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Liver disease and *Helicobacter*

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INTRODUCTION

The human upper gastrointestinal tract is often infected with *Helicobacter pylori* (*H. pylori*). This urea splitting bacterium is now considered to be a causal agent in some diseases, including antral gastritis and frank duodenal ulceration, in addition to an association with gastric carcinoma and mucosa associated lymphoid tissue (MALT) lymphoma[1]. Since the discovery of *H. pylori*, a number of additional *Helicobacter* species have been isolated from the stomachs and intestinal tracts of a variety of mammalian species. At least eighteen separate *Helicobacter* species have been recognized (Table 1)[2,3]. The discovery of these *Helicobacter* species, has raised the possibility of a relationship between *Helicobacter* infection and liver diseases[3].

Table 1 Helicobacter species and their hosts

Species	Hosts	Primary site	Other sites
*H. pylort**	Human, macaque, cat	Stomach	
H. mustelae	Ferret, mink	Stomach	
*H. felis**	Cat, dog	Stomach	
*H. bizzozeronii**	Dog, human	Stomach	
H. helimannii△*	Dog, cat, human, monkey	Stomach	
H. nemestrinae	Pig-tailed macaque	Stomach	
H. suis△	Swine	Stomach	
H. acinonyx	Cheetah	Stomach	
*"H. rappini"**	Sheep, dog, human, mice	Intestine	Liver (sheep), stomach
*H. canis**	Dog, human	Intestine	Liver (dog)
H. hepaticus	Mice	Intestine	Liver
H. bilis	Mice, dog	Intestine	Liver, stomach (dog)
H. trogontum	Rat	Intestine	
H. muridarum	Mice, rat	Intestine	Stomach (mich)
*H. cinaedi**	Human, hamster	Intestine	
H. fennelliae	Human	Intestine	
*H. pullorum**	Chicken, human	Intestine	Liver (chicken)
H. pametensis	Bird, swine	Intestine	
H. cholecystus	Hamsters	Intestine	

*Some data suggest zoonotic potential
△Closely related, may be same species

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HELICOBACTER PYLORI AND PEPTIC ULCER IN CIRRHOSIS

Historically, it is well recognized that duodenal ulcer disease is more common in patients with cirrhosis as compared with non-cirrhotic patients[4]. However, a number of early studies suggested that in cirrhotic patients there was no clear relationship between duodenal ulcers and *H. pylori* infection, suggesting the possibility of other causes[5]. Other studies suggested that *H. pylori* infection, as measured by IgG, *H. pylori* serum antibodies, was more common in cirrhotic patients than in non-cirrhotics[6]. A study showed that cirrhotic patients were more likely to have a positive *H. pylori* ELISA with a negative histologic examination for *H. pylori* as compared with noncirrhotic patients[7]. Whether *H.pylori* is a risk factor for peptic ulcer in cirrhosis remains controversial. In a cross-sectional study by Wang *et al*, 49 cirrhotic patients underwent upper gastrointestinal endoscopy and 75 controls (healthy examinees) without liver disease were also examined by endoscopy. Thirty (61%) of the 49 cirrhotic patients had peptic ulcers as compared with 24 (32%) of the 75 controls. The frequency of *H. pylori* in the antrum in the cirrhotic group was significantly lower than in the control group (39% *vs* 69%). The presence of *H. pylori* was more frequent in control patients with gastric (75%) and duodenal ulcers (95%) than nonulcerous control patients (59%), the difference between patients with and without peptic ulcer (40% *vs* 37%) was not significant in cirrhotic patients. *H. pylori* was identified in 40% of the cirrhotic patients with duodenal ulcers as against 95% of controls with duodenal ulcer($P<0.05$). Nevertheless, this difference was not significant among patients with a gastric ulcer between the two groups (40% *vs* 75%). There was no significant difference in the frequency of *H. pylori* infection among nonulcerous patients between the cirrhotic and control groups (37% *vs* 59%). No evidence was found to substantiate an etiologic role of *H. pylori* in the development of duodenal ulcer in cirrhotic patients[8]. In 153 consecutive patients with cirrhosis, Siringo *et al*'s[9] assessed the prevalence of IgG to *Helicobacter pylori* and compared it with that in 1010 blood donor-residents in the same area and the relationship of IgG to *H. pylori* with clinical and endoscopic features and with the risk of

