

Bacterial translocation in cirrhotic rats. Its role in the development of spontaneous bacterial peritonitis

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Abstract

Bacterial translocation occurs in ascitic cirrhotic rats, but its association with ascites infection is unknown. The aim of this study was to assess the relation between bacterial translocation and ascites infection in cirrhotic rats. Male Sprague-Dawley rats were induced to cirrhosis with intragastric CCl₄. Ascitic fluid, portal and peripheral blood, mesenteric lymph nodes, liver and spleen samples were cultured before death in those cirrhotic rats with less (group A) or more (group B) than 250 polymorphonuclear neutrophils/mm³ in ascitic fluid, as well as in healthy control rats. Histological examination of jejunum, ileum, and caecum was also performed. Bacterial translocation occurred in 45% of ascitic rats (without differences between groups A and B), but in 0% controls ($p=0.01$). Bacterial translocation was associated with positive ascitic fluid culture in 60% of the cases. In all of them the same bacterial species was isolated in both mesenteric lymph node and ascitic fluid. Submucosal caecal oedema (100%), ileal lymphangiectasia (41%), and caecal inflammatory infiltrate (41%) occurred in ascitic rats, the last being associated with ascitic fluid positive culture ($p=0.04$). These results suggest that bacterial translocation occurs frequently in ascitic cirrhotic rats, and may play a permissive, but not unique, part in a number of ascites infections. Whether histological changes seen in cirrhotic ascitic rats favour bacterial translocation remains to be elucidated.

(Gut 1994; 35: 1648–1652)

Cirrhotic patients have increased susceptibility to severe infections, mainly spontaneous bacterial peritonitis and bacteraemia. Most of them (75%) are caused by aerobic organisms of enteric origin.^{1–3}

In the pathogenic hypothesis for spontaneous bacterial peritonitis two complementary mechanisms have been proposed. Firstly, the passage of enteric bacteria into the bloodstream after crossing the gut barrier,^{3,4} and secondly, the inability of the systemic and local – that is, peritoneal-host defences to eradicate them. Enough data on this second mechanism are available. In fact, both hepatic reticulo-endothelial system impairment⁵ and systemic

immune alterations⁶ have been reported in cirrhotic patients. Moreover, a facilitating role of decreased opsonic and bactericidal activities, C3 concentrations, and protein concentration in ascitic fluid upon the appearance of spontaneous bacterial peritonitis has been shown.^{7–11}

In animal models, gut bacteria has been proved to cross the intestinal barrier to the bloodstream in several situations.^{12,13} This phenomenon, known as bacterial translocation, usually occurs with those aerobic bacterial species most often responsible for spontaneous bacterial peritonitis, whereas anaerobic organisms rarely translocate.¹⁴ However, direct evidence of bacterial translocation in cirrhosis is scarce.^{15,16} Also, no data are available about the association between bacterial translocation and systemic infections or spontaneous bacterial peritonitis in cirrhosis despite the fact that eradication of aerobic enteric organisms, by means of selective intestinal decontamination, is effective in preventing infections in cirrhosis, especially spontaneous bacterial peritonitis.^{17–19}

The aim of this study was to investigate the incidence of bacterial translocation in cirrhotic rats with ascites, as well as to assess the possible relation between bacterial translocation and the presence of ascitic fluid infection in those rats.

Methods

Seventy three male Sprague-Dawley rats weighing 100–175 g were included in the study. Animals were caged individually in a constant room temperature of 21°C, and a 17/7 hour light/dark cycle, and fed 20–25 g/day of standard rodent chow (A04, Panlab, Barcelona, Spain). The study was conducted, in agreement with the guidelines for animal research, according to the Guide for the Care and Use of Laboratory Animals.

INDUCTION OF CIRRHOSIS

Cirrhosis was induced by giving 1.5 mmol/l phenobarbital in drinking water until the animals reached 200 g body weight. Then, weekly intragastric CCl₄ was added, starting at a dose of 20 µl. Subsequent doses were adjusted based upon the change in body weight 48 hours after the last dose, according to Runyon *et al.*²⁰ CCl₄ was given through an appropriate orogastric feeding tube (Popper

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Accepted for publication
11 March 1994.

