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# Failure to induce proliferative ileitis in golden hamsters (*Mesocricetus auratus*) by simultaneous infection with *Campulobacter jejuni* and *Escherichia coli*

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*Introduction*

Enteritis with clinical signs of diarrhoea is the most commonly recognized disease and the primary cause of spontaneous death in golden hamsters (*Frisk* 1987). Fifteen years ago, during necropsy of dead conventionally kept hamsters, we observed ileitis (hamorrhagic, necrotizing, proliferative). In the last 5 years the pathologic picture has changed: caecitis (typhlitis) and colitis, only sometimes accompanied by proliferative ileitis, have been regularly observed. In both cases, the past and the more recent one, no *Campylobacter jejuni* (*C. jejuni*) could be cultivated (*Kunstýr & Kaup* 1986). Besides *Pasteurella pneumotropica* (*Krause et al.* 1989) and *Giardia sp.* (found occasionally) which cannot be considered as primary agent, no pathogens could be isolated. In the latter case intracellular spiral-shaped bacteria could be revealed under the electron microscope (*Kunstýr & Kaup* 1986).

In the literature dealing with proliferative ileitis in hamsters, 11 bacterial, 3 viral, 5 parasitic as well as some neoplastic and dietary agents or factors were claimed to be the cause of the disease or were discussed as etiologic agents (*Frisk* 1987, *Kunstýr & Kaup* 1986, *Frisk & Wagner* 1977). Only few authors succeeded in reproducing some aspects of the disease, namely using *C. jejuni* (*Humphrey et al.* 1985), *E. coli* (*Frisk et al.* 1981) or ileal homogenates from sick hamsters (*Jacoby et al.* 1975, *Amend et al.* 1976, *Frisk & Wagner* 1977, *Jacoby* 1978, *Johnson & Jacoby* 1978, *Jacoby & Johnson* 1981, *Stills & Hook* 1989). It was shown that the ability of *C. jejuni* to invade epithelial cells is significantly enhanced by the presence of other enteropathogens as coinfectants (*Bukholm & Kapperud* 1987). A hypothesis on a possible synergism of two etiologic agents, *E. coli* and *Campylobacter sp.* in inducing hamster enteritis was postulated (*Frisk* 1987, *Frisk & Wagner* 1977).

In order to test this hypothesis we infected golden hamsters simultaneously with different, mainly pathogenic, *E. coli* strains and with *C. jejuni* isolate which originated from a case of spontaneous hamster enteritis (*Jelínek & Aldová* 1986).

*Materials and Methods*

Bacterial strains

The bacterial strains used for experimental infection are listed in Table 1. The *C. jejuni* strain (C 43) isolated from a golden hamster with enteritis (*Jelínek & Aldová* 1986) was kindly supplied by Dr. F. Jelínek, State Institute of Drug Control, Prague. All four *E. coli* strains were kindly supplied by Dr. L. Beutin, Federal Health Office, Berlin.

Cultivation procedures

*E. coli* strains were either cultivated on tryptic soy broth (TSB, Oxoid), on NaCl-free Mac Conkey agar (Oxoid) or sheep blood agar (SBA; 5 % v/v defibrinated sheep blood in Columbia agar, Oxoid) for 16–24 h at 37°C. *C. jejuni* strain was cultivated on *Brucella* broth (BB, Difco) for 24 h at 42°C. *Campylobacter* blood-free selective agar

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**Table 1** Bacterial strains studied (as coinfectant or mono-infectant)

| Species and entero-pathogenicity | Serovar/ resp. strain designation | Origin | Heat labile enterotoxin (lt) | Verotoxin (vt) | Sereny test |
|---|---|---|---|---|---|
| EIEC [a] | 0143 | human | - | - | + |
| Non-EIEC | 0124 | human | - | - | - |
| ETEC [b] | 0138 | pig | - | + | - |
| ETEC | 0138 | pig | + | - | - |
| *C. jejuni* (isolated from clinical process) | C 43 | hamster | | | |

a) EIEC - Enteroinvasive *E. coli*

b) ETEC - Enterotoxigenic *E. coli*

base (modified CCDA-Preston, Oxoid) with cefoperazone selective supplement (Oxoid) served as solid medium. *C. jejuni* was incubated under microaerophilic conditions (Anaerocult C$^{TM}$, Merck) at 42°C for 48–72 h.

