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Experimental *Campylobacter jejuni* Infection of Adult Mice

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HA-ICR adult mice were studied to develop an animal model for *Campylobacter jejuni* enteritis in humans. Fecal and ileal cultures made by selective and nonselective methods showed that *C. jejuni* and related organisms are not bowel commensals. Intragastric feeding of 10^8 CFU of three different strains of *C. jejuni* produced infection in 100% of the animals, and infection rates were dose dependent. Pretreatment with antibiotics or opiates was not necessary to induce infection. Fresh isolates and strains passed on artificial media yielded similar infection rates. Infected mice did not show signs of illness, but transient bacteremia within 10 min of oral infection was observed in nearly 100%. The small intestine was the principal target organ, with epithelial inflammation seen 48 h after infection. Control mice of four species had undetectable serum immunoglobulin G antibody specific for the infecting strain, but infected mice showed peak titers at 1 week with rapid decline. Immunoglobulin M titers rose minimally, and immunoglobulin A titers did not rise. Infected mice uniformly became chronic asymptomatic excretors, shedding 10^4 to 10^6 CFU/g of feces; a minority were biliary carriers. Intestine carriage was most pronounced in the stomach and proximal small intestine. Because this experimental infection led to bacteremia, transient pathological changes, and immunoglobulin G titer rises, this model may be useful for evaluating the effects of prophylactic and therapeutic interventions.

Because *Campylobacter jejuni* is now recognized as a major bacterial cause of enteritis in humans (4, 5), definition of a suitable model for human infection has been sought in laboratory animals. Recent limited studies of experimental infection have been done with nonhuman primates (11), neonatal chickens (23), and gnotobiotic dogs (20), but because of the expense of developing and maintaining gnotobiotic animals, the diminished availability of primate species, and the difficulty of reproducing infections in chickens (5, 21), attention has focused on the use of small laboratory animals as potential models.

Spiral-shaped organisms resembling *Campylobacter* spp. have been shown to colonize transiently the colons of suckling HA-ICR mice (8), and *Campylobacter* spp. have been isolated from the ceca of other healthy 6- to 8-week-old laboratory mice (22). *Campylobacter* spp. also have been isolated from the intestinal contents of healthy wild bank voles and laboratory-raised (9) and wild (18) rats. Bank voles experimentally infected with *Campylobacter fetus* isolates did not become ill, had no pathological changes, and did not persistently excrete the organisms in their feces (7).

When *C. jejuni* was introduced into the ilea of laparotomized mice, a gradual decrease in number was noted, but colonic colonization developed which persisted for at least 21 days; no signs of illness or pathological changes were noted (16). Madge fed *C. jejuni* cultures to young (4 to 6 week) and older (24 to 26 week) mice and then measured carbohydrate absorbtion in the small intestines (14). The young mice had decreased D-glucose and D-galactose absorption in the distal four-fifths of their small intestines, whereas absorption in the older mice was unimpaired. When Field and colleagues fed *C. jejuni* to neonatal mice, transient intestinal colonization was noted (10). Mortality after infection varied from 0 to 13%. As mice matured, they became increasingly refractory to colonization after oral infection. Paradoxically, four dams of infected neonates developed diarrhea with blood and mucus, and *C. jejuni* was isolated. Recently, weanling ferrets experimentally infected with *C. jejuni* developed acute diarrheal illnesses with persistent asymptomatic intestinal colonization (J. Ackerman, J. Fox, and J. Murphy, Abstr. Annu. Meet. Am. Soc. Microbiol. 1982, B143, p. 41).

Experimental infections are most useful as a

TABLE 1. Infection rates in groups of five adult HA-ICR mice fed various doses of *C. jejuni*

Dose (no. of organisms)	% infected with strain:		
	T1	T2	T3
10^8	100	100	100
10^7	ND[a]	80	60
10^6	60	80	40
10^5	ND	60	80
10^4	0	20	40
10^2	0	ND	ND
10^0	0	ND	ND

[a] ND, Not done.

model when both the clinical and pathological features closely resemble the features of the natural infection. *Campylobacter* enteritis in humans has not been reproduced in a laboratory animal; however, these previous studies by Madge, Field et al., and Ackerman et al. suggest that under suitable experimental conditions, laboratory rodents could provide an appropriate model. For these reasons, we studied experimental infections in adult HA-ICR mice, a species with which we have had experience (2).