peptic ulcer. The prevalence of IgG to *H. pylori* of cirrhosis was significantly higher than in blood donors (76.5% *vs* 41.8%; $P<0.0005$) and was not associated with sex, cirrhosis etiology, Child class, gammaglobulins and hypertensive gastropathy. In both groups, the prevalence of IgG to *H. pylori* was significantly higher in subjects aged over 40. Multivariate analysis identified high age and males as risk factors for a positive *H. pylori* serology and no independent risk factors for peptic ulcer. The high prevalence of *H. pylori* positive serology found in this series was related to age and sex and might also be explained by previous hospital admissions and/or upper gastrointestinal endoscopy. Their results did not confirm the role of *H. pylori* as a risk factor for peptic ulcer in patients with liver cirrhosis. *H. pylori* infection is the major pathogenic factor for peptic ulcer disease. Its epidemiology is not fully known; few data are available in patients with chronic liver disease. To investigate the seroprevalence and factors associated with *H. pylori* infection, a series of studies or liver cirrhosis patients is necessary. Two hundred and twenty consecutive patients were prospectively included in a study aimed to evaluate the effect of dietary intervention on cirrhosis complications and survival. An epidemiological and clinical questionnaire was completed. Sera were obtained and stored at -70℃ until analyzed. They were tested for *H. pylori* antibodies using a commercial ELISA kit. Eleven of 220 patients had borderline anti-*H. pylori* -IgG titers. Of the remaining 209 patients, 105 (50.2%) showed positive titers of *H. pylori* IgG. Univari ate analysis showed that *H. pylori* infection was more frequent in older patients, those born outside Catalonia, and in patients with a low educational level. Past ethanol consumption and current smoking were correlated negatively with *H. pylori* infection. Selected age (OR 3.1, 95% CI 1.46 - 6.45), educational level (OR 2.2, 95% CI 1.18 - 4.2) and alcohol consumption (OR 0.7, 95% CI 0.4 5-0.99) as the variables were independently related to *H. pylori* infection in multivariate analysis. Their conclusions of *H. pylori* infection in cirrh osis has the same epidemiological pattern as in the general population. Suggestions that the etiology or the severity of the liver disease could be related to *H. pylori* infection were not confirmed by their study[10].

HELICOBACTER PYLORI AND PORTAL HYPERTENSIVE GASTROPATHY

Yang *et al*[11] have recently investigated the possible relationship between *H. pylori* infection and portal hypertensive gastropathy (PHG) in cirrhotic patients. Yang's conclusion is that *H. pylori* colonization of the stomach of cirrhotic patients was likely to be contributed to the development of PHG. In other reports, *H. pylori* infection in patients with PHG differed from that in the normal population[12], in contrast with what can be observed in patients with chronic gastritis. Some authors do not agree, however, on Balan's findings that gastric mucus secretion was unaltered in PHG patients. Althoughed there was no difference between *H. pylori*-positive or-negative patients, a previous study showed that both mucus and bicarbonate secretion (so-called mucus-bicarbonate barrier) were impaired in cirrhotic patients with PHG[13], a phenomenon that might account for the high sensitivity of portal hypertensive mucosa to the damaging agents[14]. Others have also detected a reduced mucus secretion in PHG patients[15]. PHG was also thought to be associated with changes in gastric mucosal blood flow, but, the available data are conflicting[16], although most studies support the concept that gastric perfusion was increased, because *H. pylori* infection had no influence on gastric mucosal blood flow, the state of local microcirculation was unaffected by eradication of the germ[17]. Another study suggested that the role of *H. pylori* infection in the pathogenesis of congestive gastropathy seemed to be unlikely and that there was no need for routine eradication in cirrhotic patients[18]. Bahnacy *et al*[18] evaluated the prevalence and signifi cance of *H. pylori* infection in patients with portal hypertension. A total of 118 patients were selected, 90 with portal hypertension (66 males, 24 females, mean age 49.1 ±2.1 years) and 28 noncirrhotic patients with nonulcerative dyspepsia as a control group (12 males, 16 females, mean age 47.6 ± 2.8 years). Endoscopy was performed and gastric biopsies were taken for histological examination and diagnosis of *H. pylori* infection in all the patients. Of the portal hypertensive patients, 42 (47%) had congestive gastropathy, 11 (26%) of whom were positive for *H. pylori* infection and 48 (53%) had no gastropathy, 12 (25%) of whom were positive for *H. pylori* infection. In the control group, 15 (54%) of 28 were positive for *H. pylori* infection. *H. pylori* was found less frequently in congestive gastropathy patients than in the control group.