### Animals and maintenance conditions

Golden hamsters (Han:Aura) of two different microbial status were used for experimental infection: conventionally bred hamsters (CH) and selectively decontaminated (*Sickel* 1990) hamsters (DH). The CH were free of antibodies against reovirus 3, pneumonia virus of mice, sendai virus, lymphocytic choriomeningitis virus, simian virus 5 and adenovirus. They had antibodies against *Bacillus piliformis* but no clinical signs of Tyzzer's disease and harboured no further characterized *E. coli, Spironucleus sp., Tritrichomonas sp.* and *Giardia sp.* (*Kunstýr* 1992).

The DH derived from the conventional colony were additionally free of *Enterobacteriaceae, Giardia sp.* and *Spironucleus sp.* (*Sickel* 1990). Only enterococci, coagulase negative staphylococci and *Bacillus* species could be isolated under aerobic conditions.

The hamsters of each group were kept separately on sterilized bedding of softwood granulate in macrolon cages (type III) covered with filter hoods. Autoclaved drinking water and pellets of a complete cereal-based diet were fed *ad libitum*. The cages were placed in a Han:Isolab$^{TM}$ at 22 ± 2°C room temperature, approximately 55 % relative humidity and the light/dark rhythm 14 h/10 h. During the experiment the hamsters were observed twice a day for clinical signs of the disease.

### Experimental infection

Groups of 4–10 golden hamsters were used for each experiment. Within the CH and DH groups the following subgroups were formed: 5 mono-infected. 4 di-infected, i.e. *C. jejuni* + *E. coli*, and 1 control subgroup. Four- to five-week-old male golden hamsters of either CH or DH status were inoculated orally by means of a plastic Eppendorf pipette under stringent aseptic conditions in a laminar flow bench. The infective dose was $2\times10^8$ cfu for *C. jejuni* and $4\times10^8$ cfu for *E. coli* cultivated on BB or on TSB respectively. On days 8 and 16 p.i. (*post infectionem*) rectal swabs were taken. These were

plated on SBA and MacConkey agar (*E. coli*) and modified CCDA-Preston agar (*C. jejuni*) and incubated as described before. Intestinal contents from jejunum, ileal junction, caecum and colon were processed at the end of the experiment (32 dpi) or from moribund hamsters on the same media.
Control groups of hamsters of both types of microbial quality were inoculated with sterile saline only and further processed in the same way as described above.

### Serological procedures

For serologic control of the infection the blood was taken by retrobulbar puncture under ether anaesthesia on 16 dpi and 32 dpi (end of the experiment) or by heart puncture under $CO_2$ anaesthesia from moribund animals. Indirect immunofluorescence assay (IIF) (*Kraft & Meyer* 1986) with modification (*Wullenweber et al.* 1990) was used.
For diagnostic slide agglutination anti-*E. coli*-antisera were used originating from the Robert-Koch-Institut, Berlin, F.R.G. and from the Rijksinstituut voor Volksgezondheid en Milieuhygiene, Bilthoven, The Netherlands. The test was performed by suspending one bacterial colony in a drop of 1:25 diluted antiserum on a slide. Observation of a clear agglutination within one minute was assumed as positive reaction. Negative control (saline) and positive control (corresponding *E. coli* strain) were included.

### Histological procedures

At the end of the experiment, sections of jejunum, ileum, caecum and colon were fixed in 10 % formalin, embedded in paraffin and HE-stained.
For immunocytochemistry, 2 cm of the terminal ileum were rinsed with phosphate-buffered saline, filled with O.C.T. compound (Miles Laboratories) and frozen at –20°C. Cryostat sections of 8 µm were prepared for indirect immunofluorescence (*Frisk & Wagner* 1981).

### *Results*

The results in CH (Table 2) which already harboured their *E. coli* bacteria differed from those in DH (Table 3).