MATERIALS AND METHODS

Mice. HA-ICR adult female mice [Hsd:(ICR) Br; Harlan Industries, Indianapolis, Ind.] that were cesarean section derived and barrier reared were used in these studies. Mice from 20 to 30 g in weight were kept in their own room in our animal quarters with 12 to 15 in a cage until inducted into the feeding studies and then were kept 2 to a cage. Mice were given antibiotic-free food (Lab Blox; Wayne Laboratories, Chicago, Ill.) and water ad libitum.

Bacterial strains. The three strains of *C. jejuni* used in this study were clinical isolates from infected humans that had been serotyped by John Penner with a passive hemagglutination assay (19). The strains designated T1, T2, and T3 were the type strains for the serotypes PEN 1, PEN 2, and PEN 3, which are three of the most common serotypes isolated from infected humans (19).

After an unknown number of passages on artificial media, these strains were fed to adult HA-ICR mice, and the resulting colonized mice were then used as sources for all future isolates. To prepare strains for experimental infections, stool specimens from colonized mice were plated on Campy-BAP medium (BBL Microbiology Systems, Cockeysville, Md.), and *C. jejuni* was isolated as previously described (1). An isolated colony was inoculated onto a Mueller-Hinton or blood agar plate, and after 24 h of incubation, the bacterial growth was harvested. Cells were washed twice in sterile distilled water and were suspended to the optical density of a McFarland 9 tube. Optical densities were then standardized to a reading of 0.545 at 450 nm on a spectrophotometer (Coleman Jr.; Coleman Inc., Maywood, Ill.), and serial dilutions to obtain colony counts were made by the Miles-Misra method (17).

Assessment of culture negativity of experimental animals. Before induction into the study, fecal specimens from each animal were suspended in sterile distilled water and were cultured on Campy-BAP medium by standard methods for isolating *C. jejuni* (1). In addition, fecal specimens from healthy adult female BALB, CBA, and B10 mice (25 from each strain) were cultured for *C. jejuni*. To determine whether other species of *Campylobacter* or campylobacter-like organisms were present in the intestinal flora of normal mice, five HA-ICR adult females were sacrificed, the cecal and ileal mucosae were scraped, and the intestinal contents were obtained. Samples of these contents were either suspended in phosphate-buffered saline (pH 7.2) or were plated directly onto Campy-BAP. They were next incubated at 37 or 42°C in an anaerobic or in a microaerobic atmosphere (5% oxygen). The suspensions were sequentially passed through 8.0-, 1.2-, and 0.65-μm filters (Millipore Corp., Bedford, Mass.), and the filtrates were plated on both chocolate and blood agar plates and were incubated under the conditions described above.

Oral challenge. Cultures were standardized turbidimetrically, diluted appropriately in sterile distilled water, and used immediately. Mice were made to fast overnight but were not deprived of water. They were infected orally by means of a gastric feeding tube consisting of a straight 1.5-inch (3.3-cm) 18-gauge stainless steel needle with 1.0 inch (2.5 cm) of 040 × 070 tygon tubing (Norton Inc., Akron, Ohio) extending distally from the needle shaft. Mice were infected with 0.1 ml of the appropriate dilution, and the dose was checked retrospectively by viable counts (17). The mice received no bicarbonate or antibiotic pretreatment. At intervals after infection, mice were anesthetized with ether and bled from the heart. Because the gastric feeding tube could have traumatized the esophageal or gastric mucosae, a subset of feeding experiments were done in which the 0.1-ml dose was applied with a ball-tipped 24-gauge 1.0-inch (2.5-cm) animal feeding needle (Popper & Sons, New Hyde Park, N.Y.) atraumatically applied to the tips of the tongues of lightly anesthetized mice. At daily intervals for three days, fresh fecal specimens obtained from mice that had not been sacrificed were cultured for *C. jejuni* as described (1). From a subset of infected mice dosed

TABLE 2. Quantitation of systemic infection in orally infected adult HA-ICR mice, by time

Time after oral dose (min)	No. of mice	*C. jejuni* in[a]:	
		Blood (CFU/ml)	Liver (CFU/g)
10	10	$2.9 \times 10^4 \pm 2.3 \times 10^4$	$1.1 \times 10^5 \pm 1.0 \times 10^5$
60	10	$2.0 \times 10^4 \pm 5.2 \times 10^3$	$1.3 \times 10^4 \pm 1.0 \times 10^4$

[a] Numbers show mean ± standard error of the mean.