HELICOBACTER AND BILE DUCT INJURY

Are there any *Helicobacter* species that can induce bile duct injury and then trigger further autoimmune liver diseases? Recent studies in animals have

provided insight into the possibility. The best model for the *Helicobacter* induced liver disease up to date is the recently isolated and characterized bacterium named *H. hepaticus*[19-22]. *H. hepaticus* is a spiral-to-curved bacterium, observed with Steiner's silver stains in livers of barrier-maintained mice suffering from multifocal necrotic hepatitis. *H. hepaticus* persistently colonized in the colon and cecum, and was associated with liver tumors in A/J Cr mice as well as hepatitis in other susceptible inbred mouse strains[19]. In A/J Cr mice, *H. hepaticus* can be seen in the liver under electron microscopy, but only infrequently and only in bile canaliculi. *H. hepaticus* is resistant to high levels of bile *in vitro*, which may help explain its ability to colonize in bile canaliculi. Other studies have suggested that *H. pylori* can colonize in the biliary tract. In one study, *H. pylori* DNA was detected by PCR in 3 out of 7 bile samples collected with percutaneous transhepatic cholangiodrainage, suggesting the possibility that this organism can cause asymptomatic cholangitis[23]. In another study, a microorganism closely resembling (by PCR and immunohistochemical staining) *H. pylori* was found in the resected gallbladder mucosa of a 41-year-old woman who was adimitted to the hospital with fever and upper right quadrant pain[24]. However, these studies inferring the presence of *H. pylori* in bile of biliary tissues are not supported by the *in vitro* findings of *H. pylori* being unable to grow in the presence of bile products[25]. The author also demonstrated that unconjugated bile salts were more toxic than conjugated bile salts[25]. Others have suggested that bile salts *in vivo* can inhibit *H. pylori* colonization. These authors found an association between the absence of *H. pylori* and previous surgery for peptic ulcers, high reflux scores, hypochlorhydria and increased bile acid concentration in the stomach[26]. Other reports have also noted that gastric *H. pylori* infection increased following cholecystectomy[27]. Nevertheless, *H. pylori* appears in some people to survive in intestinal fluids with bile present as noted by the ability to isolate *H. pylori* from the feces of children and adults[28,29]. The sensitivity of *H. pylori* to bile acids is contrasted by the ability of *Helicobacter* colonizing in the l iver, i.e. *H. hepaticus, H. bilis, H. canis, H. cholecystus* and *H. pullor um*, to grow in the presence of bile. In addition to *H. hepaticus*, other *Helicobactersp* can colonize in the hepatobiliary tract. A bacterium was identified in the diseased livers and intestines of aged inbred mice. It has been characterized biochemically by 16s rRNA sequence data, and named *H. bilis*[30].

HELICOBACTER AND DIARRHOEA IN CIRRHOSIS

It was observed that *H. hepaticus* can cause inflammatory bowel disease when inoculated into germ free mices. In addition, *H. hepaticus* was associated with colitis and typhlitis in immunocompromised mice[20,31,32]. It is well known that *H. cinaedi* and *H. fennelliae* are isolated from the diarrheic feces of immunocompromised patients with proctitis and/or colitis[33,34]. *H. canis*, cultured from diarrheic and asymptomatic dog feces as well as feces from humans with diarrhea were isolated from the liver of a dog with acute hepatitis[35,36]. Cirrhotic patients often had diarrhea, could it be possible that *H. hepaticus* can cause inflammatory bowel disease in cirrhosis This deserves further studies. As many intestinal *Helicobacters* appeared to cause diarrheal diseases (and perhaps liver disease) in humans, could positive IgG-*H. pylori* antibodies reflect cross-reactivity with other *Helicobacter* species Sera from abbatoir workers in direct contact with internal organs of poultry were more frequently positive (ELISA>300) than the sera from other employees[37,38]. It is worth noticing that although the prevalence of *H. pylori* infection was not different from controls in the other groups, their *H. pylori* IgG antibody levels were statistically higher[37,38].