TABLE I General features (mean (range)) of ascitic rats studied

	Group A (<250 polymorphonuclear neutrophils/mm ³)	Group B (>250 polymorphonuclear neutrophils/mm ³)
Weeks receiving CCl ₄	10.2 (8–18)	11.9 (7–19)
Polymorphonuclear neutrophils in ascitic fluid (cells/mm ³)	70.5 (26–180)	722.4 (280–3024)
Polymorphonuclear neutrophils in ascitic fluid (%)	14.4 (8–17)	22.6 (15–36)

and Sons, New Hyde Park, NY) without general anaesthesia. When ascites was found, a fixed dose of 40 µl was given weekly, throughout the study. This model, a modification of the classic experimental models of cirrhosis,^{21 22} has been reported to have a high incidence of spontaneous bacterial peritonitis.²⁰

STUDY DESIGN

Ten of 73 rats were used as controls, and five were laparotomised after three doses of CCl₄. Samples of stomach, jejunum, ileum, and caecum were taken for light microscopy to rule out gastrointestinal damage caused by CCl₄. The remaining 58 animals were induced to cirrhosis as described above. Thirty four rats died before ascites was identified (overall mortality for the model: 58%), none of them showing longterm intestinal damage attributable to CCl₄. In 25, death occurred before cirrhosis, probably resulting from acute hepatic CCl₄ toxicity. In addition, nine rats died when cirrhosis was already established (two were found to have ascites after death with a polymorphonuclear neutrophils count higher than 250 cells/mm³).

Thus, 24 cirrhotic rats with clinically evident ascites and 10 healthy controls were available for bacterial translocation assessment. Ascitic fluid was obtained by paracentesis using a sterile technique, after depilation and iodine sterilisation of the abdominal wall. The presence of more than 250 polymorphonuclear

neutrophils/mm³ in the ascitic fluid was used as the diagnostic criterion for ascites infection in rats.²⁰ Accordingly, two groups were studied: 12 ascitic rats were evaluated as soon as ascites with less than 250 polymorphonuclear neutrophils/mm³ (group A) was identified, whereas in the remaining 12, diagnostic paracenteses were performed every 48–72 hours and were studied when the polymorphonuclear neutrophils count was above 250 cells/mm³ (group B). Only 10 rats of the second group, however, could be studied because two died before reaching this end point, and were not included despite a polymorphonuclear neutrophils count >250 cells/mm³, which was found after death in one.

Bacterial translocation was defined as the presence of viable enteric organisms in mesenteric lymph nodes.²³ Bacterial translocation assessment was always performed before death, and consisted of bacteriological studies of mesenteric lymph nodes, ascitic fluid, portal and peripheral blood, and abdominal viscera. In addition, histological samples of mesenteric lymph nodes, liver, spleen, jejunum, ileum, and caecum were also studied. For these purposes, a laparotomy was carried out under strict aseptic conditions and general anaesthesia (subcutaneous ketamine HCl, atropine, and diazepam). Potential sources of secondary peritonitis were carefully searched for. Samples were obtained in the following order: ascitic fluid, portal and peripheral (inferior vena cava) blood, mesenteric lymph nodes, liver, spleen, jejunum, ileum, and caecum.

LABORATORY METHODS

Ascitic fluid cell count was performed by hand using a Neubauer camera. Blood and ascitic fluid samples were cultured by immediate inoculation into blood culture bottles (modified Castañeda medium, thioglycolate broth; Knickerbocker Lab, Barcelona, Spain), a method that has been validated in humans.²⁴ Parenchymatous viscera were immediately cultured in brain-heart medium. Samples for histological examination were collected in 10% formaldehyde, subsequently embedded in paraffin wax, sliced in 5 µm sections, and stained with haematoxylin and eosin. They were examined by light microscopy by a 'blinded' pathologist.

STATISTICAL ANALYSIS

Unless stated, results are expressed as mean (SEM) or proportion as required. Comparison of means was performed by the Student *t* test for unpaired data or its non-parametric counterpart (Mann-Whitney test) as required. Proportions were compared by means of Fisher's exact test.