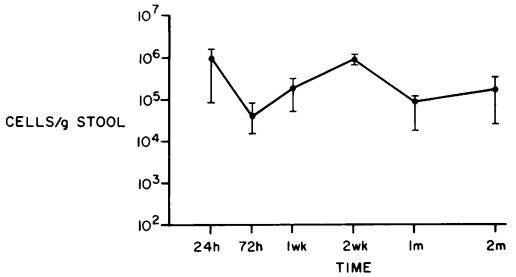

FIG. 1. Fecal excretion of *C. jejuni* in five colonized adult HA-ICR mice. Means ± standard errors of the mean are shown.

with 10^8 CFU of *C. jejuni*, quantitative cultures for *C. jejuni* were obtained at intervals over a 2-month period. Paired infected and uninfected mice were sacrificed at intervals, and the ratios of spleen weight to body weight were calculated.

Evaluation of the clinical status of animals. To determine whether infection was associated with illness, 12 mice were infected with 10^8 CFU of *C. jejuni* (T1) that had only one passage on artificial medium after isolation from a mouse, and 12 other mice were fed phosphate-buffered saline only. Mice were kept two to a cage, fed food and water ad libitum, and examined daily for 1 week by a blinded evaluator who did not know which mice were which. Stool consistency was scored arbitrarily as follows: 0, normal; 1, soft; 2, unformed; 3, diarrhea. Changes in posture and fur consistency were graded by similar criteria, and stool specimens were examined daily for leukocytes and erythrocytes on Giemsa-stained slides of fecal smears.

Histological techniques. Specimens for histological examination were obtained from paired uninfected and infected mice 1, 2, 4, 7, 14, and 60 days postinfection. For the examinations of tissue 2 and 4 days after infection, three pairs of mice were examined on each day. Tissues examined included esophagus, stomach, spleen, liver, gall bladder, mesenteric lymph nodes, first through fourth quarters of the small intestine, cecum, and distal colon. Tissue specimens for light microscopy were fixed in 10% Formalin and were stained with hematoxylin and eosin. All slides were read by one of us (G.H.W.) without knowing the origin of the material. Multiple sections were examined on each animal, and step-level sections were examined only to aid photography on specimens previously diagnosed abnormal.

Serological techniques. Serum was obtained from uninfected mice and from infected mice at various intervals after being fed 10^8 *C. jejuni* organisms. Serum from five sets of mice were pooled and stored at −20°C until used. Indirect immunofluorescence studies were performed as previously described (1). Monospecific fluorescein isothiocyanate-conjugated goat anti-mouse immunoglobulin G (IgG), IgM, and IgA were obtained commercially (Cappel Laboratories, Cochranville, Pa.). Slides were read blindly with a Zeiss fluorescence microscope equipped with epiillumination.

Data presentation and statistical methods. Data are presented as mean ± standard error of the mean and were evaluated statistically by analysis of variance for either paired or unpaired data or were evaluated by the Fisher exact test.

RESULTS

Culture surveys of healthy mice. *C. jejuni* was not isolated from any of 200 healthy HA-ICR adult females or from the 75 mice of other strains. No *Campylobacter* spp. or related organisms were isolated from the cecal or ileal contents of the five adult HA-ICR mice studied intensively.

Oral challenge. Adult HA-ICR mice became orally infected with each of the three test strains of *C. jejuni*, and a dose-response relationship was shown, as determined by fecal culture positivity during the 72 h after infection (Table 1). In subsequent studies with 78 mice, an oral dose of 10^8 *C. jejuni* organisms was associated with a 95% infection rate. Another five mice that were dosed with 10^8 CFU of the T1 *C. jejuni* strain that had been passaged five generations on artificial media all became infected.

Groups of five mice orally infected with the gastric gavage tube with 10^8 *C. jejuni* organisms

TABLE 3. Colonization of infected mice by site and by time after initial infection

Site	*C. jejuni* ($\log_{10}$ CFU/g) at time[a]:							
	60 min	Days						
		1	2	4	7	14	30	60
Stomach	4.7	3.9	4.4	4.2	4.7	3.1	5.1	3.4
Small intestine								
First quarter	3.5	5.1	3.9	3.9	3.1	2.7	3.4	1.9
Second quarter	3.1	4.2	2.7	3.0	2.2	1.0	3.4	3.2
Third quarter	4.0	3.6	3.0	2.2	2.0	2.1	2.8	0
Fourth quater	4.2	4.0	2.9	2.3	2.0	2.1	3.2	2.2
Cecum	2.9	3.9	2.7	2.5	1.8	2.3	3.7	0
Colon	3.0	3.5	3.2	3.3	2.4	2.1	2.9	0

[a] Means of results for three mice at each time.