HELICOBACTER AND HEPATITIS AND LIVER CANCER

Mice infected with *H. hepaticus* developed chronic liver inflammation, with oval cell, Kupffer cell and Ito cell[20] hyperplasia, hepatomegaly and bile duct proliferation[20]. Eventually, with longstanding infection, A/J Cr mice developed a chronic proliferative hepatitis and hepatocellular carcinoma. There are some similarities of this murine hepatitis to human primary biliary cirrhosis including portal hepatitis, ductular proliferation, and scaring. The murine hepatitis also had features of autoimmune cholangitis[20]. The mechanism in which *H. hepaticus* infection caused liver injury is still unclear at present. *H. hepaticus*, like several other *Helicobacter* species, exp ressed urease enzyme which generated ammonia, the toxic product may damage hepatocytes adjacent to the bacteria. In addition, a soluble cytotoxin has been identified in *H. hepaticus* that produced significant *in vitro* cytopathic effects in a murine hepatic cell line[39]. A recently discovered bacterium, *H. hepaticus*, could infect the intrahepatic bile canaliculi of mice, causing a severe chronic hepatitis culminating in liver cancer. Thus, it affords an animal model for study of bacteria-associated tumorigenesis including

H. pylori related gastric cancer. Reactive oxygen species are often postulated to contribute to this process. Sipowi *et al*[40] recently reported that hepatitis of male mice infected with *H. hepaticus* showed significant increases in the oxidatively damaged DNA deoxynucleoside 8-hydroxydeoxy-guanosine, with the degree of damage increased with progression of the disease. Perfusion of infected liver with nitro blue tetrazolium revealed that superoxide was produced in the cytoplasm of hepatocytes, especially in association with plasmacytic infiltrates near portal triads. Contrary to expectations, Kupffer cells, macrophages, and neutrophils were rarely involved. However, levels of cytochrome P450 (CYP) isoforms 1A2 and 2A5 in hepatocytes appeared to be greatly increased, as indicated by the number of cells positive in immunohistochemistry and the intensity of staining in many cells, concomitant with severe hepatitis. The CYP2A5 immunohistochemical staining co-localized with formazan deposits resulting from nitro blue tetrazolium reduction and occurred in nuclei as well as cytoplasm. These findings suggest that CYP2A5 contributes to the superoxide production and 8-hydroxydeoxyguanosine formation, although it is possible that reactive oxygen species from an unknown source in the hepatocytes may lead to CYP2A5 induction of coincidental occurrence of these events. Three glutathione S-transferase isoforms, mGSTP1-1 (pi), mGSTA1-1 (YaYa), and mGSTA4-4, also showed striking increases evidencing major oxidative stress in these livers. Luzza *et al*[41] assessed a sample of 705 resident subjects (273 males, aged 1-87 years, median 50) who attended the outpatient medical centre of the rural town of Ciro, Southern Italy (11000 inhabitants) for blood test. All subjects completed a structured questionnaire. A serum sample was drawn from each subject and assayed for *H. pylori* IgG by a validated in-house enzyme linked immunosorbent assay. Antibodies to HAV were determined in 466 subjects (163 males, aged 16-87 years, median 49). The Kappa statistical method was used to measure the agreement between *H. pylori* and HAV seropositivity. Overall, 466 (63%) subjects were seropositive for *H. pylori*. Of the 466 subjects screened for both *H. pylori* and HAV, 291 (62%) were seropositive for *H. pylori*, and 407 (87%) for HAV. Cross-tabulation of these data showed that 275 (59%) were seropositive and 43 (9%) seronegative for both *H. pylori* and HAV; 16 (3%) were seropositive for *H. pylori* and 132 (28%) were seropositive for HAV (OR = 5.6, CI 3-10). There was a parallel, weakly correlated (r = 0.278) rise in the seroprevalence of the two infections with increasing age. However, the agreement between *H. pylori* and HAV seropositivity was a little better than chance (Kappa =0.21), and in those aged less than 20 years, it was worse than chance (Kappa = -0.064). Furthermore, multiple logistic regression analysis did not show any risk factor shared by both infections. The correlation between *H. pylori* and HAV reflected the age-specific seropre valence of both infections rather than a true association. This study provided evidence against a common mode of transmission of *H. pylori* and HAV. Chen *et al*[42] examined the seroprevalences of chronic infection with hepatitis B and C viruses and *H. pylori* in Matzu, a group of small islets with 5566 civilian residents who have extremely high mortalities from cancers of the stomach and liver. The standardized mortality ratios (SMR) of all cancer sites combined, liver cancer and stomach cancer in 1984-1993 were calculated using the general population in Taiwan as the reference (SMR = 100). The SMRs (95% CI) for all cancer sites combined, liver cancer and stomach cancer were 160 (131-195), 252 (170-360) and 351 (229 - 516), respectively, in Matzu. A health survey was carried out with 485 civilian residents aged 30 years or more, giving a response rate of 69% among those who were eligible. Serum samples were tested for antibodies against *H. pylori* (anti-Hp) by enzyme-linked immunosorbent assay and hepatitis B surface antigen (HBsAg) and antibodies against hepatitis C virus (anti-HCV) by enzyme immunoassay. The seroprevalence was 61% for anti-Hp, 24.7% for HBsAg and 1.8% for anti-HCV in Matzu. While mortality rates of liver and stomach cancers were significantly higher in Matzu than in Taiwan, the seroprevalences of an ti-Hp, HBsAg and anti-HCV in Matzu were similar to or even lower than those in Taiwan. Their findings suggest the existence of risk factors other than microbial agents involved in the development of stomach and liver cancers. Rudi *et al*[43] examined staff members of an acute care hospital for serum antibodies to *H. pylori* IgG (n = 457) and to hepatitis A virus (n = 434). The staff members were assigned to three groups: nonmedical staff (n = 110); medical and nursing staff (n = 272); and medical and nursing staff working in a gastroenterology and endoscopy unit (n = 75). Serum antibodies were measured by valid ated enzyme immunoassays. A questionnaire inquiring about medical and professional history, history of upper GI pain and ulcer, as well as about the use of nonsteroidal anti-inflammatory drugs or medication for GI complaints and smoking habits was completed by each person. The seroprevalence of