Results

Table I details the data regarding length of CCl₄ exposure, polymorphonuclear

TABLE II Bacterial isolated in mesenteric lymph nodes, ascitic fluid, and other specimen culture

Rat	Mesenteric lymph nodes	Ascitic fluid	Portal blood	Other*
1	<i>E coli</i>	<i>E coli</i> <i>E faecalis</i>	<i>E coli</i>	<i>E coli</i> <i>E faecalis</i>
2	<i>E coli</i>	<i>E coli</i>	<i>E coli</i>	<i>E coli</i>
3	<i>E coli</i>	<i>E coli</i>	<i>E coli</i>	<i>E coli</i>
4	<i>E faecalis</i> <i>Proteus sp</i>	<i>E faecalis</i> <i>Proteus sp</i>	<i>E faecalis</i> <i>Proteus sp</i>	<i>E faecalis</i> <i>Proteus sp</i>
5	<i>E faecalis</i>	<i>E coli</i> <i>E faecalis</i> <i>Proteus sp</i>	<i>E coli</i> <i>E faecalis</i> <i>Proteus sp</i>	<i>E coli</i> <i>E faecalis</i>
6	<i>E coli</i>	<i>E coli</i> <i>P aeruginosa</i>	–	–
7	<i>E coli</i> <i>E faecalis</i>	–	–	–
8	<i>E coli</i>	–	–	–
9	<i>E coli</i>	–	–	–
10	<i>P aeruginosa</i>	–	–	–
11	–	<i>E coli</i> <i>Proteus sp</i>	<i>E coli</i> <i>Proteus sp</i> <i>E faecalis</i>	<i>E coli</i> <i>Proteus sp</i> <i>E faecalis</i>
12	–	<i>E coli</i> <i>E faecalis</i> <i>Proteus sp</i>	–	–
13	–	<i>E coli</i> <i>E faecalis</i>	–	–
14	–	<i>E coli</i> <i>Proteus sp</i>	–	–
15	–	<i>Proteus sp</i>	<i>Proteus sp</i>	<i>Proteus sp</i>

*Other samples: portal and peripheral blood, liver, and spleen. No bacteria were isolated in seven rats.