TABLE 4. Ratio of spleen weight to body weight in experimentally infected and sham-fed HA-ICR adult mice, by time after infection

Day after infection	No. of pairs studied	Ratio of spleen wt to body wt ($\times 10^{-3}$)[a]	
		Infected	Control
0	5	3.93 ± 0.31	4.59 ± 0.27
2	8	4.31 ± 0.45	4.03 ± 0.28
4	8	4.28 ± 0.48	4.60 ± 0.35
6	5	4.17 ± 0.20	4.04 ± 0.26
8	5	4.65 ± 0.24	4.34 ± 0.43

[a] Mean ± standard error of the mean.

were bacteremic 10 min (80%), 1 h (40%), 6 h (40%), 12 h (20%), and 24 h (20%) after the dosing. Because the bacteremia may have resulted from trauma to the upper gastrointestinal tract during feeding, 10 mice more were given *C. jejuni* atraumatically. Of these 10, 9 were bacteremic within 1 h after the dose. In quantitative studies (Table 2), all 20 mice infected atraumatically were bacteremic within 1 h. Although counts in the infected mice varied greatly, there was no significant difference in mean counts at 10 and at 60 min. Because previous studies have shown that the liver has a major role in clearing *C. jejuni* from the bloodstream (M. J. Blaser and D. J. Duncan, unpublished data), we also counted *C. jejuni* in the livers of the orally infected mice (Table 2). There were no significant differences in the concentrations of *C. jejuni* in the bloodstreams and the livers of the infected mice at either 10 or 60 min.

Serial fecal cultures were performed on a subset of infected mice. Virtually all those infected became chronic excretors of *C. jejuni*; in the longest experiment to date, colonization was still present 14 months after infection. Quantitation of feces showed that a carrier state with 10^4 to 10^6 CFU/g of stool was present for at least 2 months (Fig. 1). Gastrointestinal tract segments obtained from mice sequentially after infection demonstrated that the entire intestine was colonized with 10^2 to 10^4 CFU of *C. jejuni* per g of tissue, but counts were consistently highest in the stomach and proximal small intestine (Table 3). Among 20 mice sacrificed during the first week postinfection, 3 (15%) were biliary carriers of *C. jejuni*. Quantitative cultures of liver and spleen tissue 1, 2, 4, 7, 14, and 60 days after dosing did not yield any *C. jejuni* organisms. Ratios of spleen weight to body weight obtained from paired groups of five infected and sham-fed mice at various intervals after dosing showed minimal differences between the two groups (Table 4).

The infected mice did not appear ill, and none died. When the total weekly scores for diarrheal findings for each of 12 infected mice were matched with those of the uninfected mice, only minor differences were observed ($F = 0.55$, $P > 0.5$). When the stool consistency findings for the infected and uninfected mice were grouped by day (Table 5), the infected mice had higher scores, but again the difference was not statistically significant. Examination of Giemsa-stained stool smears from the infected mice did not reveal any fecal shedding of leukocytes or erythrocytes.

Histology. By light microscopy, no differences were noted in the tissues obtained from infected and sham-fed mice 1, 7, 14, and 60 days after dosing. However, tissues obtained from infected mice 2 and 4 days after dosing showed acute inflammatory changes, primarily in the small intestines. The acute small intestinal lesions were characterized by mild, focal, nonulcerative infiltrates of neutrophils predominantly localized to the intercryptal laminae propriae (Fig. 2 and 3). The lacteals and connective tissue of the villi were spared, and there was no alteration of the normal villus-crypt ratio. Occasionally, neutrophils infiltrated crypt epithelium (cryptitis), but only a single crypt abscess was identified (Fig. 4). Typically only a half-dozen or fewer glands were involved, and areas of inflammation sometimes appeared or disappeared within three step-level sections.The earliest change appeared to arise just above the muscularis mucosae and occasionally lay near lymphoid follicles, but microabscesses were not seen in lymphoid aggregates. This lymphoid tissue either appeared normal or showed an increase in activity reflected by clusters of nuclear fragments (nuclear dust). Of 12 small intestinal quarters obtained from three infected mice, 6 showed these pathological changes versus 1 of 12 quarters obtained from sham-fed mice ($P = 0.034$, Fisher exact test).

