡ Piglet necropsied four to eight hours after death.

**FIG 1:** Stunted villi in terminal small intestine (site 5). Numerous cryptosporidia are visible in the brush borders of epithelial cells as round basophilic bodies. Giemsa × 500.
and largely confined to the mid-gut. Cryptosporidium infection appeared more extensive in the upper gut with no evidence of infection of the large bowel. Piglets 7, 8, 9, 10 and 2 killed between 11 and 17 days after exposure, when clinical recovery appeared complete, had neither histological lesions nor, except for piglet 7, any evidence of cryptosporidium infection.

Bacteriological examination of daily faecal swabs over the experimental period and of mid-small intestinal contents yielded a mixed growth of alpha-haemolytic streptococci and non-haemolytic E. coli. A few of the E. coli colonies possessed the adhesion pili 987P (987P+) or K99 (K99+). Of the 10 piglets exposed, three shed 987P+ E. coli on one occasion (piglets 4, 7 and 9) and from three piglets (3, 4 and 10) isolation was made from the mid-small intestine at necropsy. K99+ E. coli was isolated from the mid-small intestine of piglet 7 at necropsy, five days after clinical recovery. There was no histological evidence of coliform adherence to the mucosa in any of these piglets at necropsy.

None of the six control piglets showed evidence of clinical illness, mucosal damage or cryptosporidium infection, nor did they shed E. coli with K88, 987P or K99 pili.

Eight of the nine dosed piglets in litter 3 had evidence of light to moderate infection with cryptosporidium in the small intestine but not in the large bowel. Mucosal changes varied from mild to moderate and were restricted to the mid and lower small intestine (sites 3 to 5) (Table 3). One control (piglet 20) showed a moderate degree of mucosal damage in the mid and lower ileum, including stunting and fusion of villi together with increased cellularity of the lamina propria and replacement of enterocytes by immature cells. These changes were similar to those of the nine dosed piglets from this litter but no cryptosporidial organisms were detected on the mucosal surface of this control piglet nor that of exposed piglet 19. There was good correlation between degree of infection with cryptosporidium, extent of mucosal damage and clinical response (Table 3). The five sucking piglets were more severely affected than the four artificially fed piglets. Under the conditions of the experiment it was impossible to assess whether sucking piglets vomited.

Litter 4 remained healthy throughout the
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FIG 3: Various forms of the parasite embedded in the microvilli of villous epithelial cells (site 5) and ranging in size from 1 to 4 μm. Bar = 4 μm.

FIG 4: Infected caecum showing cryptosporidium as basophilic round bodies in surface areas and extending into caecal crypts. Giemsa × 500.
FIG 5: Normal villi in lower small intestine (site 4). Compare with Fig 6. Bar = 100 μm

FIG 6: Villi in lower small intestine (site 4) of cryptosporidium infected piglet showing stunting, fusion and cross-bridging. Bar = 100 μm
observation period despite two successive exposures at four and nine days old respectively. Mucosal damage, which was confined to the ileum, was slight. In four of the nine dosed piglets, infection was not detected, either by histological examination or by searching Giemsa-stained faecal smears for oocysts. In this litter, there was also good correlation between absence of clinical signs, light or undetected infection and minor intestinal changes (Table 4). In neither litters 3 nor 4 did the large bowel appear to be involved.

Experiment 3

None of the six piglets of litter 5 showed any signs of illness. The undosed control piglet, killed four

| Group                              | Piglet number | Incubation (days) | Clinical manifestations | Necropsy findings (sites 3 to 5) |
|------------------------------------|---------------|-------------------|-------------------------|---------------------------------|---------------------------------|
|                                    |               |                   |                         |                                 |                                 |
| Infected suckling                  | 11            | 0                 | 0                       | 0                              | ++                              |
|                                   | 12            | 6                 | 2                       | 1                              | ++                              |
|                                   | 13            | 7                 | 1                       | 0                              | ++                              |
|                                   | 14            | 7                 | 2                       | 0                              | ++                              |
|                                   | 15            | 3                 | 2                       | 0                              | +                               |
| Infected artificially reared      | 16            | 5                 | 1                       | 0                              | ++                              |
|                                   | 17            | 4                 | 1                       | 0                              | +                               |
|                                   | 18            | 2                 | 1                       | 0                              | +                               |
| Controls artificially reared       | 20            | 0                 | 0                       | 0                              | –                               |
|                                   | 21            | 0                 | 0                       | 0                              | –                               |

