INFECTION AND IMMUNITY, Apr. 1988, p. 930–935
0019-9567/88/040930-06$02.00/0

Vol. 56, No. 4

Genetic Control in the Susceptibility of Germfree Inbred Mice to Infection by *Escherichia coli* O115a,c:K(B)

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Received 21 September 1987/Accepted 21 December 1987

We studied the susceptibility of five germfree inbred strains of mice to oral infection by murine pathogenic *Escherichia coli* O115a,c:K(B) (MPEC), the causative agent of mouse megaenteron. Although MPEC colonized all strains of mice at 10^9/g of feces, the mouse strains could be divided into three groups according to their intestinal lesions. In CF1 and C3H/He mice, intestinal lesions were produced in the cecum and colon with hyperplasia of epithelial cells accompanied by severe inflammatory reactions and erosion. The lesions in NC and C57BL/6 mice were restricted to the tip of the cecum, and hyperplasia of epithelial cells was more severe in these mice than in CF1 or C3H/He mice. BALB/c mice had no lesions. Analysis of F_1 hybrids of CF1, NC, and BALB/c mice and offsprings from backcrosses of F_1 mice to parental strains showed that susceptibility to MPEC seemed to be controlled genetically by a single locus which may be related to the receptors on epithelial cells for MPEC adherence. However, the differences in lesions between CF1 and NC mice suggest that a combination of this locus and another locus to which it may be related regulates the hyperplasia of intestinal epithelial cells.

Infectious megaenteron of mice was originally described by Muto et al. (21). Nakagawa et al. (22) isolated characteristic murine pathogenic *Escherichia coli* O115a,c:K(B) (MPEC) as the causative agent of this disease. Clinically severe diarrhea with high mortality was observed in suckling mice at 2 to 3 weeks of age (21, 22) and in specific-pathogen-free adult mice (16, 17), but not in conventional adult mice (16, 17, 21). Macroscopically, the disease produces thickened walls in both the small and large intestines of suckling mice before 4 weeks of age and only in the large intestine after 4 weeks of age (21). Microscopic lesions are characterized by hyperplasia of crypt-type epithelial cells. There is little inflammatory reaction in the lesions of suckling mice (21), but in specific-pathogen-free mice with severe diarrhea, there are marked inflammatory lesions with erosion (16). In germfree mice monoassociated with MPEC, the infection is not fatal and there are no severe inflammatory lesions of epithelial cells of the intestine, although hyperplastic lesions appear (16). Thus, the presence of intestinal flora appears necessary to produce severe inflammatory lesions in specific-pathogen-free mice.

The differences between CF1 and ICR mice in their susceptibility to MPEC infection have been reported previously (18). In CF1 germfree mice, intestinal lesions are produced in the cecum, colon, and rectum. But in ICR germfree mice, the intestinal lesions are localized in the tip of the cecum. The inoculated MPEC attach to surfaces of lesions in both mouse strains but not to normal epithelia. However, the genetics of the susceptibility of mice to MPEC infection was not analyzed.

This infectious disease is modified by intestinal flora (16, 17), so that in some cases, the mice are protected from the infection, and in other cases, the infection is enhanced. Consequently, germfree mice are required as models in examining the intrinsic susceptibility of mice to this infection. In the present study, we tested the susceptibility to MPEC of five inbred germfree mice, F_1 mice with each combination of a resistant strain and two types of sensitive strains, and the offsprings from backcrosses of F_1 mice to both parental strains. Also, the possible genetic control of susceptibility to MPEC infection is discussed.

MATERIALS AND METHODS

Mice. Male and female inbred germfree CF1, C3H/He, NC, and BALB/c mice were bred in the Institute of Physical and Chemical Research, Wako, Japan. C57BL/6 inbred germfree mice were obtained from Teikyo University School of Medicine. All mice were housed in metal cages in Trexler-type flexible vinyl isolators sterilized with 2% peracetic acid. The mice were fed with FR-1 pellets (Funabashi Farm Co.) sterilized by gamma irradiation at doses of 5 Mrads. Metal cages containing wood shavings and water were introduced into the isolators after sterilization at 121°C for 2 h. The mice were used at 8 to 16 weeks of age. F_1 mice and the offsprings from backcrosses of F_1 mice were used at 8 weeks of age.