H. pylori was 35.5% in group I, 34.6% in group II, and 24.0% in group III (not significant). The seroprevalence of *H. pylori* antibodies increased with age ($P < 0.01$), and antibodies were present more frequently in women than in men (36.2% *vs* 25.4%, $P < 0.05$). After adjustment for age, the duration of experience and the number of years working in the gastroenterology or endoscopy unit did not increase *H. pylori* seropositivity. No significant association was found between *H. pylori* seropositivity and history of upper GI pain, ulcers, use of nonsteroidal anti-inflammatory drugs or medication for GI complaints, or tobacco use. The prevalence of hepatitis A antibodies was similar in the three groups (group I, 26.4%; II 26.5%; III 21.7%; not significant). Cross-tabulation showed that 67 (15.4%) subjects were seropositive for both *H. pylori* and hepatitis A ($P < 0.01$), and that 245 (56.5%) were negative for both. Seventy-seven (17.7%) and 45 (10.4%) were seropositive for only *H. pylori* and for only hepatitis A respectively. Occupational exposure to patients in an acute care hospital as well as to patients and to endoscopic procedures of a gastroenterology and endoscopy unit does not increase the rate of infection with *H. pylori*. The significant correlation between the seroprevalence of *H. pylori* and hepatitis A antibodies suggests the fecal-oral transmission of *H. pylori*.