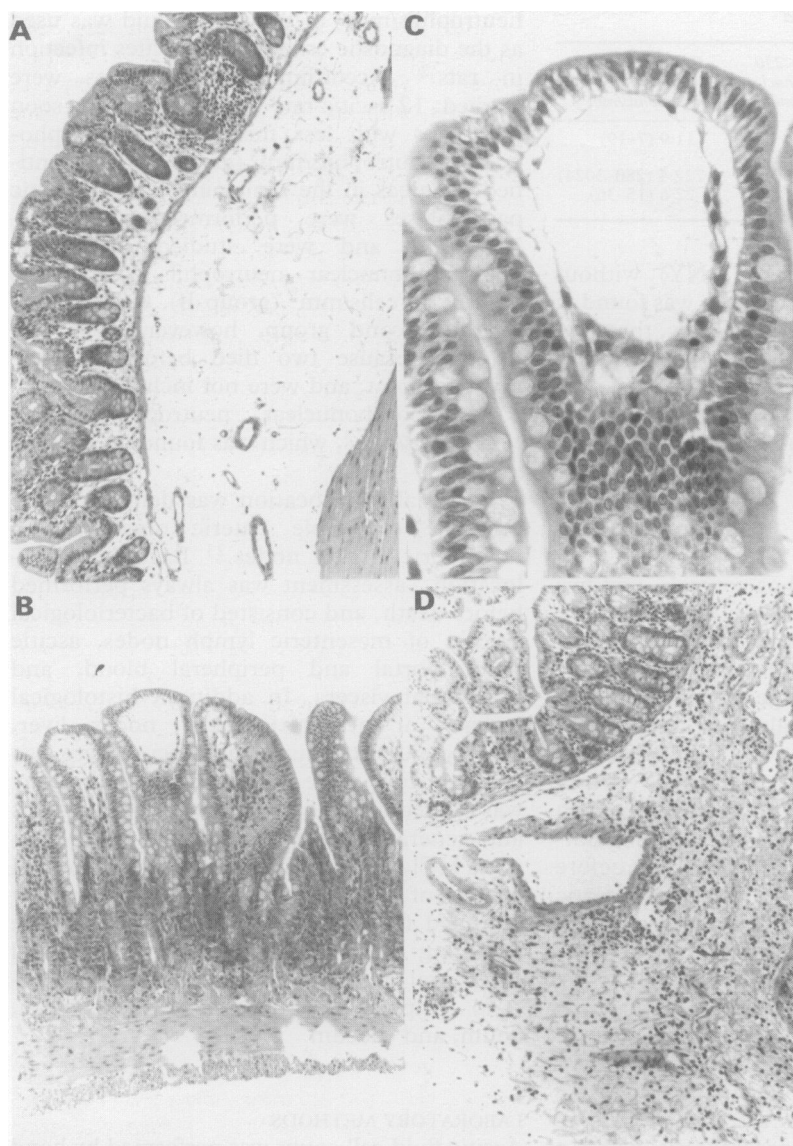


Figure 1: Histological changes seen in cirrhotic rats with ascites (haematoxylin and eosin). (A) Submucosal caecal oedema (original magnification $\times 40$); (B, C) ileal lymphangiectasia (original magnification $\times 100$; $\times 400$); (D) submucosal caecal inflammatory infiltrate (original magnification $\times 100$).

neutrophils count, and percentage in ascitic fluid of rats included in the study.

None of the 10 control rats showed bacterial translocation – that is, mesenteric lymph nodes positive culture – whereas this occurred in 10 of 22 (45%) ascitic rats ($p=0.01$). The prevalence of bacterial translocation, however, was not different between rats with polymorphonuclear neutrophils counts in ascitic fluid greater or lower than 250 cells/mm^3 , 50% *v* 41%, respectively.

As a differential count greater than $250 \text{ polymorphonuclear neutrophils/mm}^3$ in ascitic fluid has been considered to be the threshold for diagnosing ascites infection in rats,²⁰ the relation between polymorphonuclear neutrophils count and positive ascitic fluid culture was studied. Not all ascitic fluid specimens with more than $250 \text{ polymorphonuclear neutrophils/mm}^3$ (group B) grew bacteria. In fact, only six of 10 (60%) rats of this group showed positive ascitic fluid culture, while this occurred in five of 12 (41%) rats

of group A. Accordingly, mean polymorphonuclear neutrophils count in ascitic fluid did not differ between rats with and without positive ascitic fluid culture ($514 (258) \text{ v } 218 (76) \text{ cells/mm}^3$, NS).

The type of micro-organisms present in mesenteric lymph nodes and ascitic fluid were compared to ascertain the possible association between bacterial translocation and ascitic fluid infection. Among the 10 rats with bacterial translocation, six showed the same bacterial species both in ascitic fluid and in mesenteric lymph nodes (Table II). In the remaining four rats, no other specimen, apart from mesenteric lymph nodes, was positive. Five of 12 ascitic rats without bacterial translocation showed positive ascitic fluid culture. In two of them the same bacteria was also cultured in portal blood.

Table II shows, in individual rats, the association between the results of ascitic fluid, portal blood, and other specimen culture and the presence or absence of bacterial translocation. The organisms isolated were all aerobes of enteric origin. The most frequent was *Escherichia coli*, which was obtained in 70% and 82% of positive cultures from mesenteric lymph nodes and ascitic fluid, respectively. Seventy two per cent of positive ascitic fluid cultures were polymicrobial, whereas this only occurred in 20% of the positive mesenteric lymph nodes cultures.

HISTOLOGICAL FEATURES

All histological specimens studied were normal in control rats. Likewise, no gastrointestinal damage was seen in those rats studied after three doses of CCl_4 .

All ascitic rats had histological evidence of cirrhosis and vascular congestion of the spleen, probably secondary to portal hypertension. About 63% of ascitic rats showed activated germinal centres of mesenteric lymph nodes ($p=\text{NS}$ *v* controls), but no relation with bacterial translocation, polymorphonuclear neutrophils count or positive culture in ascitic fluid was seen.

Three abnormal features were present in the gut of ascitic animals. These were submucosal caecal oedema (Fig 1A), which occurred in all of them ($p<0.0005$ *v* controls), ileal lymphangiectasia (Fig 1B and C), which was present in nine of 22 cases ($p=0.017$ *v* controls), and caecal inflammatory infiltrate (lymphocytic in six and mixed, lymphocytes + polymorphonuclear neutrophils, in three) was found in nine of 22 rats ($p=0.017$ *v* controls) (Fig 1D). The infiltrate involved the submucosal, muscular, and serosal layers in six cases and was confined to the submucosa in the remaining three. Mucosal infiltrate was not seen.