Bacteria and inoculation. *E. coli* O115a,c:K(B) Ex-33 (MPEC) was isolated from the cecal contents of a spontaneous case of infectious megaenteron. The organisms were cultured in semisolid Trypticase soy medium (BBL Microbiology Systems) and then stored at −80°C. MPEC was prepared for inoculation into mice as follows. The frozen organisms were inoculated into Trypticase soy broth and incubated at 37°C overnight. The growth (0.5 ml) was added to 4.5 ml of Trypticase soy broth and incubated with shaking at 37°C for 2.5 h. Viable counts in the broth usually reached 4×10^8 cells per ml. The culture (0.2 ml) was then inoculated into the mouse stomach via a metal catheter attached to a 1-ml syringe.

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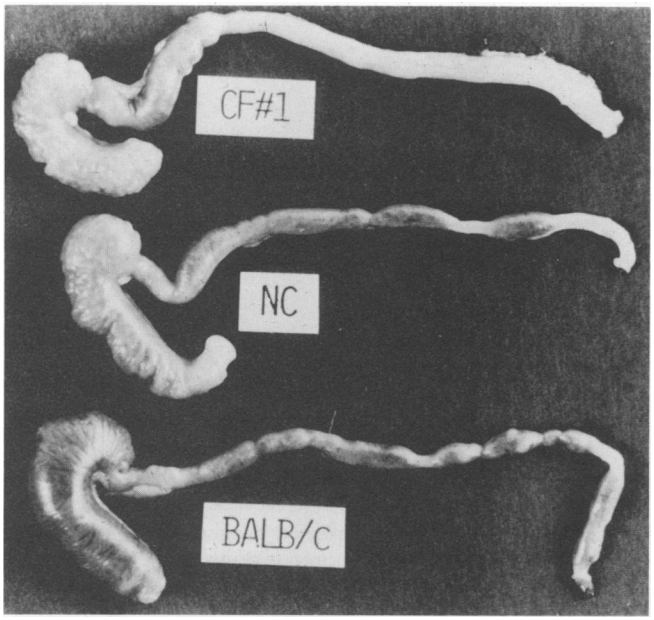

FIG. 1. Macroscopic changes in CF1, NC, and BALB/c mice 7 days after infection with *E. coli* O115a,c:K(B). Note the thickened walls of the cecum and colon of the CF1 mouse and the tip of cecum of the NC mouse (arrow). There were no changes in the BALB/c mouse.

Enumeration of viable organisms. A 1:100 fecal suspension was prepared in sterilized phosphate-buffered saline (pH 7.0) by using a glass homogenizer. To quantify the *E. coli* closely attached to the wall of the cecum or colon, tissue segments were excised and the contents were washed three times with 40 ml of sterilized phosphate-buffered saline. The remaining phosphate-buffered saline was removed by swabbing with sterilized filter paper. A 1:10 emulsion was then made in sterilized phosphate-buffered saline by using a glass homogenizer. The emulsion or dilution (0.1 ml) was spread onto desoxycholate-hydrogen sulfide-lactose agar (Eikin) plates. The plates were incubated at 37°C for 18 to 24 h.

Histological examination. The cecum and colon were fixed with 10% buffered Formalin and embedded in paraffin. Sections (3 to 4 μm) were stained with hematoxylin and eosin stain.

Statistical analysis. Student's *t* test was used to determine the significant differences between mouse strains with respect to numbers of bacteria in feces or on the walls of the large intestines. The χ^2 test was used to compare observed and expected data for genetic analysis.

RESULTS

Macroscopic lesions. A total of 15 germfree mice of each strain was orally inoculated with MPEC and examined macroscopically and microscopically for lesions on days 3, 5, 7, and 14 after infection. The lesions were localized within the large intestine. In CF1 and C3H/He mice, thickening of the walls of both the cecum and colon appeared on days 5, 7, and 14. The lesions on day 14 were more severe than those on days 5 and 7. The lesions in NC mice were located at the tip of the cecum on days 5 and 7 but did not appear on day 14. In C57BL/6 mice, the lesions were located at the tip of the cecum, as in NC mice on days 5 and 14, and on day 7 only, a slight thickening of the wall of a part of the colon also appeared. BALB/c mice showed no lesions (Fig. 1).

Histological lesions. In CF1 and C3H/He mice, there was hyperplasia of the epithelial cells of the large intestine. There was also an inflammatory reaction in the lamina propria and submucosa, with edema of the submucosa. Desquamatory reactions, erosion and slight ulceration, also appeared. The muscle layer thickened with cell infiltration. In CF1 and C3H/He mice, MPEC adhered to the epithelial cells at the tip, the side wall, and the base of crypts. MPEC formed microcolonies on some parts of mucosal epithelia (Fig. 2).