**Table 2** Experimental infection of conventionally bred hamsters (CH) with *C. jejuni* and/or *E. coli*

| Infective agent | Cultural isolation [1] | | | | Serological response [1] | | | |
|---|---|---|---|---|---|---|---|---|
| | *C. jejuni* | | *E. coli* | | *C. jejuni* | | *E. coli* | |
| | n pos./n total | % | n pos./n total | % | n pos./n total | % | n pos./n total | % |
| *C. jejuni* | 8/10 | 80 | | | 4/10 | 40 | | |
| *E. coli O143* | | | 0/9[2] | 0 | | | 2/9 | 22 |
| *E. coli O124* | | | 0/10 | 0 | | | 1/10 | 10 |
| *E. coli O138vt+* | | | 0/9[2] | 0 | | | 6/9 | 67 |
| *E. coli O138lt+* | | | 0/9[2] | 0 | | | 0/9 | 0 |
| *C. jejuni + E. coli O143* | 5/9 | 55 | 0/9[2] | 0 | 2/9 | 22 | 3/9 | 33 |
| *C. jejuni + E. coli O124* | 6/10 | 60 | 0/10 | 0 | 1/10 | 10 | 3/10 | 30 |
| *C. jejuni + E. coli O138vt+* | 9/9 | 100 | 0/9[2] | 0 | 2/9 | 22 | 6/9 | 33 |
| *C. jejuni + E. coli O138lt+* | 6/9 | 66 | 0/9[2] | 0 | 1/9 | 11 | 0/9 | 0 |

[1] Results on 32 dpi
[2] one hamster died with signs of aspiration pneumonia after oral infection
pos. = positive finding

**Table 3** Experimental infection of decontaminated hamsters (DH) with *C. jejuni* and / or *E. coli*

| Infective agent | Cultural isolation [1] | | | | Serological response [1] | | | |
|---|---|---|---|---|---|---|---|---|
| | *C. jejuni* | | *E. coli* | | *C. jejuni* | | *E. coli* | |
| | n pos./n total | % | n pos./n total | % | n pos./n total | % | n pos./n total | % |
| *C. jejuni* | 3/6 | 50 | | | 4/6 | 66 | | |
| *E. coli O143* | | | 2/5[2] | 40 | | | 5/5 | 100 |
| *E. coli O124* | | | 6/6 | 100 | | | 4/6 | 66 |
| *E. coli O138vt+* | | | 4/4 | 100 | | | 3/4 | 75 |
| *E. coli O138lt+* | | | 2/2[3] | 100 | | | 2/2 | 100 |
| | | | 1/1[3] | 100 | | | 1/1 | 100 |
| *C. jejuni + E. coli O143* | 3/6 | 50 | 5/6 | 80 | 4/6 | 66 | 4/6 | 66 |
| *C. jejuni + E. coli O124* | 5/6 | 80 | 6/6 | 100 | 3/6 | 50 | 4/6 | 66 |
| *C. jejuni + E. coli O138vt+* | 3/4 | 75 | 4/4 | 100 | 0/4 | 0 | 4/4 | 100 |
| *C. jejuni + E. coli O138lt+* | 6/6 | 100 | 4/6 | 66 | 2/6 | 33 | 4/6 | 66 |

[1] Results on 32 dpi
[2] one hamster died with signs of aspiration pneumonia after oral infection
[3] 4 resp. 3 animals died earlier with signs of enteritis
pos. = positive finding

All CH – both infected and non-infected – remained healthy. Histologic investigation did not reveal any pathologic alterations of the intestine. *C. jejuni* could be reisolated from the intestine on 32 dpi in 55 to 100 % of the infected animals. *E. coli* strains used for infection could neither be isolated from rectal swabs on day 8 and 16 dpi nor from intestinal contents on 32 dpi. Antibodies against *C. jejuni* were detected in about 10 % of CH infected with *C. jejuni* + *E. coli* O124/O138 lt+, and in about 20 % of CH infected with *C. jejuni* + *E. coli* O138 vt +/ O143 (see Table 2). Forty percent of CH infected with *C. jejuni* alone were seropositive. Antibodies against *E. coli* were detected on 32 dpi, depending on the strain: in none of the CH infected with *E. coli* O138 lt+ and in 67 % of the CH infected with *E. coli* O138 vt +.