* Degree of cryptosporidial infection: +++ heavy; ++ moderate; + light; — no cryptosporidium detected
† Degree of mucosal damage: +++ stunting and fusion of villi, replacement of enterocytes by immature cells, increased cellularity of lamina propria; ++ only the first two of above; + only the first one above; — no mucosal changes
days before exposure of three littermates to cryptosporidium, had light infection of cryptosporidium throughout the small intestine but no histological abnormalities. Three to 13 days after exposure the small intestines of the three dosed and one other control piglet were moderately infected with cryptosporidium. Histological changes included a mild to moderate degree of stunting and fusion of the villi with loss of definition of brush borders, increased cellularity of the lamina propria and crypt hyperplasia. The large bowel appeared unaffected and oocysts could not be detected in the faeces. The third control piglet, killed at the end of the experiment, showed neither histological evidence of cryptosporidial infection nor any mucosal changes.

**Other observations**

Except for the isolation of *E. coli* possessing pili in litter 2 none of the exposed or control piglets showed evidence of infection with other known porcine enteropathogens.

Analysis of the bodyweights of the four litters showed that there was no significant difference in bodyweight gains over the experimental period between artificially reared dosed and artificially reared control piglets or between dosed and undosed weaned piglets.

**Immunofluorescent results**

All the pre-exposure sera from the 22 piglets of litters 3 and 4 were positive in the indirect IF test, producing extensive fluorescence in the brush borders of infected sections. Weak reactions were produced by the pre-exposure sera of seven piglets in litters 1 and 2 while nine others were negative. Sera from piglets or litter 5 were not examined by the IF test.

**Discussion**

The results of these experiments show that cryptosporidium can, under certain conditions, act as an enteropathogen in very young piglets. The clinical response varied among the four litters exposed in the first week of life, from moderate illness with anorexia, vomiting and diarrhea, to subclinical infection only. However, the variations were much greater between litters than within, indicating that external factors, such as the level of maternal immunity or the nature of the inoculum, could have been responsible. The correlation between length of incubation period, manifestation of clinical illness, extent and severity of mucosal damage and extent and degree of intestinal infection by cryptosporidium, indicates that it was the causative agent. Full assessment of the enterocolitis which cryptosporidium induces in piglets may have to be assessed in animals devoid of maternal protection and free from previous exposure to cryptosporidium.

It seems possible that cryptosporidium infection is prevalent. Two undosed control piglets from litter five were found to be infected with cryptosporidium and as one of these was killed four days before dosing of littermates with cryptosporidium the infection may have been contracted naturally rather than due to accidental cross-contamination from experimentally exposed piglets. A serological study conducted recently on a variety of species, including pigs, further supports the theory that cryptosporidium infection is widespread (Tzipori and Campbell 1981). The extent of infection in the national pig herd is unknown at present. Whether