In NC and C57BL/6 mice, the lesions consisted mainly of hyperplasia of epithelial cells; erosion and ulceration of the muscle layer usually did not occur. The hyperplastic epithelial folds in these mice were higher than those in CF1 or C3H/He mice, and the number of mitotic figures in the epithelial cells was greater. The epithelial cells were detached from the tips of the folds. MPEC adhered only to the tips of the folds and did not form microcolonies (Fig. 3). There was no histological change or adherence of MPEC in BALB/c mice (Fig. 4 and 5).

Organism numbers in feces and on walls of the large intestine. At 3 and 7 days after MPEC inoculation, 10^9 cells per g of feces were recovered from all mice. On days 3 and 7, the numbers of organisms on the colon wall of NC mice and on the cecum and colon walls of BALB/c mice were lower than those in other mouse strains. On the cecal wall of NC mice, the numbers of organisms on day 3 were 10^8 to 10^9/g, but decreased to 10^6 to 10^7/g by day 7. In CF1, C3H/He, and C57BL/6 mice, there were no differences in the numbers of organisms on the cecal wall between days 3 and 7. Although only very few lesions were observed in the colon of C57BL/6 mice on day 7, the number of organisms cultured was the same as those in CF1 and C3H/He mice (Table 1).

Genetic analysis. Mouse strains were divided into three groups on the basis of differences in the location of lesions,

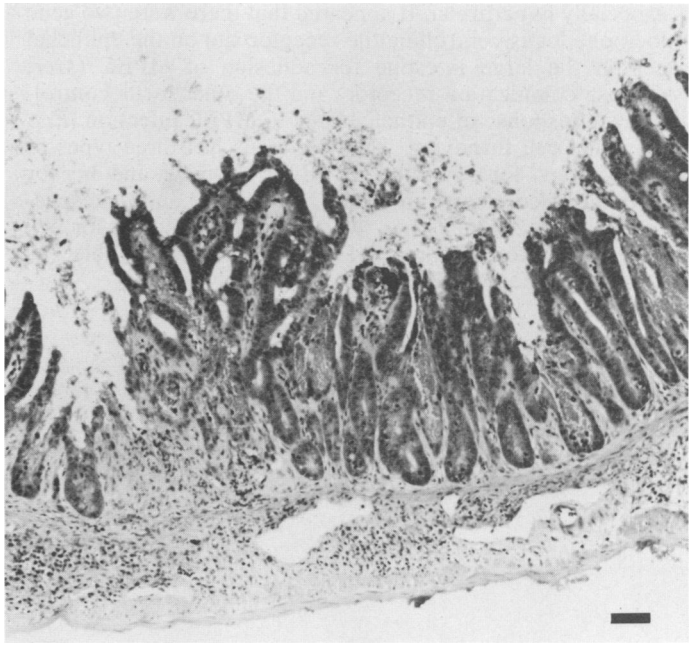

FIG. 2. Cecum of a CF1 mouse 7 days after infection. Hyperplasia of crypt-type cells and erosion appeared in addition to severe inflammatory reactions in the lamina propria, submucosa, and muscle layer. Bar, 50 μm.

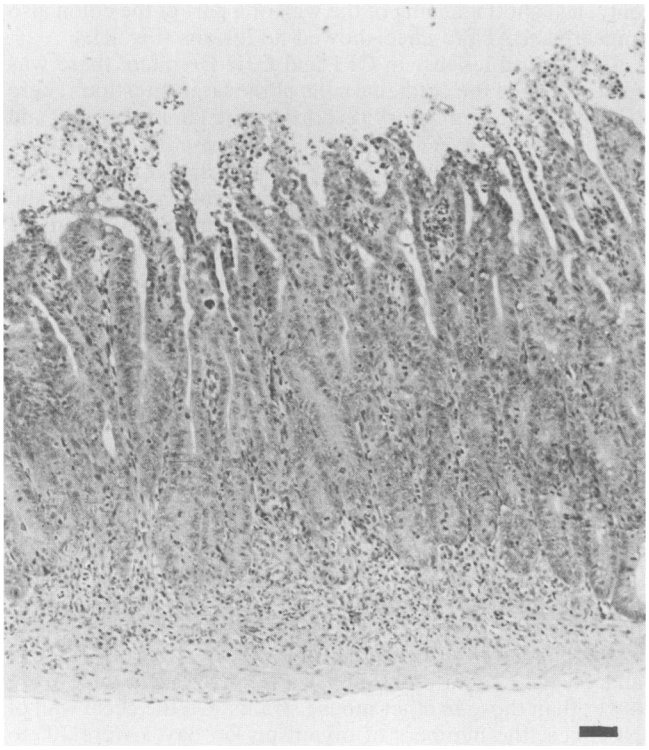

FIG. 3. Cecum of an NC mouse 7 days after infection. There was severe hyperplasia and detachment of epithelial cells from the tip of mucosa. Bar, 50 μm.