When the relation between histological findings and bacterial translocation, polymorphonuclear neutrophils count or positive ascitic fluid culture was studied, only a weak association was found between caecal inflammatory infiltrate and positive ascitic fluid culture ($p=0.04$).

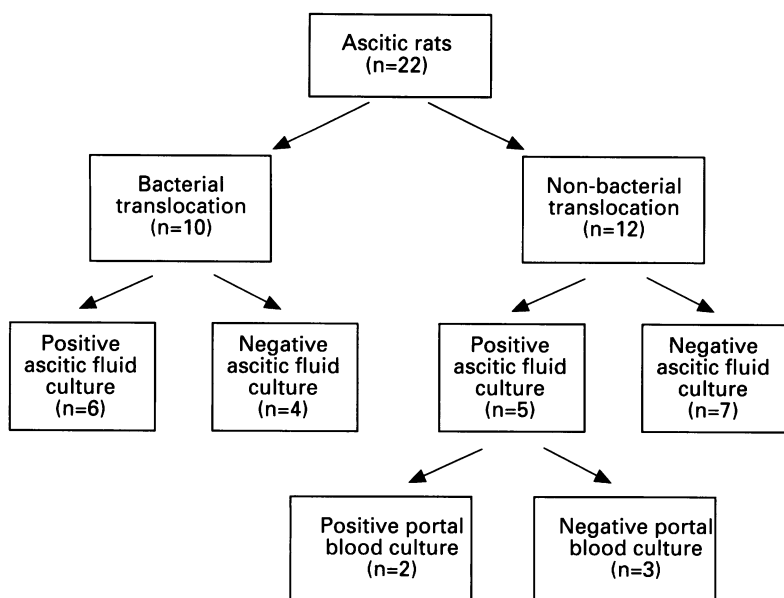


Figure 2: Possible pathogenic role of bacterial translocation in the development of ascitic fluid infection. (See text for details).

Discussion

The induction of cirrhosis and ascites by orogastric CCl_4 feeding in rats is the only reported method for an experimental model of ascitic fluid infection.²⁰ The study provides additional data to understand better the characteristics of ascitic fluid infection in cirrhotic rats and its differences with human spontaneous bacterial peritonitis. In agreement with Runyon *et al*²⁰ we found a 50% rate of ascitic fluid positive culture, most of them (70%) being polymicrobial. This occurred even though secondary peritonitis was carefully searched for. In addition, the fact that all cases were diagnosed before death rules out the possibility of ascitic fluid colonisation after death. All organisms isolated in ascitic fluid were of enteric origin, the most frequent being *E coli* (58%). The comparatively high frequency of *Enterococcus faecalis* and *Proteus* sp infection is noteworthy as they, especially the second, are seldom reported in humans.¹⁻³ Although it is difficult to extrapolate from animals to humans, the fact that all microorganisms found in ascitic fluid were of enteric origin without evidence of intestinal lesions raises the possibility of its use in the study of the spontaneous bacterial peritonitis pathogenesis.

On the other hand, in contrast with the previous report, not all ascitic fluid specimens with more than 250 polymorphonuclear neutrophils/ mm^3 grew bacteria. In fact, we found a 40% rate of culture negative neutrocytic ascites. The fact that we performed diagnostic paracentesis every 72 hours increases the possibility of early spontaneous bacterial peritonitis diagnosis, compared with the previous report in which animals were studied until death, or even after death. Because our animals were laparotomised immediately after the polymorphonuclear neutrophils count reached 250 cells/ mm^3 , however, it could not be shown that culture negative neutrocytic ascites rats would develop a culture positive spontaneous bacterial peritonitis later. Further investigations are needed to find out if the polymorphonuclear neutrophils threshold used in humans applies to rats.