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**TABLE 4: Summary of histological findings in litter 4 which did not develop clinical illness after two challenges with cryptosporidium at four days (inoculum B) and nine days (inoculum C) old**

| Group          | Piglet number | Shedding of oocysts * | Age at death (days) | Cryptosporidial infection† | Necropsy findings |
|----------------|---------------|------------------------|---------------------|----------------------------|-------------------|
| Sucking        | 22            | +                      | 12                  | +                          | +                 |
|                | 23            |                        | 15                  | +                          | +                 |
|                | 24            |                        | 16                  | +                          | +                 |
|                | 25            |                        | 16                  | -                          | -                 |
|                | 26            |                        | 17                  | -                          | +                 |
| Artificially reared | 27            |                        | 12                  | -                          | +                 |
|                | 28            | +                      | 15                  | -                          | -                 |
|                | 29            | +                      | 16                  | +                          | -                 |
|                | 30            | +                      | 17                  | -                          | +                 |
| Controls       | 31            |                        | 15                  | -                          | +                 |
| artificially reared | 32            |                        | 17                  | -                          | +                 |

*: + Oocysts detected in faeces, — oocysts not detected
†: Degree of cryptosporidial infection: + + moderate, + light, — no cryptosporidium detected
‡: + Minor changes of shortening villi and increased cellularity of lamina propria; — no mucosal changes
Cryptosporidiosis occurs as a primary disease, a subclinical infection, or as a predisposing agent to other enteric pathogens also remains to be determined.

Cryptosporidiosis in other animals is now recognised as a cause of diarrhoea. It has been suggested as a potential zoonosis (Tzipori et al 1980a,b; Tzipori and Campbell 1981) and the oocysts are extremely resistant to many common disinfectants (Campbell, Tzipori, Hutchison and Angus unpublished data), factors which should be considered in relation to the management of effluent disposal.

Examination of pre-exposure sera by the indirect IF test has shown that two of the litters described in this work received little or no specific maternal antibodies against cryptosporidium and differences in levels of antibodies may have accounted for the clinical variations observed between litters. The serological reaction between pig sera and lamb ileum infected with a calf-derived cryptosporidium further supports the view that both calf and pig cryptosporidium share a common antigen (Tzipori and Campbell 1981) or may even constitute a single species (Tzipori et al 1980d).

The experiments were conducted over a five month period and methods thus far evaluated for long term storage of the organism in the laboratory or quantification of the infectious dose have not been successful. Although the three inocula were derived from the same original source, calf cryptosporidium, they were passed in different special animal and were probably administered at different concentrations which may in part explain the variation in response observed. The passage of cryptosporidium in rodents does not appear to affect the virulence of the organism for SPF lambs (Tzipori et al 1981b).

The isolation of 987P and K99 possessing E. coli in litter 2 may have been a factor in precipitating a more acute disease in this litter compared with litters 3 and 4. The limited excretion of these pilus-possessing E. coli over the experimental period and the lack of bacterial adherence to the mucosa at necropsy suggest, however, that their role at best was minor. It could be argued that the mucosal damage and digestive disturbance in the piglets dosed with cryptosporidium were changes which could favour luminal proliferation of these bacteria. No pilus-possessing E. coli were isolated from the faeces of four littermate control piglets.

The demonstration of oocysts in the faeces as a means of diagnosing cryptosporidium infection in piglets is unsatisfactory. Even in acute cases of diarrhoea, shedding of the oocysts began one to three days after the onset of illness. In less acute cases, detection of oocysts in faeces was extremely difficult and often based on observation of very few oocysts.

The histological changes observed in one control piglet of litter 3 cannot be explained. No cryptosporidial organisms were seen attached to the mucosa nor were other recognised enteropathogens detected. Litter 4 remained healthy throughout the observation period despite two successive exposures at four and nine days old respectively. However, unlike litters 1, 2 and 3, the longer interval between dosing and necropsy could account for the failure to detect infection and the mildness of the mucosal damage at necropsy.

The pathogenesis and clinical manifestations of the disease, apart from vomiting which appears characteristic of man and piglets, were similar to those observed in lambs, calves and deer.

It was unexpected that suckling piglets were more severely affected by cryptosporidium infection than artificially reared piglets. In contrast rotavirus infection induces severe diarrhoea and mortality in artificially reared, colostrum-fed piglets but very little in sucking litters (Tzipori and Williams 1978).

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