the site of MPEC adhesion to epithelial cells, and the histology of the lesions (Table 2). The differences in susceptibility to MPEC among the mouse strains could depend on the differences in receptor sites on the epithelial cells of the large intestine and on the response of the epithelial cells, especially hyperplasia. It appeared that there were two gene loci, one locus controlling the receptor site on the epithelial cell in the large intestine for adhesion of MPEC (*Mcr*, mucosa colonization receptor) and the other locus controlling the response of epithelial cells to MPEC infection (*Ect*, epithelial cell turnover). The *Mcr* locus has three types of genes: *Mcr-1* for CF1 mice, *Mcr-2* for NC mice, and *mcr* for BALB/c mice (shown in Table 3 as A_1, A_2, and *a*, respectively). The *Ect* locus has two types of genes: *Ect* for NC mice and *ect* for CF1 and BALB/c mice (shown in Table 3 as *B* and *b*, respectively).

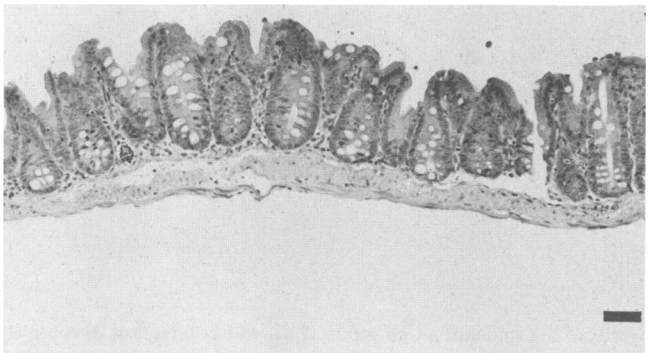

FIG. 4. Cecum of a BALB/c mouse 7 days after infection. No lesions appeared. Bar, 50 μm.

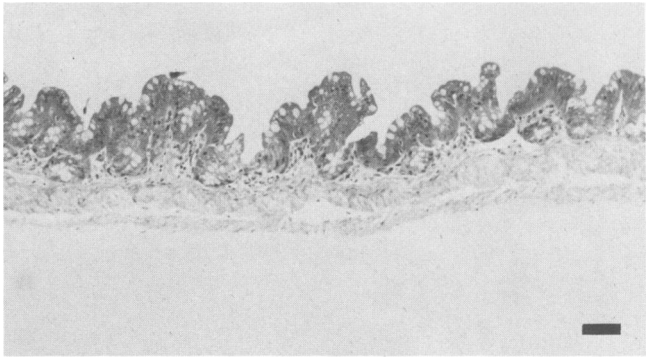

FIG. 5. Cecum of an uninfected germfree mouse (BALB/c). There were no histological differences between strains of uninfected germfree mice. Bar, 50 μm.

F_1 hybrids of CF1 × BALB/c, NC × BALB/c, and NC × CF1 crosses and their backcrossed progeny were examined for macroscopic and microscopic lesions in the large intestine 7 days after oral inoculation with MPEC. The results are summarized in Table 3. All the F_1 hybrids of CF1 × BALB/c, NC × BALB/c, and CF1 × NC crosses had NC-type lesions. In F_1 (CF1 × BALB/c) × CF1 backcrossed mice, the ratio of CF1-type lesion to NC-type lesion was 15:16. These F_1 × BALB/c backcrossed mice showed BALB/c- and NC-type lesions at a ratio of 13:17. In the offsprings derived from backcrosses of F_1 (NC × BALB/c) mice to either parental strain, all of the F_1 × NC backcrossed mice had NC-type lesions. The F_1 × BALB/c backcrossed mice had both BALB/c- and NC-type lesions at a ratio of 8:11. All F_1 (NC × CF1) × NC backcrossed mice had NC-type lesions, and the F_1 × CF1 backcrossed mice had both NC- and CF1-type lesions at a ratio of 15:3. There were no differences between male and female mice in each mouse group as to type of intestinal lesion. Also, in F_1 hybrids and backcrossed offsprings, the lesion types were unrelated to the sex of the parent strains.