Although bacterial translocation has been widely shown to occur in rats in several situations,^{12 13} information about its occurrence in cirrhosis with ascites is scarce.^{15 16} In our study, 45% of ascitic rats showed translocation of aerobic gut flora to mesenteric lymph nodes. In contrast, no control rat showed bacterial translocation. In fact, mesenteric lymph nodes in pathogen free rats and in healthy humans are sterile^{12 25} because bacteria either do not pass through gastrointestinal mucosa, are cleared in transit to the mesenteric lymph nodes, or are killed by macrophages in the mesenteric lymph nodes itself.^{12 26}

The high rate of bacterial translocation found in our study, as well as in recently reported abstracts (88%,¹⁵ 56%¹⁶), suggests that certain factors favouring bacterial translocation may occur in ascitic rats, and probably also in human cirrhotic patients with ascites. Although they have not been evaluated in this study, some conditions associated with an experimentally shown high rate of bacterial translocation, such as intestinal bacterial overgrowth,²⁷ portal hypertension,²⁸⁻³⁰ haemorrhagic shock,^{28 31} endotoxaemia,³² impaired host defence mechanisms,³³ and malnutrition,³⁴ are common in cirrhosis.^{1 3 35-37} Particularly, endotoxaemia should be assessed in future studies, because some authors argue that endotoxin precedes and promotes bacterial translocation.³²

The possibility that CCl_4 induced gut damage could account for this high bacterial translocation rate seems unlikely because gastrointestinal lesion was ruled out in our study.

To our knowledge, there are no published data about the relation between bacterial translocation and spontaneous bacterial peritonitis in cirrhotic rats. In our study, no differences in the bacterial translocation rate were seen between those rats with or without ascitic fluid positive culture, suggesting that bacterial translocation is not a sine qua non condition for ascitic fluid infections, although it may play a permissive part in some cases. Nevertheless, some of the observed associations between positive culture in mesenteric lymph nodes and other samples may help to better define the role of bacterial translocation in the spontaneous bacterial peritonitis pathogenic hypothesis.

Among the 10 rats with bacterial translocation (Fig 2), six showed the same bacterial species both in mesenteric lymph nodes and ascitic fluid, supporting the hypothesis that a number of enteric bacteria finally colonising ascitic fluid reach the bloodstream through the lymphatic route. In fact, bacterial translocation to mesenteric lymph nodes has been reported to be the main mechanism of the entrance of gut bacteria to the systemic circulation in multiple experimental situations.^{12 13} In contrast, four rats showed bacterial translocation with no other positive samples, suggesting that the presence of viable bacteria in mesenteric lymph nodes does not always point to an impending systemic infection. Thus, despite the presence of the above described factors favouring bacterial translocation, the access of

bacteria to the bloodstream and ascitic fluid requires an impaired systemic or local (peritoneal) host defence, or both.

On the other hand, in five of 12 cases without bacterial translocation a positive ascitic fluid culture was found. Two of them showed positive cultures from portal and systemic blood and viscera. Although a positive portal culture can occur in the setting of a systemic infection, it could be speculated that the passage of gut bacteria to portal blood may be an alternative route of access for enteric bacteria to the bloodstream in cirrhosis. Interestingly, such a mechanism has already been reported in experimental models of peritoneal inflammation.³⁸ In the remaining three rats, there is no explanation for ascitic fluid positive culture in terms of this study. Passage through other mesenteric lymph nodes, however, not harvested for culture, transient portaemia, or an extraintestinal septic focus, for example, urinary infection may account for these cases.

Two of the most conspicuous histological features found in this study, namely submucosal caecal oedema and ileal lymphangiectasia, are probably related to the presence of portal hypertension.^{29 30} Even though they were not statistically associated with bacterial translocation, polymorphonuclear neutrophils count or positive ascitic fluid culture, their possible role favouring the passage of gut bacteria into mesenteric lymph nodes cannot be ruled out. Caecal inflammatory infiltrate was weakly associated with positive ascitic fluid culture. It remains to be elucidated if it is a manifestation of chronic inflammation, which has been reported in experimental portal hypertension,^{29 30} or is related to acute peritoneal infection.

In the light of these results, it is concluded that bacterial translocation occurs frequently in ascitic cirrhotic rats and may play a permissive, but not unique, part in ascites infection. Further investigations are required to find out if the polymorphonuclear neutrophils threshold used in humans applies to cirrhotic rats, and also to discover a possible pathogenic link between the intestinal histological changes seen in this study and bacterial translocation.

Preliminary results of this study were presented at the 94th Annual Meeting of the American Gastroenterological Association held in Boston, May 1993. This study was partly supported by a grant of the FISs (No 92/0764) of the Spanish National Institute of Health.

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Gut 1994 35: 1648-1652

doi: 10.1136/gut.35.11.1648

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