HELICOBACTER AND CHRONIC HEPATIC ENCEPHALOPATHY

Chronic hepatic encephalopathy is a neuropsychiatric disorder with protein manifestations, the pathogenesis of which is poorly understood[44]. Ammonia is of key importance in the pathogenesis of hepatic encephalopathy[45,46], and hyperammonemia in patients with cirrhosis is considered to be produced by bacterial urease in the gut flora. The initial study implicating *H. pylori* as a risk factor for hepatic encephalopathy was published in 1993[47]. Gastric ammonia production must be evaluated to assess whether the ammonia produced by *H. pylori* can cause hyperammonemia. *H. pylori* has strong urease activity. Ammonia produced by *H. pylori* in the stomach can be a source of systemic ammonia in patients with hepatic dysfunction. The effect of the eradication of *H. pylori* on hyperammonemia was examined in patients with liver cirrhosis. Ammonia concentrations in blood and gastric juice were analysed in 50 patients with liver cirrhosis and hyperammonemia. All patients were first treated with a low protein diet, kanamycin, lactulose, and branched chain enriched amino acid solution. Hyperammonemia remained in 18 patients. These 18 patients were divided into three groups according to the status of *H. pylori* infection: group I, with a diffuse distribution of *H. pylori* in the stomach; Group II, with a regional distribution; and group III, without *H. pylori*. In group I, ammonia concentrations in blood and gastric juice were significantly reduced after *H. pylori* eradication. The blood ammonia concentration at 12 weeks after the eradication was still significantly lower than that before eradication. In groups II and III, the ammonia concentrations in blood and gastric juice were not significantly reduced after eradication therapy. The authors' conclusion is that diffuse distribution of *H. pylori* in the stomach contributes partly to hyperammonaemia in patients with liver cirrhosis, and the eradication of *H. pylori* is effective in patients with liver cirrhosis, and the eradication of *H. pylori* is effective in patients with hyperammonemia with diffuse *H. pylori* infection in the stomach[48]. These findings suggest that the contribution of ammonia produced by *H. pylori* to the systemic concentration depends on the number of bacteria and their distribution in the stomach[48]. Quero *et al*[49] also reported a fall in blood ammonia with the eradication of *H. pylori*, but the blood ammonia rose two months after treatment to baseline values in patients after the eradication of *H. pylori*, suggesting that the effect of the eradication of *H. pylori* on hyperammonemia is a non-specific effect of antibiotics rathe than an effect of the eradication of the organism. Plevris *et al*[50] found no significant effect of the presence of *H. pylori* on blood ammonia up to two hours after administration of oral urea. They also suggested that the improvement seen in our initial report may be attributed to a non-specific effect of antibiotics rather than to an effect of the eradication of *H. pylori*.

CHRONIC ATROPHIC GASTRITIS AND H. pylori INFECTION IN PBC

Primary biliary cirrhosis (PBC) is a chronic liver disease characterized by exocrine gland impairment. Up to now there has been no report dealing with gastric mucosa involvement in this autommune condition which is frequently associated with Sjogren syndrome. Floreani *et al*[51] investigated the morphologic, bilochemical and immunological features of the gastric mucosa in PBC. A cross-sectional matching study was performed. Thirty-three PBC patients (30 women, 3 men, mean age 58 years; 17 with stage II - III, and 16 with stage IV disease) and 33 sex- and age-matched dyspeptic controls were included. Six biopsy specimens from

the fundus (2), body (2) and antrum (2) were taken from all patients and controls. A serological assessment was made for each subject, including pepsinogen A (PGA), pepsinogen C (PGC), gastrin (G), and antibodies against *H. pylori* (anti-Hp IgG). Endoscopic gastritis was found in 22 PBC patients (66.6%). There was no difference between PBC patients and controls regarding the percentage of subjects with mild, moderate, severe or atrophic gastritis (AG). There was no difference in gastric mucosal involvement between PBS subjects with or without secondary Sjogren syndrome. A discrepancy was observed in the data obtained with respect to *H. pylori* infection. *H. pylori* colonization was significantly more frequent in controls than in PBC patients (79% *vs* 49%, $P < 0.002$), but anti-Hp IgG was detected in the same percentage in the two groups (90% *vs* 83%). There was no difference between the two groups in the PGA, PGC, PGA/PGC ratio, or gastrin. Eight PBC patients had esophageal varices. PBC patients were not characterized by chronic atrophic gastritis. Even though they presented chronic gastritis with the same prevalence as dyspeptic controls, and showed signs of previous *H. pylori* infection as frequently as dyspeptic patients, they are actually much less frequently infected. The reasons for this observation are unclear[47]. In summary, many liver diseases in humans though well characterized clinically and pathologically, do not have well defined etiologies. Perhaps like the discovery of *H. pylori* associated gastric disease, the recognition of *Helicobacter SP* induced liver disease in animals, should stimulate studies to ascertain whether these or similar Helicobacters play an important role in pathogenesis of idiopathic hepatitis and liver neoplasia in humans.

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