The combination of *a*/*a* showed the BALB/c-type lesion irrespective of the combination of *B* and *b*, and only the combination of A_1/A_1 *b*/*b* showed the CF1-type lesion. The other combinations, A_1, A_2, or *a* and *B* or *b*, produced the NC-type lesion. There were no differences between the experimental data obtained and the theoretical incidence rate of the lesion types as determined by the χ^2 test.

DISCUSSION

There are many reports of differences among mouse strains in their susceptibility to infection by various bacteria, e.g., *Salmonella typhimurium* (14, 15, 24), *Mycobacterium bovis* (8, 12), *M. lepraemurium* (4), *M. intracellulare* (11), *Listeria monocytogenes* (2, 28), *Corynebacterium kutscheri* (13), and *Bacillus anthracis* (29). These bacteria, except for *B. anthracis*, are intracellular pathogens (27). *E. coli* O115a,c:K(B) (the causative agent of megaenteron) in mice is not an intracellular pathogen. Adhesion of this bacteria to intestinal epithelial cells is thought to be the most important step in infectious megaenteron (18, 21). In this study, we demonstrated differences in susceptibility to MPEC infection among inbred germfree mouse strains. These differences concerned the location of intestinal lesions, the adhesion of MPEC to epithelial cells, and the type of histological lesions, as summarized in Table 2. From these results, we found that mouse strain differences in susceptibility to MPEC infection

TABLE 1. Viable counts[a] of *E. coli* O115a,c:K(B) in feces and walls of the large intestine of five infected strains of germfree mice

Mouse strain	Count at 3 days after infection in:			Count at 7 days after infection in:		
	Cecum wall	Colon and rectum walls	Feces	Cecum wall	Colon and rectum walls	Feces
CF1	8.5 ± 0.16**[b]	8.5 ± 0.28**	9.5 ± 0.39†[b]	9.0 ± 0.22**	9.0 ± 0.22**	9.6 ± 0.31†
C3H/He	8.2 ± 0.37**	8.6 ± 0.16**	9.6 ± 0.21†	8.6 ± 0.31**	8.8 ± 0.19**	9.4 ± 0.10†
NC	8.6 ± 0.19**	7.9 ± 0.16*[b]	9.6 ± 0.22†	6.9 ± 0.31*	7.7 ± 0.38†	9.4 ± 0.28†
C57BL/6	8.5 ± 0.43**	8.1 ± 0.11**	9.6 ± 0.08†	8.7 ± 0.24*	8.7 ± 0.24**	9.9 ± 0.08†
BALB/c	7.4 ± 0.31	7.5 ± 0.22	9.0 ± 0.19	7.3 ± 0.13	7.3 ± 0.11	9.3 ± 0.11

[a] Mean ± standard deviation (log count per gram); $n = 5$.
[b] Significance against BALB/c mice: **, $P < 0.001$; *, $0.001 \leq P < 0.05$; †, not significant.

TABLE 2. Comparison of microscopical lesions in five inbred germfree mice monoassociated with *E. coli* O115a,c:K(B)

Mouse strain(s)	Location of lesions	Adhesion of *E. coli*	Histological lesions
CF1 and C3H/He	Cecum and colon	From tips to crypts of mucosal epithelia; production of microcolony in epithelia	Hyperplasia of epithelial cells; inflammatory reaction in lamina propria, submucosa, and muscle layer; erosion and ulceration
NC and C57BL/6	Tip of cecum	Only the tip of mucosal epithelia	Severe hyperplasia; severe detachment of epithelial cells from the tip of mucosa; large number of epithelial cells with mitosis
BALB/c	No lesions	No adhesions	No lesions

are due to differences in the receptors on epithelial cells of the intestine and to the hyperplasia response of epithelial cells.

There may be no receptors or only a very few receptors for the adhesion of MPEC to epithelial cells of the cecum and colon of BALB/c mice and of the colon of NC and C57BL/6 mice. There are many reports of different susceptibilities of animals to bacterial infection caused by differences in the distribution of receptors on the host cells. Examples include K88-fimbriated enteropathogenic *E. coli* in pigs (25, 26), P-fimbriated uropathogenic *E. coli* in humans (19, 20), 987P-fimbriated enteropathogenic *E. coli* in rabbits (5, 7), and streptococcus on human oral epithelial cells (23). There were differences between NC and C57BL/6 mice and between

TABLE 3. Genetic analysis of susceptibility of mice to *E. coli* O115a,C:K(B) infection