Colonic changes were similar but milder, and no significant difference was found in the amount of pathology between infected and sham-fed mice. The spleens occasionally suggested an increase in the activity of white pulp in infected animals, but this was inconsistent. Mesenteric lymph nodes, stomachs, gall bladders, and livers showed no inflammatory changes.

Serological response to infection. In the indi-

TABLE 5. Scoring of stool consistency in 12 mice infected with *C. jejuni* and 12 uninfected controls, by day[a]

Mice	Total scores for group on day:						
	1	2	3	4	5	6	7
Infected	14	7	12	14	13	13	11
Control	5	16	8	12	9	12	7

[a] $F = 1.62$, $P > 0.2$, by analysis of variance.

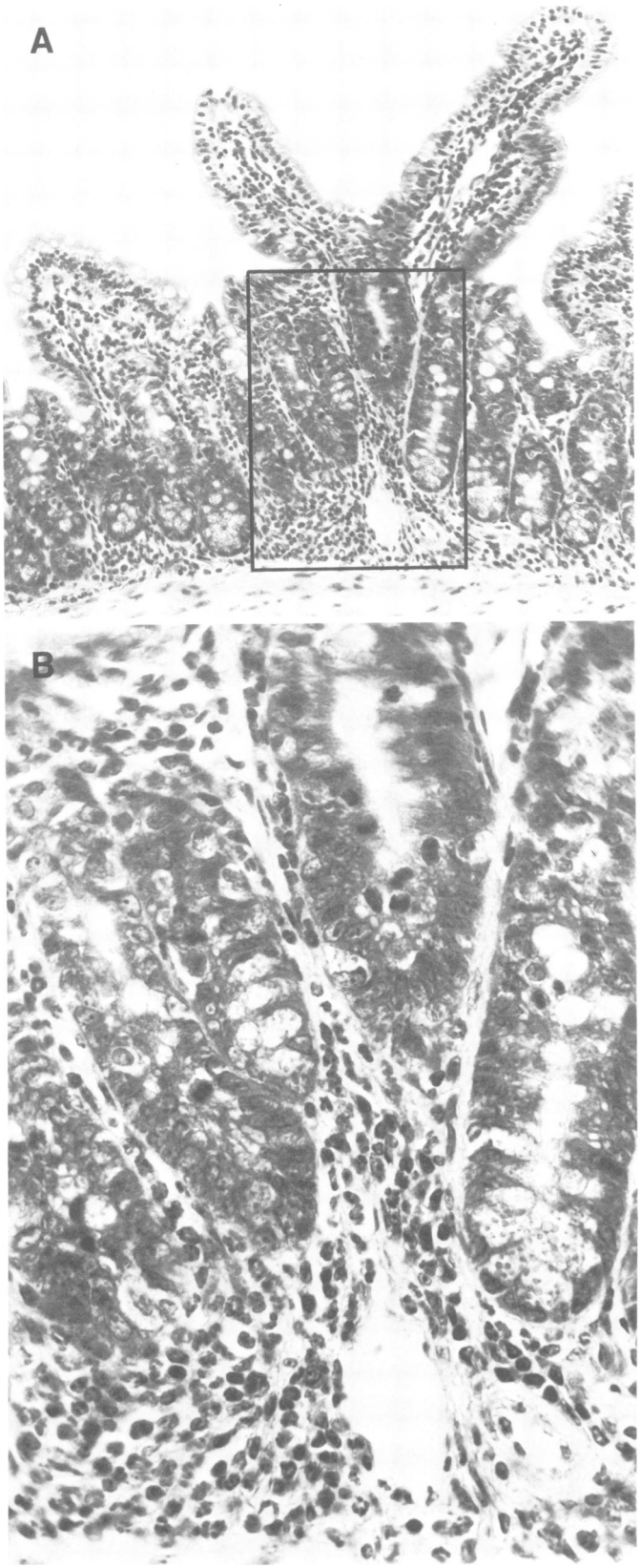

FIG. 2. (A) Small intestinal mucosa from an infected mouse, showing intact villi, tangentially sectioned. Rectangle defines a small patch of inflammation just above the muscularis mucosae (see Fig. 2B). Hematoxylin and eosin; magnification, ×100. (B) Detail of A. Higher magnification reveals neutrophils infiltrating lamina propria with sparing of glandular epithelium. Hematoxylin and eosin; magnification, ×320.