By means of the immunocytochemical technique the infective agents could be demonstrated on the surface of the intestinal mucous membrane and/or in the lumen but not intracellularly (not shown). Similarly, all DH remained healthy with the exception of one subgroup mono-infected with *E. coli* O138 lt + (see Table 3). On 18 dpi 4 of 6 animals of this subgroup became clinically ill including diarrhoea. These hamsters were sacrificed under anaesthesia and dissected. Histopathologic examination showed slight to moderate oedema of the caecum wall and infiltration of the mucous membrane and the submucosal tissue with polymorphonuclear granulocytes, and some lymphocytes and histiocytes. Small abscesses in the crypts were always present. In addition, in two out of four diseased animals a purulent inflammation of the colon was observed accompanied by ileitis characterized by necrosis of the tips of the villi. All these changes resembled an acute enteritis, not a chronic proliferative ileitis.

In these particular cases, the immunocytochemical examination of ileal sections revealed fluorescent bacterial rods deep between the villi or within the enterocytes,

whereas in the remaining two healthy DH, fluorescent rods were only present in the intestinal lumen and on the surface of the mucous membrane (not shown). This experiment was repeated, whereby 3 of 4 animals became ill.

In contrast, there was no evidence of a disease in the group of DH where this particular enterotoxigenic *E. coli* strain O138 was administered together with *C. jejuni.*

*Discussion*

Mixed infections play increasingly an important role in human and veterinary microbiology (*Fernie et al.* 1975, *Mayr & Köhler* 1980, *Rübsamen et al.* 1982). In the light of recent experiences it has become evident that practically all diseases have a multifactorial etiology (*Isenberg* 1988, *Kunstýr* 1991). This stimulated our work to follow the hypothesis of a multifactorial etiology of hamster enteritis (*Frisk* 1987, *Frisk & Wagner* 1977) which, to our knowledge, has not been attempted before.

Recently (*Stills* 1991) a novel small intracellular bacterium was isolated from hamsters with proliferative ileitis in an intestinal cell culture and the disease was successfully reproduced with cell-free filtrates. The lack of cross-reactivity with *E. coli, C. jejuni* and *C. hyointestinalis* suggests that this organism is antigenically distinct and probably not a member of the genus *Campylobacter.* Thus, an important step seems to have been taken toward elucidating the etiology of the proliferative ileitis. Nevertheless, as long as the results of *Stills* (1991) have not yet been reproduced or verified by others a multifactorial etiological hypothesis seems to be worth testing.

*C. jejuni* was shown to participate in the polymicrobial enteritis of humans (*Lassen & Kapperud* 1984, *Melamed et al.* 1985, *Georges-Courbot et al.* 1987). Its invasiveness was an important pathogenicity factor in the induction of enteral disease (*Butzler & Skirrow* 1979, *Newell* 1984, *Newell et al.* 1985). It was shown that the presence of enteroinvasive *Salmonella, Shigella* and *E. coli* strains enhanced the ability if *C. jejuni* to localize intracellularly in epithelial cells *in vitro* (*Bukholm & Kapperud* 1987).

Several reports indicate that enteritis or at least some forms of enteritis in hamsters (*Frisk* 1987, *McOrist et al.* 1989), rabbits (*Schoeb & Fox* 1990) and pigs (*McOrist et al.* 1989, *McOrist et al.* 1987) are caused by a novel *Campylobacter*-like intracellular organism. In view of the fact that *C. cinaedi* and other *Campylobacter* species belong to the normal intestinal flora of hamsters (*Stills et al.* 1989, *Gebhart et al.* 1989), the strains of bacteria studied were chosen according to their involvement with pathological processes *in vivo.* They were isolated from diseased hamsters (*C. jejuni*) or from diseased pigs or humans (*E. coli* strains). Using selective staining, layers of *Campylobacter*-like bacteria could be revealed in intimate contact with the intestinal mucous membrane in hamsters with enteritis; however, not in every section and not in each animal (*Jelínek* 1990).