Mouse strain [genotype(s)]	Genotype(s) of offspring	No. of mice challenged	No. of mice with histopathological lesions[a,b]			Theoretical incidence rate (%) of lesions[b]		
			−	+	++	−	+	++
CF1 × CF1 (A_1/A_1 *b/b*) (A_1/A_1 *b/b*)	A_1/A_1 *b/b*	20	0	0	20	0	0	100
NC × NC (A_2/A_2 *B/B*) (A_2/A_2 *B/B*)	A_2/A_2 *B/B*	18	0	18	0	0	100	0
BALB/c × BALB/c (*a/a b/b*) (*a/a b/b*)	*a/a b/b*	18	18	0	0	100	0	0
CF1 × BALB/c (A_1/A_1 *b/b*) (*a/a b/b*)	A_1/a *b/b*	16	0	16	0	0	100	0
F_1 × CF1 (A_1/a *b/b*) (A_1/A_1 *b/b*)	A_1/A_1 *b/b* and A_1/a *b/b*	31	0	16	15	0	50	50
F_1 × BALB/c (A_1/a *b/b*) (*a/a b/b*)	A_1/a *b/b* and *a/a b/b*	30	13	17	0	50	50	0
NC × BALB/c (A_1/A_2 *B/B*) (*a/a b/b*)	A_2/a *B/b*	13	0	13	0	0	100	0
F_1 × NC (A_2/a *B/b*) (A_2/A_2 *B/B*)	A_2/A_2 *B/B*, A_2/A_2 *B/b*, A_2/a *B/B*, and A_2/a *B/b*	14	0	14	0	0	100	0
F_1 × BALB/c (A_2/a *B/b*) (*a/a b/b*)	A_2/a *B/b*, A_2/a *b/b*, *a/a B/b*, and *a/a b/b*	19	8	11	0	50	50	0
CF1 × NC (A_1/A_1 *b/b*) (A_2/A_2 *B/B*)	A_1/A_2 *B/b*	23	0	23	0	0	100	0
F_1 × CF1 (A_1/A_2 *B/b*) (A_1/A_1 *b/b*)	A_1/A_1 *b/b*, A_1/A_1 *B/b*, A_1/A_2 *b/b*, and A_1/A_2 *B/b*	18	0	15	3	0	75	25
F_1 × NC (A_1/A_2 *B/b*) (A_2/A_2 *B/B*)	A_1/A_2 *B/b*, A_1/A_2 *B/b*, A_2/A_2 *B/B*, and A_2/A_2 *B/b*	20	0	20	0	0	100	0

[a] Mice were killed on day 7 after inoculation.
[b] Symbols: −, BALB/c-type lesion; +, NC-type lesion; ++, CF1-type lesion (Table 2).

CF1 and C3H/He mice with respect to the location of adhesive sites for MPEC on the mucosal epithelial cells. In NC and C57BL/6 mice, MPEC adhered only to the tips of the hyperplastic epithelial folds, but in CF1 and C3H/He mice, the organism adhered to all parts of the epithelium from tip to crypt. It has been reported (1, 10) that there are differences between the glycolipid distribution in the tips of the villi of rat small intestine and that in the crypts. There also may be differences between the distribution of receptors to MPEC adherence in tips and that in crypts in the cecal epithelium of NC mice. Cohen et al. reported that the receptor in mouse colonic mucus for a human fecal *E. coli* is a glycoprotein (3). Dean and Isaacson (6) also found that the receptor in rabbit small intestines for 987P-fimbriated *E. coli* is a glycoprotein and proved that the different susceptibilities to *E. coli* 987P are related to the distribution of the receptors on epithelial cells, which varies with age (7). In megaenteron in mice, the type of intestinal lesion and the susceptibility to infection are different depending upon the age of the mice (21, 22). Studies of the mechanisms determining the differences of susceptibility to MPEC on the basis of age or mouse strain should be focused on the distribution of the receptors on intestinal epithelial cells.

Hyperplasia of the intestinal epithelial cells is most likely the most important factor affecting the differences between the type of lesions seen in CF1 and C3H/He mice. In NC and C57BL/6J mice, histological lesions were restricted to the epithelial cells with severe mucosal hyperplasia detachment of epithelial cells, from the tip of hyperplastic mucosa. In contrast, only slight hyperplasia occurred in CF1 and C3H/He mice compared with that in NC and C57BL/6J mice, although histological lesions of CF1 and C3H/He mice were very severe. Ganaway (9) suggested that the hyperplasia response may be a defense mechanism to replace infected cells with newly migrated, uninfected epithelium. For example, mouse colitis associated with *Citrobacter freundii* is characterized by marked mucosal hyperplasia and various degrees of inflammation. We have formulated the following hypothesis. MPEC easily colonizes the epithelial cells of CF1 and C3H/He mice since the hyperplasia response of these mice is very weak. MPEC then causes desquamation erosion, and ulcerative lesions are produced. On the other hand, the hyperplasia response of NC and C57BL/6 mice is very severe, and the infected cells are replaced with newly migrated epithelial cells. Consequently, the histology is restricted only to hyperplasia of the epithelial cells.