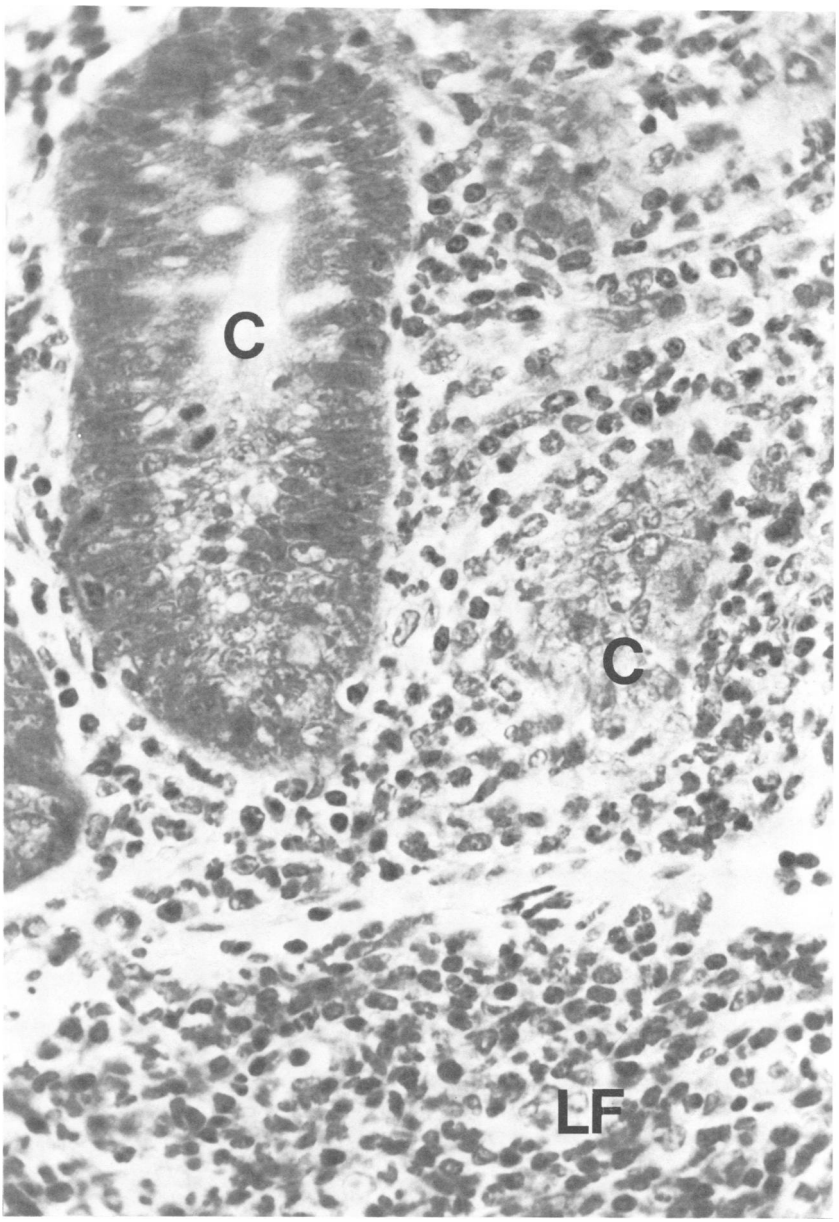

FIG. 3. Small intestinal mucosa from a second infected mouse, showing a mild infiltrate of neutrophils within the deep lamina propria overlying a lymphoid follicle (LF). Again, crypts (C) are spared. Hematoxylin and eosin; magnification, ×410.

rect fluorescent antibody assay with homologous cells as the source of antigen, neither control nor infected groups of mice had any IgA response to *C. jejuni*. In infected mice an early rise in IgG antibody was observed (Fig. 5), but minimal IgM response was seen.