The failure to reproduce ileitis by infection with *C. jejuni* and *E. coli* indicates that the strain of *C. jejuni* was not – or not alone – the cause of hamster ileitis described by *Jelínek & Aldová* (1986) and that the co-infectant *E. coli* strains are most probably not the additional factor necessary for the induction of the disease. Although we used two *E. coli* strains of the same serovar O124 (an enteroinvasive and a non-enteroinvasive one) as done by *Bukholm & Kapperud* (1987) the invasive capacity of *C. jejuni* could not be induced under *in vivo* conditions. Thus, the "double agent hypothesis" tested can be rejected. Our results are in agreement with the results of *Stills* (1991) and support his etiological study.

Interestingly enough, different results could be achieved in selectively decontaminated hamsters (DH), which seem to be a worldwide rarity up to now (*Sickel* 1990), and in conventional hamsters (CH). These results underline the general importance of the resi-

dent microbial flora and of the awareness of the microbial status of the animals used in experiments with infectious agents. Obviously, the autochthonous *E. coli* strains present in the gut of CH prevented the intestinal colonization with experimentally administered *E. coli* strains. Colicinogenic activity did not give a satisfactory explanation for the phenomenon: the autochthonous *E. coli* showed colicinogenic activity against the indicator strains and *vice versa* (results not shown). On the other hand, the induction of enteritis observed in DH mono-infected with *E. coli* O138 (It+) could surprisingly be prevented in animals to which *C. jejuni* was given as co-infectant. An explanation for this interaction has not yet been found.

*Summary*
Conventionally bred golden hamsters (CH) and selectively decontaminated golden hamsters (DH) of a strain Han:AURA were experimentally infected with *Campylobacter jejuni* (*C. jejuni*) strain isolated from a case of proliferative ileitis and one of four *Escherichia coli* (*E. coli*) strains of either porcine or human origin (serovars O124, O138 and O143). Experimental infection was monitored 32 days post infectionem by watching the clinical signs of diarrhoea, by cultivation of the infective agents and by detection of specific IgG antibodies (indirect immunofluorescence technique).
All animals infected with *C. jejuni* alone remained healthy. No combination of *C. jejuni* and *E. coli* led to enteritis and diarrhoea. The enteritis induced by mono-infection with *E. coli* O138 It+ showed histologic signs of an acute process unlike changes characteristic for proliferative ileitis. Surprisingly, the addition of *C. jejuni* to this disease-provoking *E. coli* strain prevented the disease.
The results suggest that simultaneous infection with *C. jejuni* and *E. coli* is not the cause of proliferative ileitis in hamsters. These findings support the results of *Stills* (1991) describing a new intracellular bacterium as a real etiologic agent of the disease.

*Sammendrag*
Konventionellt uppfödda guldhamstrar (CH) och selektivt dekontaminerade guldhamstrar av stam Han:AURA blev i experimentellt syfte infekterade med *Campylobacter jejuni* (*C. jejuni*) isolerad från ett fall av proliferativ ileit och en av fyra stammer *Escherichia coli* (*E. coli*) av antingen svin eller mänskligt ursprung (serovars O124, O138 och O143). Den experimentella infektionen blev kontrollerad 32 dygn post infectionem genom iakttagelse av kliniska tecken på diarré, kultivering av bakterier som används för infektion och genom upptäckt av specifiska Igg antikroppar (indirect immunofluorescence technique).
Alla djur endast infekterade med *C. jejuni* förblev friska. Ingen kombination av *C. jejuni* och *E. coli* ledde til enterit eller diarré. Diarréen som uppstått genom en monoinfektion med *E. coli* O138 It+ visade histologiska tecken på en akut process olik de charakteristiska ändringar för proliferativ ileit. Överraskande visade tillägget av *C. jejuni* till den sjukdomsprovozerande *E. coli* stam en förebyggning av sjukdomen. Resultaten tyder på att simultan infektion med *C. jejuni* och *E. coli* inte är orsaken till proliferativ ileit på hamstrar. Dessa resultat stödjer *Stills* (1991) utlåtande som beskriver en ny intracellulär bakterie som en reell framkallande agens till denna sjukdom.

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