The differences among mouse strains in susceptibility to MPEC infection were also analyzed genetically. Since the susceptibility to MPEC infection is thought to be controlled by the receptor on the intestinal villous epithelial cell, it appeared that only the autosomal locus *Mcr* was involved. We observed lesions in all F_1 mice of CF1 × BALB/c and NC × BALB/c crosses. Mice obtained from the backcross of F_1 hybrids (from a CF1 × BALB/c or a NC × BALB/c cross) to BALB/c mice were distributed at a ratio of 1:1 with respect to resistance or sensitivity. These results suggested that the mice are sensitive or resistant to MPEC infection according to genetic control by only one locus; *Mcr-1* (CF1 type) and *Mcr-2* (NC type) are dominant to *mcr* (BALB/c type). In F_1 mice (CF1 × NC) and the progeny obtained from the backcross to CF1, the combination of genes, *Mcr-1*/*Mcr-2*, produced NC-type lesions. However, we thought that the type of lesion was controlled by more than the *Mcr* locus, since F_1 mice (CF1 × BALB/c) had the gene combinations *Mcr-1*/*mcr* and *ect*/*ect* and yet showed only NC-type lesions.

We looked at the *Ect* locus as the other genetic factor which might control the hyperplasia of intestinal villus epithelial cells. *Ect* (NC type), which controls the high response of epithelial cells to hyperplasia against MPEC infection, was dominant to *ect* (CF1 and BALB/c types), as demonstrated by F_1 mice (from NC × CF1 and NC × BALB/c crosses) and the progeny obtained from the backcross to each parent strain. However, further studies are required to determine whether the *ect* of CF1 mice and the *ect* of BALB/c mice are the same genes.

In summary, inbred germfree mouse strains showed different susceptibilities to MPEC, and these differences were controlled genetically. From genetic analysis, we suggest that the production of intestinal lesions is controlled by one locus and the histopathological differences among intestinal lesions are controlled by at least two loci.

ACKNOWLEDGMENTS

We thank H. Tamura, Animal Center, Teikyo University School of Medicine, for supplying germfree mice and T. Yamamoto, A. Ozaki, and T. Oowada for taking care of the germfree mice.

LITERATURE CITED

1. **Bouhours, J. F., and R. M. Glickman.** 1976. Rat intestinal glycolipids. II. Distribution and biosynthesis of glycolipids and ceramide in villus and crypt cells. Biochim. Biophys. Acta **441:** 123–133.
2. **Cheers, C., and I. F. C. McKenzie.** 1978. Resistance and susceptibility of mice to bacterial infection: genetics of listeriosis. Infect. Immun. **19:**755–762.
3. **Cohen, P. S., J. C. Arruda, T. J. Williams, and D. C. Laux.** 1985. Adhesion of a human fecal *Escherichia coli* strain to mouse colonic mucus. Infect. Immun. **48:**139–145.
4. **Curtis, J., and J. L. Turk.** 1984. Resistance to subcutaneous infection with *Mycobacterium lepraemurium* is controlled by more than one gene. Infect. Immun. **43:**925–930.
5. **Dean, E. A., and R. E. Isaacson.** 1982. In vitro adhesion of piliated *Escherichia coli* to small intestinal villous epithelial cells from rabbits and the identification of a soluble 987P pilus receptor-containing fraction. Infect. Immun. **36:**1192–1198.
6. **Dean, E. A., and R. E. Isaacson.** 1985. Purification and characterization of a receptor for the 987P pilus of *Escherichia coli*. Infect. Immun. **47:**98–105.
7. **Dean, E. A., and R. E. Isaacson.** 1985. Location and distribution of a receptor for the 987P pilus of *Escherichia coli* in small intestines. Infect. Immun. **47:**345–348.
8. **Forget, A., E. Skamene, P. Gros, A-.C. Miailhe, and R. Turcotte.** 1981. Differences in response among inbred mouse strains to infection with small doses of *Mycobacterium bovis* BCG. Infect. Immun. **32:**42–47.
9. **Ganaway, J. R.** 1982. Bacterial and mycotic diseases of the digestive system, p. 9–11. *In* H. L. Foster, J. D. Small, and J. G. Fox (ed.), The mouse in biomedical research, vol. 2. Diseases. Academic Press, Inc., New York.
10. **Glickman, R. M., and J. F. Bouhours.** 1976. Characterization, distribution and biosynthesis of the major ganglioside of rat intestinal mucosa. Biochim. Biophys. Acta **424:**17–25.
11. **Goto, Y., R. M. Nakamura, H. Takahashi, and T. Tokunaga.** 1984. Genetic control of resistance to *Mycobacterium intracellulare* infection in mice. Infect. Immun. **46:**135–140.
12. **Gros, P., E. Skamene, and A. Forget.** 1981. Genetic control of natural resistance to *Mycobacterium bovis* (BCG) in mice. J. Immunol. **127:**2417–2421.
13. **Hirst, R. G., and M. E. Wallace.** 1976. Inherited resistance to *Corynebacterium kutscheri* in mice. Infect. Immun. **14:**475–482.
14. **Hormaeche, C. E.** 1979. Natural resistance to *Salmonella typhimurium* in different inbred mouse strains. Immunology **37:**311–318.
15. **Hormaeche, C. E.** 1979. Genetics of natural resistance to salmonellae in mice. Immunology **37:**319–327.
16. **Itoh, K., K. Maejima, K. Ueda, and K. Fujiwara.** 1978. Effect of