DISCUSSION

The results of this study demonstrate that adult HA-ICR mice can be orally infected with *C. jejuni*, although the infectious dose is high. Recently, Field and colleagues reported that adult mice could not become colonized with *C. jejuni* unless they had been pretreated with antibiotics, an effect that could be blocked with the intragastric injection of fecal flora just before the *C. jejuni* challenge (L. H. Field, J. L. Underwood, and L. J. Berry, Abstr. Annu. Meet. Am. Soc. Microbiol. 1982, B144, p. 42). With the HA-ICR species, we have consistently found

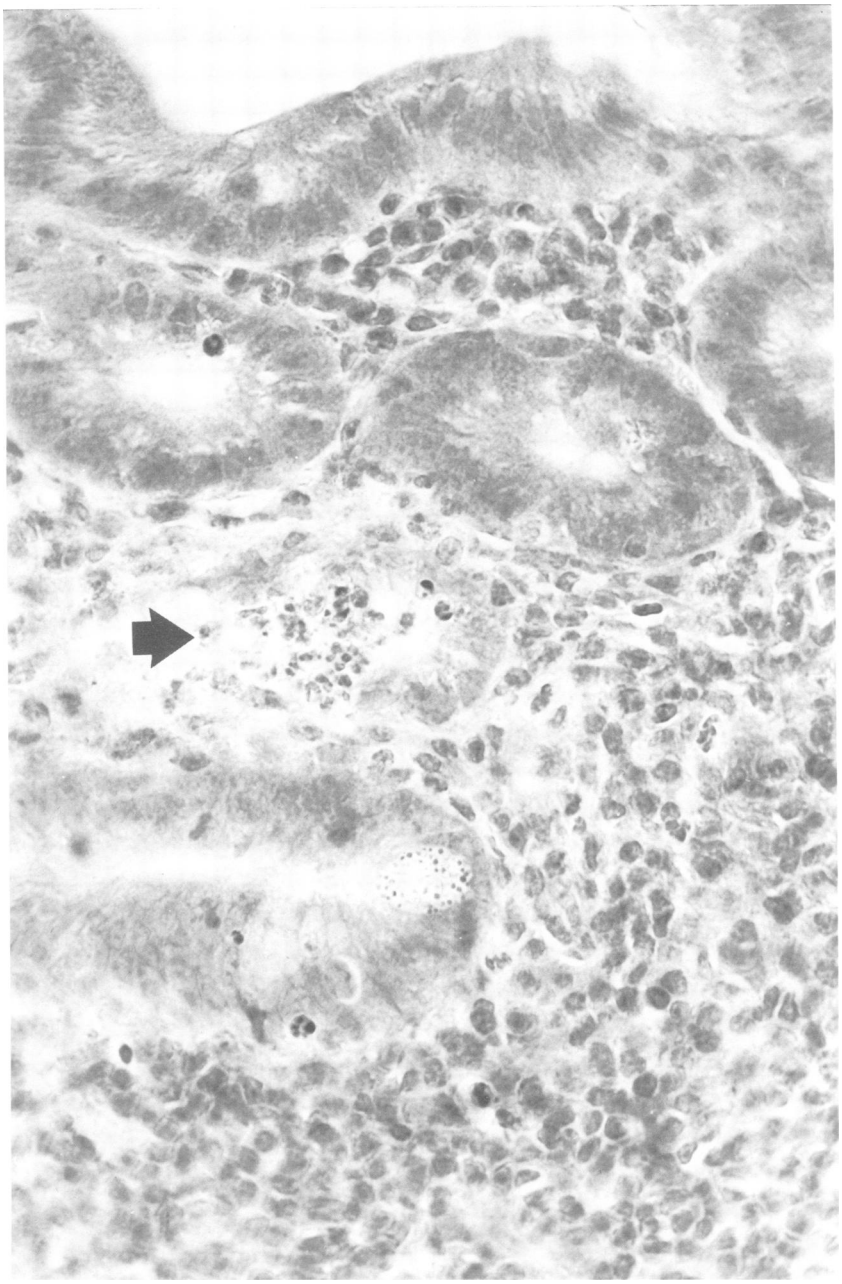

FIG. 4. Colonic mucosa from an infected mouse, showing neutrophils infiltrating crypt epithelium and lumen (arrow). This was the only crypt abscess identified. Hematoxylin and eosin; magnification, ×410.

that pretreatment is not necessary, although low challenge doses were not usually infectious. Such factors as differences in the strains of mice used, differences in their intestinal flora as a result of different rearing practices or ages, or differences in the infectivity of the *C. jejuni* strains used could possibly explain why our results and those of Field et al. were at variance.