intestinal flora on megaenteron of mice. Microbiol. Immunol. **22**:661–672.

17. **Itoh, K., K. Maejima, K. Ueda, and K. Fujiwara.** 1979. Difference in susceptibility of mice raised under barrier-sustained (SPF) or conventional conditions to infectious megaenteron. Microbiol. Immunol. **23**:909–913.
18. **Itoh, K., K. Ueda, and K. Fujiwara.** 1980. Susceptibility of germfree mice to infectious megaenteron. Microbiol. Immunol. **24**:281–290.
19. **Kallenius, G., R. Mollby, S. B. Svenson, J. Winberg, A. Lundblad, S. Svensson, and B. Cedergren.** 1980. The Pk antigen as receptor for the haemagglutination of pyelonephritogenic *Escherichia coli*. FEMS Microbiol. Lett. **7**:297–302.
20. **Kallenius, G., S. B. Svenson, R. Mollby, and J. Winberg.** 1981. Structure of carbohydrate part of receptor on human uroepithelial cells for pyelonephritogenic *Escherichia coli*. Lancet **ii**: 604–606.
21. **Muto, T., M. Nakagama, Y. Isobe, M. Saito, T. Nakano, and K. Imaizumi.** 1969. Infectious megaenteron of mice. I. Manifestation and pathological observation. Jpn. J. Med. Sci. Biol. **22**: 363–374.
22. **Nakagawa, M., R. Sakazaki, T. Muto, M. Saito, T. Hagiwara, and K. Imaizumi.** 1969. Infectious megaenteron of mice. II. Detection of coliform organisms of an unusual biotype as the primary cause. Jpn. J. Med. Sci. Biol. **22**:375–382.
23. **Ofek, I., E. H. Beachey, F. Eyal, and J. C. Morrison.** 1977. Postnatal development of binding of streptococci and lipoteichoic acid by oral mucosal cells of humans. J. Infect. Dis. **135**: 267–274.
24. **Plant, J., and A. A. Glynn.** 1976. Genetics of resistance to infection with *Salmonella typhimurium* in mice. J. Infect. Dis. **113**:72–78.
25. **Sellwood, R.** 1983. Genetic and immune factors in the susceptibility of piglets to *Escherichia coli* diarrhea. Ann. Rech. Vet. **14**: 512–518.
26. **Sellwood, R., R. A. Gibbons, G. W. Jones, and J. M. Rutter.** 1975. Adhesion of enteropathogenic *Escherichia coli* to pig intestinal brush borders: the existence of two pig phenotypes. J. Med. Microbiol. **8**:405–411.
27. **Skamene, E.** 1983. Genetic regulation of host resistance to bacterial infection. Rev. Infect. Dis. **S4**:5823–5832.
28. **Skamene, E., P. A. L. Kongshann, and D. H. Sacks.** 1979. Resistance to *Listeria monocytogenes* in mice: genetic control by genes that are not linked to the H-2 complex. J. Infect. Dis. **139**:228–231.
29. **Welkos, S. L., T. J. Keener, and P. H. Gibbs.** 1986. Differences in susceptibility of inbred mice to *Bacillus anthracis*. Infect. Immun. **51**:795–800.