In these studies, there were no demonstrable clinical signs of infection, despite daily gross and microscopic examination of stool specimens. For each of the three strains tested, results were similar. Previous passage of these strains on artificial media may have resulted in the loss of a necessary virulence factor, although we attempted to minimize that possibility by using *C.*

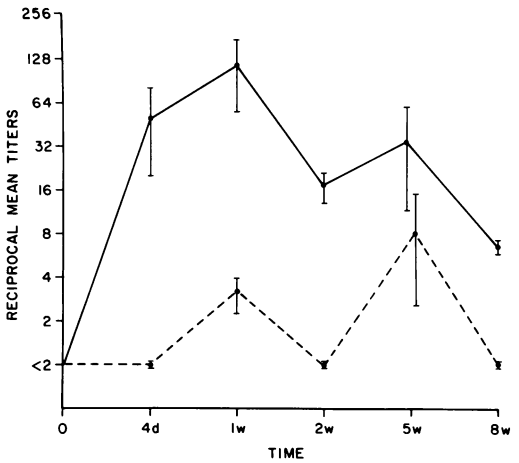

FIG. 5. Reciprocal mean serum antibody titers by indirect fluorescent antibody assay in groups of mice orally infected with *C. jejuni* by time after dosing. Solid line, IgG; broken line, IgM. Means ± standard errors of the mean are shown.

jejuni strains one passage after isolation from colonized mice. These studies suggest that adult HA-ICR mice would not be a suitable model for *C. jejuni* infections in humans unless their native immunity was naturally or experimentally diminished.

Nevertheless, infected mice showed pathological lesions in their intestinal mucosae that resembled those seen in infections of humans (3). In our studies, the small intestine rather than the colon was the primary target organ; for humans the relative importance of the large (3) and small (13) intestines as target organs is unknown. Experimentally infected guinea pigs that die early from shigellosis have prominent small intestinal lesions, whereas those that die late show primarily cecal and colonic pathology (12).

In studies of gnotobiotic puppies experimentally infected with *C. jejuni*, mild illness was produced with pathological changes similar to those we describe but limited to the ceca and colons (20). Although bacteremia was demonstrated in these dogs, none showed signs of severe systemic illness. These puppies did not demonstrate any increase in serum IgG titers 1 week after infection.

C57BL/10 mice that were relatively resistant to *Listeria monocytogenes* infection showed little increase in spleen weight, whereas relatively susceptible BALB/c mice showed a marked increase that peaked at 5 days after infection (15). The lack of increase in the ratio of spleen weight to body weight that we observed in infected mice correlates with resistance of the host to the infecting strain. Apparently the host defenses of these mice are adequate to contain acute *C. jejuni* infection without serious consequences. Once established, however, colonization persists in the gall bladder, the small intestine, or both. Unlike naturally infected humans, experimentally infected mice are not able to clear naturally their intestinal colonization. The presence of a biliary reservoir explains chronic carriage in only a minority of cases. With heat-labile antigens for serotyping, the original strain and strains isolated from three mice each at 1 and 2 months postinfection were identical (serotype LIO 2) (H. Lior, personal communication). Assuming that the colonies serotyped were representative, no shifts of these heat-labile antigens had occurred during the colonization.

The lack of preexisting antibodies to *C. jejuni* correlates with the absence of *Campylobacter* spp. or related species in the culture studies of uninfected mice. However, the early rise in IgG antibody suggests an anamnestic immune response possibly due to shared antigenic sites with other organisms. This early rise in specific antibody may be protective or may reflect other immune phenomena that protect these mice from becoming ill.

An immediate consequence of oral infection in these mice was the rapid development of bacteremia. By analogy with experimental *Salmonella* infections in mice (6), the presence of bacteremia within 10 min after oral infection with *C. jejuni* suggests that penetration of the bowel is immediate and occurs in the upper half of the intestinal tract. That the number of organisms reaching the bloodstream is several logs lower than the initial oral dose does not appear to be related to a significant sequestration of viable cells by the liver. The bacteremia observed could have been responsible for seeding the biliary tract of some of the infected animals.

Although this experimental infection does not produce overt illness in mice, examination of tissue shows mucosal lesions resembling those found in human infections (3). Thus, this model might be useful to evaluate the effects of prophylactic or therapeutic interventions. Further work is in progress to develop this model into one in which clinical symptoms are produced.

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